Schlüsselfrage:

CCA 01 (1) Vorerkrankungen (CCA)
Welche Vorerkrankungen erhöhen das Risiko für die Entstehung von biliären Karzinomen (Gallenblasenkarzinom oder CCA)?

Inhalt: *6 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Atchison, E. A. 2011	3	retrospective cohort study
de Valle, M. B. 2012	4	retrospective prognostic study
Huang, Y. 2017	1	Systematic Review and Meta Analysis
Jing, W. 2012	2	systematic review and meta analysis
Palmer, W. C. 2012	1	systematic review and meta analysis
Wongjarupong, N. 2017	1	systematic review and meta analysis

OXFORD (2011) Appraisal Sheet: Systematic Reviews: *4 Bewertung(en)*

Huang, Y. et al. Smoking and risk of cholangiocarcinoma: a systematic review and meta-analysis. Oncotarget. 8. 100570-100581. 2017

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 **Study type:** Systematic Review and Meta Analysis **Databases:** Embase, PubMed and Cochrane Central Register of Controlled Trials databases, International Standard Randomised Controlled Trial Number registry, World Health Organization International Clinical Trials Registry Platform, and ClinicalTrials.gov. **Search period:** inception to April 11, 2017	**Population:** individuals who smoke **Intervention:** none **Comparison:** none	**Primary:** pooled OR with 95% CI for developing CCA in people who smoke **Secondary:** none **Results:** Smoking and risk of CCA - A total of 22 case-control studies involving 7,216 CCA cases and 317,117 control cases were analyzed -Significant heterogeneity existed among the studies (P=0.001; I^2=52.6%). - The summary odds ratio (OR) of CCA was 1.31 [95% confidence interval (CI), 1.15 to 1.51] in the random-effects model for smokers versus nonsmokers Smoking and risk of intrahepatic CCA - Twelve studies involving 3,759 patients with intrahepatic CCA and 308,278 healthy controls investigated the association between smoking and risk of intrahepatic	22 articles included see article for references

Inclusion Criteria: (1) randomized controlled trials or non-randomized studies; (2) full-text articles and abstracts that included smoking as an exposure of interest; (3) the outcome of interest was CCA, intrahepatic CCA, extrahepatic CCA, perihilar CCA, or distal CCA; and (4) ORs or relative risk (RRs) with 95% CIs were reported or can be calculated. **Exclusion Criteria:** (1) reviews, letters, editorials and case reports; (2) without data specific for CCA; (3) without appropriate data that could be extracted or calculated. In the case of multiple publications from the same population, only the most comprehensive one was included.		CCA - significant heterogeneity existed among the studies (P=0.000; I^2=66.2%). - pooled data using the random effects model showed an increased OR of developing intrahepatic CCA in smokers (OR, 1.31; 95% CI, 1.06 to 1.63) <u>Smoking and risk of extrahepatic CCA</u> - Twelve studies involving 3029 patients with extrahepatic CCA and 110,608 healthy controls explored the association between smoking and risk of extrahepatic CCA - A significant heterogeneity existed among the studies (P=0.034; I^2=45.1%). The pooled data using the random-effects model showed that smoking was associated with improved risk of extrahepatic CCA (OR, 1.32; 95% CI, 1.10 to 1.59) **Author's Conclusion:** In conclusion, the results of our meta-analysis support the hypothesis that there is a moderate association between cigarette smoking and risk of CCA. Further large-scale and well-conducted studies that investigate potential effect modification with confounders and the dose-response relationship between cigarette smoking and risk of CCA are needed. This conclusion delivers an important public health message to areas of both high CCA incidence and high smoking prevalence such as in China.	

Methodical Notes

Funding Sources: no statement

COI: The authors declare no conflicts of interest.

Study Quality: - methodological quality was assessed independently by three reviewers using the NOS
- Studies with 7 (out of 9) or more stars were considered to be of high quality.
- 1 study was awarded 4 stars, 2x 5 stars, 6x 6 stars, 4x 7 stars, and 8x 8 stars. 1 study was not assessed.

Heterogeneity: - Statistical heterogeneity between studies was measured by using the Chi-square (χ2, or Chi2) test and quantified via I^2 statistic; P value < 0.10 or I^2 > 50% was considered statistically significant.
- overall, Significant heterogeneity existed among the studies (P = 0.001; I^2 = 52.6%).
- see results, for further I^2 values

Publication Bias: - No evidence of significant publication bias was noted from visual inspection of the funnel plots, Begg's test or Egger's test for risk of CCA (Begg's P = 0.626, Egger's P = 0.954), risk of intrahepatic CCA (Begg's P = 0.463, Egger's P = 0.887), or extrahepatic CCA (Begg's P = 0.584, Egger's P = 0.564).

Notes:
- evidence level 1: SR and MA
- significant heterogeneity among studies

Jing, W. et al. Diabetes mellitus and increased risk of cholangiocarcinoma: a meta-analysis. Eur J Cancer Prev. 21. 24-31. 2012

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 2 **Study type:** systematic review and meta analysis **Databases:** Medline and Embase **Search period:** Medline (from 1 January 1966) and Embase (from 1 January 1974), through 30 November 2010 **Inclusion Criteria:** (i) case–control or cohort design; (ii) diabetes as one of the exposure of interests; (iii) ICC,ECC, or CC as one of the outcome of interests; and (iv) reported relative risk (RR) in cohort studies (rate ratio) or in case–control studies [odds ratio, (OR)] with their 95% confidence intervals (CIs), or sufficient information provided to calculate them **Exclusion Criteria:** We did not consider studies in which the exposure of interest was type 1 diabetes, which was defined as early-onset (age≤30 years) of diabetes. If data were duplicated in more than one study, the estimate effects controlled for the most appropriate confounders were included. This resulted in the exclusion of three articles from our study (Adami et al., 1991; Hou et al., 2006; Hsing et al., 2008). Articles or reports from non peer-reviewed sources were also not considered for this analysis.	**Population:** individuals with or without diabetes **Intervention:** none **Comparison:** none	**Primary:** risk ratios for cholangiocarcinoma (including ICC and ECC) **Secondary:** none **Results:** Diabetes mellitus and risk of cholangiocarcinoma - 4 case–control studies and 1 cohort study reported results on DM and risk of CC -summary RRs and corresponding 95% CIs were 1.60 (1.38–1.87) in a random-effects model for those with diabetes compared with those without diabetes. Diabetes mellitus and risk of extrahepatic cholangiocarcinoma - 9 studies (4 case–control and 5 cohort studies) presented results on diabetes and risk of ECC - summary RRs and corresponding 95% CIs were 1.63 (1.29–2.05) in a random-effects model for those with diabetes compared with those without diabetes - A positive association between DM and ECC risk was found in studies conducted in non-Asian regions (the USA and Europe) (summary RRs, 1.64; 95% CI, 1.31–2.06) and a positive, but non-significant association was found in Asia (summary RR, 1.32; 95% CI, 0.58–2.99). Diabetes mellitus and risk of intrahepatic cholangiocarcinoma - 9 studies (4 case–control and 5 cohort studies)with results on diabetes and risk of ECC - summary RRs and corresponding 95% CIs were 1.97 (1.57–2.46) **Author's Conclusion:** In total, the results from this meta-analysis suggest an association between diabetes and increased risks of CC (including ICC and ECC). Nevertheless, it cannot be ruled out that the positive association may be due to bias or confounding among these studies. More studies, both epidemiological and	case-control studies Yamamoto, 2004, Cancer Sci Shaib, 2007, Am J Gastroenterol Shaib, 2005, Gastroenterology Lee, 2008, Am J Gastroenterol Zhou, 2008, World J Gastroenterol: WJG Welzel, 2007, Clin Gastroenterol Hepatol Tao, 2010, Liver Int Welzel, 2007, Int J Cancer J Int du Cancer, Welzel, 2006, J Natl Cancer Inst Shebl, 2010, Br J Cancer Grainge, 2009, Br J Cancer cohort studies Adami, 1996, J Natl Cancer Inst Khan, 2006, Asian Pac J Cancer Prev El-Serag, 2009, Hepatology Jamal, 2009, World J Gastroenterol Hemminki, 2010, Oncologist

		mechanistic, are needed to further clarify this association in the future.	

Methodical Notes

Funding Sources: no statement

COI: There are no conflicts of interest.

Study Quality: no quality assessment

Heterogeneity: - no significant heterogeneity among studies (P= 0.992;I2= 0%) included in CC-analysis
- significant heterogeneity among studies (P= 0.005,I2= 63.8%) included in ECC-analysis
- significant heterogeneity among studies (P=0.025,I2= 54.3%) included in ICC-analysis

Publication Bias: The funnel plot revealed no evidence for publication bias concerning diabetes and the risk of ICC and ECC. P values for Begg's adjusted rank correlation test and Egger's regression asymmetry test were 0.529 and 0376, respectively, both suggesting that publication bias probably has little effect on summary estimates.

Notes:
- evidence level 2: systematic review and meta analysis, downgraded due to missing quality assessment
- uncertainty if data from all listed studies are included in meta analysis (Welzel, 2006, J Natl Cancer Inst might not be included)

Palmer, W. C. et al. Are common factors involved in the pathogenesis of primary liver cancers? A meta-analysis of risk factors for intrahepatic cholangiocarcinoma. J Hepatol. 57. 69-76. 2012

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 **Study type:** systematic review and meta analysis **Databases:** PubMed and Google Scholar **Search period:** - restricted to studies performed after 1990 - The most recent search was performed on August 12, 2011 **Inclusion Criteria:** a) case–control study design; (b) reported outcomes specifically for cases of IH-CCA; (c) examined individual risk factors using defined criteria; (d) provided enough information to calculate the odds ratio. **Exclusion Criteria:** Studies where the Materials and methods were inadequately described, raw data was	**Population:** individuals with IH-CCA (cases) or without IH-CCA (controls) **Intervention:** none **Comparison:** none	**Primary:** odds ratio for risk factors for intrahepatic cholangiocarcinoma **Secondary:** none **Results:** a total of 334 citations were identified, of which 11 studies qualified for inclusion. Cirrhosis - 7 case-control studies with a total study population of 399,608 patients with or without IH-CCA - Cirrhosis was associated with an overall OR of 22.92 (95%CI=18.24–28.79) for IH-CCA Hepatitis B - 8 case-control studies with a total study population of 294,828 patients with or without IH-CCA - presence of hepatitis B virus was associated with a combined OR of 5.54, with 95% confidence intervals of 3.19–9.63 for IH-CCA.	Yamamoto, 2004, Cancer Sci Shaib, 2007, Am J Gastroenterol Shaib, 2005, Gastroenterology Welzel, 2007, Clin Gastroenterol Hepatol Donato, 2001, Cancer Causes & Control: CCC Lee, 2008, Am J Gastroenterol Zhou, 2008, World J Gastroenterol: WJG Welzel, 2011, Hepatology Zhou, 2010, Eur J Cancer Tao, 2010, Liver Int Welzel, 2007, Int J Cancer J Int du Cancer

unavailable, or where cases did not specifically include intrahepatic cholangiocarcinoma (IH-CCA) were excluded		- A separate analysis did not reveal any significant difference between regions of high prevalence (Eastern nations such as Japan, Korea, and China) and low-to-intermediate prevalence (Western nations such as USA and Italy) Hepatitis C - 8 case-control studies with a total study population of 396,754 patients with or without IH-CCA - presence of hepatitis C virus was associated with an overallOR of 4.84, with a 95% confidence interval of 2.41–9.71 - - A separate analysis revealed a higher OR for regions with low-to-intermediate prevalence (Western nations), but nor for regions of high prevalence (Eastern nations) obesity - 3 case-control studies with a total study population of 304,134 patients with or without IH-CCA - obesity was associated with an overall OR of 1.56 (95%CI =1.26-1.94) for IH-CCA Diabetes mellitus type II - 9 case-control studies with a total study population of 400,167 patients with or without IH-CCA - diabetes was associated with an overall OR of 1.89 with 95% confidence intervals of 1.74–2.07 for IH-CCA. smoking - 8 case-control studies with a total study population of 396,347 patients with or without IH-CCA - An overall OR of 1.31 with 95% confidence intervals of 0.95–1.82 was estimated. alcohol - 10 case-control studies with a total study population of 398,048 patients with or without IH-CCA - alcohol use was associated with an overall OR of 2.81 (95% CI = 1.52–5.21) for IH-CCA **Author's Conclusion:** Cirrhosis, chronic hepatitis B and C, alcohol use, diabetes, and obesity are major risk factors for intrahepatic cholangiocarcinoma. These data suggest a common pathogenesis of primary intrahepatic epithelial cancers.	

Methodical Notes

Funding Sources: Supported in part by NIH grant DK 069370 (TP).

COI: The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

Study Quality: The quality of individual studies was evaluated based on reported study methodology, analyses, and identification of cases and controls. The criteria reviewed included (a) description of the subject selection for both cases and controls, to ensure that there were no obvious biases; (b) methods used to determine presence or absence of risk factor, and (c) approach for analysis of results and their interpretation. Studies were selected for inclusion in our meta-analysis in an unblinded standardized manner by one of the authors. None of the identified studies were excluded from the analysis.

Heterogeneity: A meta-analysis was performed using a random effects model using the Der Simo-nian and Laird method where there was significant heterogeneity (Q: $p<0.01$ or $I^2>60\%$), or using a fixed effect model and the Mantel–Haenszel weighting algorithm where there was no significant heterogeneity.
cirrhosis
- moderate degree of heterogeneity ($I^2= 62.4\%$)
HBV
- high degree of heterogeneity ($I^2= 86.3\%$; Q: 51.2, $p<0.0001$)
HCV
- high degree of heterogeneity ($I^2= 83.6\%$; Q: 42.7, $p<0.0001$)
smoking
- high degree of heterogeneity ($I^2= 83.1\%$, Q: 41.4, $p<0.0001$)
alcohol
- high degree of heterogeneity ($I^2= 90\%$; Q: 90.3, $p<0.0001$)
diabetes
- moderate degree of heterogeneity ($I^2= 57.8\%$; Q: 18.9, $p=0.015$)
obesity
- no degree of heterogeneity ($I^2= 0.0\%$; Q: 0.6, $p=0.754$)

Publication Bias: - Funnel plots did not identify any possible bias in the studies
- sensitivity analysis revealed no significant difference observed in the overall OR for cirrhosis, chronic HBV, HCV, alcohol use, tobacco use or diabetes
- A sensitivity analysis was not performed for studies evaluating obesity because of the small number of studies.

Notes:
- evidence level 1: SR and MA
- heterogeneity high for most risk factors

Wongjarupong, N. et al. Non-alcoholic fatty liver disease as a risk factor for cholangiocarcinoma: a systematic review and meta-analysis. BMC Gastroenterol. 17. 149. 2017

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 **Study type:** systematic review and meta analysis **Databases:** Ovid MEDLINE, Epub Ahead of Print, Ovid Medline In-Process & Other Non-	**Population:** patients with NASH or NAFLD **Intervention:** none	**Primary:** Pooled OR along with 95% confidence interval (CI) for CCA, iCCA, and eCCA **Secondary:** none **Results:** - 8 studies met the criteria: 7 case-control studies and 1 cohort study.	Welzel et al, 2007, Clin Gastroenterol Hepatol Zhou et al. 2009, Zhonghua Gan ZangBing Za

Indexed Citations, Ovid MED-LINE, Ovid Cochrane Central Register of Controlled Trials, Ovid EMBASE and Scopus **Search period:** inception of the databases through April 5, 2017 **Inclusion Criteria:** (i) case-control, cohort or trial study, (ii) NAFLD or NASH, defined by either histopathological examination, imaging study or International Classification of Diseases, Ninth Revision (ICD-9) or ICD-10 codes, as one of the exposure of interests, (iii) CCA either iCCA, eCCA, or both as outcome of interest, (iv) study that provided adequate information for calculation of odds ratio (OR) or relative risk for case-control study and cohort study, respectively. **Exclusion Criteria:** Studies of patient cohorts with recurrent CCA or combined hepatocellular-cholangiocarcinoma were excluded.	**Comparison:** none	7 case-control studies were included in this meta-analysis. The single cohort study was analyzed separately because this study provided limited information - There was a total of 9102 CCA patients (5067 iCCA and 4035 eCCA) and 129,111 controls in 7 case-control studies NAFLD and risk of CCA - pooled OR of NAFLD was 1.95 (95% CI: 1.36–2.79; I^2=76%, P<0.01) for CCA risk - The pooled ORs for CCA were 1.83 (95% CI: 1.05–3.18,I^2=65%;P= 0.06), and 2.13 (95%CI: 1.47–3.10,I^2=37%;P= 0.19) for studies conducted in Western and Asian countries, respectively - good quality studies had pooled OR of 1.33 (95% CI: 1.07–1.65,I^2=0%;P= 0.39) and the fair quality studies had pooled OR of 2.48 (95% CI: 2.13–2.90,I^2=0%;P= 0.79) - The pooled adjusted OR for CCA was 1.97 (95% CI: 1.41–2.75,I^2= 71%;P< 0.001) NAFLD and risk of iCCA and eCCA subtype - 6 studies presenting results of NAFLD and iCCA risk - pooled OR of NAFLD were 2.22 (95%CI: 1.52–3.24,I^2=67%;P= 0.01) for iCCA risk - 4 studies presenting results of NAFLD and risk of eCCA - significant association between NAFLD and eCCA was detected, with pooled OR of 1.55 (95% CI: 1.03–2.33,I^2= 69%;P= 0.02) based on only one study were NAFLD was significantly associated with eCCA - The pooled adjusted ORs for iCCA and eCCA were 1.98 (95%CI: 1.26–2.69,I^2= 47%;P= 0.11) and 2.05 (95%CI: 1.59–2.64,I^2= 0%;P= 0.90) **Author's Conclusion:** This meta-analysis suggests that NAFLD may potentially increase the risk of CCA development. The magnitude of NAFLD on CCA risk is greater for iCCA than eCCA sub-type, suggestive of a common pathogenesis of iCCA and hepatocellular carcinoma. Further studies to elucidate both the strength of the association between NAFLD and CCA, as well as the mechanisms that underlie this relationship are warranted.	Zhi Chang et al. 2013, PloS one Lee et al. 2015, Liver Int Kinoshita et al. 2016, J Surg Oncol Choi et al. 2016, Hepatology Stepien et al. 2016, Cancer Epidemiol

Methodical Notes
Funding Sources: This meta-analysis received funding from the Grant for International Research Integration: Chula Research Scholar, Ratchadaphiseksomphot Endowment Fund. The funder has no role in the project design, data analysis, or paper publication. **COI:** The authors declare that they have no competing interests **Study Quality:** - The quality of studies was evaluated using Newcastle-Ottawa scale (NOS), with a maximum of 9 points. The study quality was classified as poor (score 0–3), fair (score 4–6) or good (score 7–9) - of the 7 studies included in MA, 4 exhibited "good" quality, 3 "fair" quality **Heterogeneity:** - Heterogeneity among studies was assessed using both the I^2 statistics and P value. An I^2 value of >50% indicates substantial heterogeneity. - see results section for I^2 values **Publication Bias:** No publication bias was detected by the Egger's regression asymmetry test, with P= 0.82 and 0.86 for unadjusted and adjusted OR of NAFLD, respectively. **Notes:** - evidence level 1: SR and MA - significant heterogeneity among studies

NEWCASTLE - OTTAWA Checklist: Cohort: *2 Bewertung(en)*

Atchison, E. A. et al. Risk of cancer in a large cohort of U.S. veterans with diabetes. Int J Cancer. 128. 635-43. 2011

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 3 **Study type:** retrospective cohort study	**Funding sources:** This research was supported by the Intramural Research Program of theNational Cancer Institute, NIH, DHHS. **Conflict of Interests:** no statement **Randomization:** none **Blinding:** none **Dropout rates:** none	**Total no. patients:** overall 4,501,578 black and white male U.S. veterans **Recruiting Phase:** July 1, 1969 and September 30, 1996 **Inclusion criteria:** black and white male veterans between the ages of 18 and 100 years, hospitalized at least once during the study period. **Exclusion criteria:** Other ethnic/racial groups and females were not included in the study due to small numbers.	**Interventions:** men with diabetes **Comparison:** men without diabetes
Notes:	evidence level 3: cohort study **Author's conclusion:** In summary, this study suggests that differences in cancerrisks exist among diabetic and nondiabetic men. In particu-lar, diabetic men		

	may be at significantly increased risk of cancers of the liver, pancreas, biliary tract, and colorectum.	
Outcome Measures/results	**Primary** relative risks (RR) and 95% confidence intervals (95%CI) for cancer (Adjusted for age, time, latency, race, number of visits, alcohol–related conditions, obesity and COPD) **Secondary**	**Results:** basics - Of the 4,501,578 men in the study cohort, 3,669,244 (81.5%) were white and 832,334 (18.5%) were black - diabetes was recorded for 594,815 (13.2%)of the total cohort and was more common among black (14.8%) than among white (12.9%) men. - The median follow-up time was 10.5 years for men with diabetes and 11.9 years for men without diabetes risk of cancer - Risk of biliary tract (RR_{adj}=1.41, 95%CI=1.22–1.62) was significantly elevated among men with diabetes. - Only white men had significantly increased risk of biliary tract carcinoma (RR_{adj}=1.39, 95%CI=1.18–1.63) risk of other cancer - Overall, men with diabetes had a significantly lower risk of developing total cancer than did men without diabetes (RR_{adj}=0.93, 95%CI=0.93–0.94) - Cancers that were significantly less likely to occur among men with diabetes were cancers of the buccal cavity, esophagus, larynx, lung, prostate and brain. - Cancers that were significantly more likely to occur among men with diabetes were cancers of the colon, rectum, liver, leukemia, melanoma, pancreas and kidney.

de Valle, M. B. et al. Mortality and cancer risk related to primary sclerosing cholangitis in a Swedish population-based cohort. Liver Int. 32. 441-8. 2012

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 4 **Study type:** retrospective prognostic study	**Funding sources:** This study was supported by grants from the Swedish federal government under the agreement concerning research and education of doctors in Västra Götaland, Sweden. **Conflict of Interests:** no statement **Randomization:** none **Blinding:** none	**Total no. patients:** 199 patients with PSC **Recruiting Phase:** 1992 to 2005 **Inclusion criteria:** - patients with primary sclerosing cholangitis - aged ≥18 years - from inpatient and outpatient registers at all hospitals in the region Västra Götaland, Sweden	**Interventions:** review of registry data regarding cases with PSC **Comparison:** For background population mortality and cancer incidence estimates, data from the Swedish population were retrieved from http://www.socialstyrelsen.se, Swedish National board of health and welfare (cancer incidence year from 1992 to 2007) and http://www.scb.se, Statistics Sweden (mortality rates each year from 1992 to 2008).

	Dropout rates: At follow up in 2008, information was available for 194 patients; five had moved outside the region and were lost to follow up	**Exclusion criteria:** - No patients are referred out of the region - no diagnostic searches were performed at paediatric clinics.	
Notes:	evidence level 4: retrospective prognostic follow-up study **Author's conclusion:** Primary sclerosing cholangitis was associated with a four-fold increase in mortality in this population-based study. In accordance with previous studies, the risk of hepatobiliary cancer was dramatically increased. However, the increased risk of colorectal cancer reported in previous studies could not be confirmed.		
Outcome Measures/results	**Primary** Standardized mortality ratio (SMR) and standardized incidence ratio (SIR) **Secondary** risk factors for liver related death or liver transplantation risk factors for cancer	**Results:** <u>Standardized mortality ratio and risk factors for liver related death or liver transplantation</u> - 4-fold increased risk of mortality (SMR 4.20; 95% CI 3.01–5.69) compared with the general population in the Västra Götaland region - multivariate analysis of risk factors: Age, female gender, cholangitis, jaundice and bilirubin in the highest quartile were statistically and significantly associated with the risk of liver-related death or OLT in the adjusted model - The strongest association was found for bilirubin (RR 3.95; 95% CI 1.46–10.75), highest vs lowest quartile) and cholangitis (RR 2.56; 95% CI 1.20–5.64), for presence vs absence of cholangitis) <u>Standardized incidence ratio and risk factors for cancer</u> - Overall, 29 incident malignancies were identified in the PSC cohort - 4-fold increased risk of any malignancy compared with the general population in Västra Götaland region (SIR 4.17; 95%CI 2.79–5.99) - the risk of cancer regardless of site was not significantly increased compared with the general population when hepatobiliary cancers were excluded (SIR for all sites excluding he-patobiliary cancer 1.12; 95% CI 0.48–2.21) - SIR for hepatobiliary cancer was 177 (95% CI 110–271) and for cholangiocarcinoma 868 (95% CI 505–1390) - SIR for colorectal cancer was not statistically and significantly increased in PSC subjects compared with the general population - age was the only variable associated with hepatobiliary cancer risk using univariate and multivariate analysis (RR 1.40; 95% CI 1.01–1.95, per decade)	

Schlüsselfrage:

CCA 01 (2) Vorerkrankungen (GBC)
Welche Vorerkrankungen erhöhen das Risiko für die Entstehung von biliären Karzinomen (Gallenblasenkarzinom oder CCA)?

Inhalt: *5 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Nagaraja, V. 2014	1	Systematic Review with Meta-Analysis
Park, J. K. 2008	4	prognostic study, observational
Park, J. Y. 2009	4	observational follow-up study
Sarici, I. S. 2017	4	prognostic study, observational, retrospective
Shrikhande, S. V. 2010	2	systematic review

OXFORD (2011) Appraisal Sheet: Systematic Reviews: *2 Bewertung(en)*

Nagaraja, V. et al. Systematic review with meta-analysis: the relationship between chronic Salmonella typhi carrier status and gall-bladder cancer. Aliment Pharmacol Ther. 39. 745-50. 2014

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 **Study type:** Systematic Review with Meta-Analysis **Databases:** - MEDLINE (from 1950), PubMed (from 1946), EMBASE (from 1949), Current Contents Connect (from 1998), Cochrane library, Google scholar, Science Direct and Web of Science to November 2013 - The reference lists of relevant articles were also searched	**Population:** patients with gall-bladder cancer **Intervention:** none **Comparison:** none	**Primary:** level of risk (odds ratio) for developing gall-bladder cancer in patients with a chronic typhoid infection **Secondary:** none **Results:** - OR for cohort studies was 19.48 (95% CI: 0.27–1418.18, P value: 0.77) - OR for case-control studies was 3.08 (95%CI: 1.67–5.71,P value<0.01). - overall OR was 4.28 (95% CI: 1.84–9.96,Pvalue<0.01) subgroup analysis Chronic S. typhi carrier state was associated with gall-bladder carcinoma based on detection methods of S. typhi antibody levels (OR: 3.52, 95% CI: 2.48–5.00,P value<0.01) and even more so on	Caygill et al. 1994, *Lancet* Nath et al. 1997, *Eur J Cancer Prev* Shukla et al. 2000, *Dig Dis Sci* Csendes et al. 1994, *Eur J Surg* Hazrah et al. 2004, *HPB* Dutta et al. 2000, *Am J Gastroenterol* Serra et al. 2002, *Int J Cancer* Nath et al. 2008, *J Infect Dev Ctries* Sharma et al. 2007, *Hepatogastroenterology* Welton et al. 1979, *Lancet* Tewari et al. 2010, *Hepatobiliary Pancreat*

for appropriate studies. - A search for unpublished literature was not performed. **Search period:** 1946- November 2013 (see also 3.1 Databases) **Inclusion Criteria:** (i) Studies identifying the population of patients with gall-bladder cancer (ii) Cohort or case–control studies explored the relationship between gall-bladder cancer and Salmonella. **Exclusion Criteria:** no information		culture (OR: 4.14,95% CI: 2.41–7.12,P value<0.01). On the other hand, a past medical history of typhoid was not associated with carcinoma of the gall-bladder (OR: 3.33, 95% CI: 0.77–14.38,P value: 0.11). **Author's Conclusion:** Chronic S. typhi carrier state is an important risk factor among patients with carcinoma of the gall-bladder. Given the high risk associated with this carrier state, management options should include either elective cholecystectomy or careful monitoring using ultrasound.	*Dis Int* Safaeian et al. 2011, *Infect Agent Cancer* Yagyu et al. 2004, *Cancer Sci* Singh et al. 1996, *Eur J Cancer Prev* Pandey et al. 2003, *Eur J Cancer Prev* Strom et al. 1995, *Cancer* Roa et al. 1999, *Rev Med Chil*

Methodical Notes

Funding Sources: no statement

COI: Declaration of personal and funding interests: None

Study Quality: Quality assessment of studies was performed by two reviewers according the Newcastle-Ottawa Scale (NOS) was used as an assessment tool for selection, comparability and outcome assessment. Study quality was rated on a scale from 1 (very poor) to 9 (high). Disagreements were resolved by consensus.
Of 17 included studies, 2 were rated with 5 points, 2 with 6 points, 12 with 7 points and 1 with 8 points.

Heterogeneity: The heterogeneity was high for overall studies: I^2 =89.14 (p=0.001); cohort studies: I^2 =96.26 (p=0.001) and case-control studies: I^2 =73.57 (p=0.001)
The reason for significant heterogeneity may be attributed to different population groups.

Publication Bias: No publication bias was detected using the Egger's regression model.

Notes:
- evidence level 1: SR with MA
- data extraction (and subsequent MA) may have errors! (Safaeian et al: OR in this MA = 11.9; OR in original publication 1.9)

Shrikhande, S. V. et al. Cholelithiasis in gallbladder cancer: coincidence, cofactor, or cause!. Eur J Surg Oncol. 36. 514-9. 2010

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References

Evidence level: 2 **Study type:** systematic review **Databases:** Medline, Embase and the Cochrane Central Register of Controlled Trials **Search period:** 1891-2009 **Inclusion Criteria:** none given **Exclusion Criteria:** Confounding factors such as the presence of Mirizzi's syndrome and its association with gallstones and gallbladder cancer have not been included in this review	**Population:** no description of population **Intervention:** none **Comparison:** none	**Primary:** - epidemiological association between gallstones and gallbladder cancer - Duration of gallstones - Number, weight and volume of gallstones - Infection - Type of stone **Secondary:** none **Results:** Gallstones and gallbladder cancer - the epidemiology -There is substantial epidemiological data to support the role of gallstones in gallbladder cancer Duration of gallstones - While gallstones present for more than 20 years have been shown to be associated with an increased risk for gallbladder cancer, other authors have found that the duration of presence of the stone did not alter the risk of gallbladder cancer already associated with gallstones. Number, weight and volume of gallstones - More stones, as well as, larger and heavier stones have been shown to be associated with an increased risk for cancer causation. - gallstone >3 cm in size as a causative factor for gallbladder cancer Infection - It is believed that the presence of infection in the bile is a risk for stone formation and hence the attendant risk of cancer. Type of stone -differences in cholesterol, calcium and magnesium composition in gallstones in patients with gallbladder cancer and chronic cholecystitis **Author's Conclusion:** Gallstones have traditionally been regarded as an aetiological factor for gallbladder cancer. Despite some epidemiological data to support this, experimental models have failed to replicate the carcinogenetic process. It is thus difficult at the present time to firmly conclude whether gallstones are the cause or mere innocent by-standers in the causation of gallbladder cancer. They may however, be regarded as cofactors. In light of the high incidence of gallstones in regions reporting gallbladder cancer, the role of prophylactic cholecystectomy needs to be further assessed to define specific circumstances in which such a procedure could be justifiable.	- Of the remaining 44 articles included in the study, 26 articles which provided clear epidemiological evidence of the relationship of gallstones to gallbladder cancer were then specifically analysed. - Citations see article
Methodical Notes			

Funding Sources: no statement

COI: We declare no conflicts of interest.

Study Quality: not analysed

Heterogeneity: not analysed

Publication Bias: not analysed

Notes:
- downgraded due to missing quality assessment of included studies
- poor description of search strategy
- no listing of the 44 included studies

OXFORD (2011) Appraisal Sheet: Prognostic Studies: *2 Bewertung(en)*

Park, J. K. et al. Management strategies for gallbladder polyps: is it possible to predict malignant gallbladder polyps?. Gut Liver. 2. 88-94. 2008

Population	Intervention	Outcomes/Results
Evidence level: 4 **Study type:** prognostic study, observational **Number of Patient:** 1. prevalence analysis: data of 24,617 healthy subjects were collected. 2. risk factor analysis: 689 eligible patients were enrolled for characteristics of GB polyp and cholecystectomy **Recruitung Phase:** 1. prevalence analysis: To investigate epidemiologic information of GB polyps without any selection bias, we used data from healthy subjects who attended SNUH Gangnam Center for a routine health examination from October 1st, 2003 to July 31st, 2005. 2. risk factor analysis: For the study patients, 689 newly diagnosed GB polyp patients at SNUH from Janurary 1st 1988 to April 30th 2006 were enrolled from electronic medical records. **Inclusion Criteria:** 1. prevalence analysis: all healthy subjects who attended SNUH Gangnam Center for a routine health examination 2. risk factor analysis: patients, newly diagnosed with GB polyp patients at SNUH and for whom electronic medical data for age, sex, presence of symptoms, initial size, mass growth, mass multiplicity, accompanied stones, and shape are available	**Intervention:** none **Comparison:** none	**Primary:** - prevalence of GB polyps in healthy subjects - risk factors of malignancy in the 180 cholecystectomy cases **Secondary:** Characteristics of GB polyp and cholecystectomy **Results:** 1. Prevalence of GB polyps in healthy subjects - A total of 24,617 healthy subjects underwent abdominal ultrasonography during the study period - 954 of 13,328 (7.1%) men and 542 of 11,289 (4.8%) women had GB polyps, - overall prevalence of 6.1% (1,496/24,617) - a particularly high prevalence was found in those aged 40 to 70 years. 2.1 Characteristics of GB polyp and cholecystectomy - 689 eligible patients (M: 409, F: 280) of median age 47 years were followed for a median 60 months. - 405 (60%) patients had a single polyp and 57 (8%) patients had accompanying GB stones. - Mean diameter of GB polyps at initial diagnosis was 7 mm (range 2 to 30 mm). 109 (20%) patients with a GB polyp of ＞10 mm and 516 (75%) patients never had size change of polyps. - 180 patients underwent surgical

Exclusion Criteria: 2. risk factor analysis: Patients were excluded if they had diseases capable of affecting survival, i.e., congestive heart failure, chronic renal failure, coronary heart disease, liver cirrhosis, malignancies and others.		resection 2.2 risk factors of malignancy in the 180 cholecystectomy cases - age (≥57 year-old), presence of symptoms, size (≥10 mm) and shape (sessile) were statistically significant risk factors by univariate analysis - multivariate analysis identified only age (≥57 year-old) and size (≥10 mm) as independent predictors of malignancy. **Author's Conclusion:** The present study shows that GB polyps ≥10mm in size in patients aged ≥57 years are the independent factors predicting malignancy of the GB.

Methodical Notes

Funding Sources: no statement

COI: no statement

Randomization: none

Blinding: none

Dropout Rate/ITT-Analysis: none

Notes: evidence level 4: retrospective observational study

Sarici, I. S. et al. Gallbladder polypoid lesions >15mm as indicators of T1b gallbladder cancer risk. Arab J Gastroenterol. 18. 156-158. 2017

Population	Intervention	Outcomes/Results
Evidence level: 4 **Study type:** prognostic study, observational, retrospective **Number of Patient:** 69 females and 40 males were included in the study. **Recruitung Phase:** January 2005 - January 2015 **Inclusion Criteria:** - patients who were confirmed to have GBPs after cholecystectomy at the Department of General Surgery, Cukurova University Medical Faculty **Exclusion Criteria:** Those with definite evidence for malignancy such as adjacent	**Intervention:** none **Comparison:** none	**Primary:** - The 10-mm cut-off sensitivity and specificity for predicting malignant polyps - cut-off diameter of T1b tumours **Secondary:** risk factors for gallbladder cancer **Results:** The 10-mm cut-off sensitivity and specificity for predicting malignant polyps - 10-mm cut-off sensitivity and specificity for predicting malignant polyps was 93.6% and 85.2%, respectively cut-off diameter of T1b tumours - Of the 15 patients with malignant pathological results, 12 had T1b tumours with polyps sizes >15 mm. - 15 mm might be the best cut-off point for predicting T1b tumours in the study risk factors for gallbladder cancer - The diameter of the polyp was a prominent risk factor for malignant GBPs ($p < 0.001$, OR = 1.724; 95% CI: 1.254–1.881). - Old age (>50 years) was associated with a higher risk of malignant GBPs ($p < 0.001$, OR = 1.241, 95% CI: 1.108–1.345). - the number of polyps and the levels of ALT, ALP, and total bilirubin did not increase the risk of malignancy

organ invasion and metastasis on preoperative imaging studies and those with lack of preoperative imaging results were excluded.		**Author's Conclusion:** In conclusion, gallbladder cancer may occur in polyps of <10 mm in size. Doppler or contrast-enhanced ultrasound should be used in the follow-up of these patients. Larger size and older age were predictors of neoplastic GBPs. We suggest 15 mm as the optimal cut-off point to predict T1b cancer. The lack of a higher number of patients in the study and its retrospective design are the limitations of our study. Furthermore, a large multicenter study will be required to create safe and definite criteria to predict malignancy and invasiveness of PLGs.

Methodical Notes

Funding Sources: no statement

COI: The authors declare that there is no conflict of interest in this article.

Randomization: none

Blinding: none

Dropout Rate/ITT-Analysis: none

Notes: evidence level 4: retrospective observational study

NEWCASTLE - OTTAWA Checklist: Cohort: *1 Bewertung(en)*

Park, J. Y. et al. Long-term follow up of gallbladder polyps. J Gastroenterol Hepatol. 24. 219-22. 2009

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 4 **Study type:** observational follow-up study	**Funding sources:** no statement **Conflict of Interests:** no statement **Randomization:** none **Blinding:** none **Dropout rates:** none	**Total no. patients:** In total, 1558 patients diagnosed with GBP were followed. **Recruiting Phase:** January 1995 and May 2005 **Inclusion criteria:** patients diagnosted with GBP at the Institute of Gastroenterology, Severance Hospital Yonsei University, Seoul, Korea between January 1995 and May 2005 **Exclusion criteria:** no specifications	**Interventions:** follow up with ultrasonography (USG) until the time of cholecystectomy, last follow-up date, or March 2007 **Comparison:** none
Notes:	evidence level 4: retrospective observational study **Author's conclusion:** n summary, we conclude that the risk for neoplastic polyps is high for large polyps and GBP with gallbladder stones or sludge. For high-risk GBP, careful evaluation or cholecystectomy is recommended. Even small polyps have		

	malignant risk, and the 10-mm criterion cannot rule out neoplastic polyps completely. The follow-up period should be long to avoid missing neoplastic polyps. Careful selection of patients with high-risk GBP and the follow up of GBP will help to detect and treat early GBC.	
Outcome Measures/results	**Primary** cumulative detection rate of neoplastic and malignant polyps **Secondary** - risk factors of neoplastic polyps - sensitivity and specificity of the 10-mm size criterion to predict neoplastic polyps	**Results:** Malignant risk of GBP - 33 cases (2.1%) were diagnosed with neoplastic polyps. 19 cases were adenoma, 2 were low-grade dysplasia, 4 were high-grade dysplasia, 4 were early GBC (stage T1), and 4 were advanced GBC (>stage T1 or N1). - cumulative detection rate of neoplastic polyps were 1.7% at 1 year, 2.8% at 5 years, and 4% at 8 years after diagnosis. - cumulative detection rate of malignant polyps were 0.2% at 1 year and 1% at 5 years after diagnosis. Risk factors for neoplastic GBP - The size of GBP was a significant risk factor for neoplastic GBP.(P<0.001, experiment B=1.207; 95% confidence interval [CI]:1.163~1.254). - GBP with gallstones or sludge also had a higher risk of neoplastic polyps (P=0.001, experiment B=4.268; 95% CI:1.849~9.854). Optimal size to predict neoplastic GBP - Polyps ≥10 mm had a 24.2 times greater risk of malignancy than polyps <10 mm. - when the size cut-off point was set to 10 mm, sensitivity and specificity of predicting neoplastic polyps were 54.5% and 94.1%, but when it was 8 mm, they were 63.6% and 85.9%. The number of cases with neoplastic polyps not predicted when the size criterion was set to 8 and 10 mm were 12 (36.4%) and 15 (45.5%) of 33.

Schlüsselfrage:

CCA 07 Diagnostik - 1
Welche Untersuchungsmethoden geben Auskunft über die maximale Ausbreitung des Tumors?

Inhalt: *4 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Kalaitzakis, E. 2011	3	retrospective diagnostic study
Navaneethan, U. 2015	1	Systematic Review and Meta Analysis
Osanai, M. 2013	3	prospective multicenter single-arm study (Japan)
Zhang, H. 2015	1	Systematic Review and Meta Analysis

OXFORD (2011) Appraisal Sheet: Systematic Reviews: *2 Bewertung(en)*

Navaneethan, U. et al. Endoscopic ultrasound in the diagnosis of cholangiocarcinoma as the etiology of biliary strictures: a systematic review and meta-analysis. Gastroenterol Rep (Oxf). 3. 209-15. 2015

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 **Study type:** Systematic Review and Meta Analysis **Databases:** - PUBMED and EMBASE database - cross-checking the bibliographies of retrieved full-text papers **Search period:** January 1980 to April 2014 **Inclusion Criteria:** - Studies investigating the use of EUS for detection of CCA or indeterminate biliary strictures were	**Population:** no specification **Intervention:** Endoscopic Ultrasound for detection of CCA or indeterminate biliary strictures **Comparison:** Confirmation of CCA by histopathology at the time of surgery or inoperable at the time of surgery or autopsy was used as the reference standard.	**Primary:** overall diagnostic utility of EUS for biliary strictures **Secondary:** role of EUS-FNA in patients in whom the results of brush cytology are negative **Results:** Six studies were included, covering 196 patients Sensitivity and negative likelihood ratio - The overall pooled sensitivity and negative likelihood ratio (LR-) of EUS-FNA for diagnosis of CCA were 66% [95% CI57–74%] and 0.34 (95% CI 0.26–0.43), respectively - In our subgroup analysis, limited to studies with a proximal biliary location of the stricture, the pooled sensitivity and negative likelihood ratio (LR-) of EUS-FNA for diagnosis of CCA were 81% [95% CI 69–89%] and 0.19 (95%CI 0.11–0.31), respectively - In our subgroup analysis limited to	Fritscher-Ravens et al., 2000, Gastrointest Endosc Fritscher-Ravens et al., 2004, Am J Gastroenterol Eloubeidi et al., 2004, Clin Gastroenterol Hepatol Lee et al., 2004, Am J Gastroenterol Rösch et al., 2004, Gastrointest Endosc Dewitt et al., 2006, Gastrointest

included. - The data needed to be sufficient to calculate the sensitivity and specificity. - Only studies that accepted only a 'positive for malignancy' cytological interpretation as indicative of malignancy were included **Exclusion Criteria:** - studies with patients who were included if only under suspicion for malignancy were excluded - studies with insufficient data - reviews, editorials, correspondence letters that did not report their own data - case reports and studies with fewer than 10 patients.		studies with a mass lesion detected during EUS, the pooled sensitivity and negative likelihood ratio (LR-) of EUS-FNA for diagnosis of CCA were 80% [95% CI 72–87%] and 0.20 (95% CI 0.13–0.28),respectively - For studies with a negative ERCP brush cytology, the pooled sensitivity and negative likelihood ratio (LR-) of EUS-FNA for diagnosis of CCA were 59% [95% CI 44–73%] and 0.41 (95% CI 0.27–0.56), respectively - Only two studies reported the value of EUS in patients without a mass lesion detected during cross-sectional imaging, the pooled sensitivity of EUS-FNA for diagnosis of CCA was 45% **Author's Conclusion:** To conclude, this meta-analysis summarizes available evidence regarding the diagnostic performance of EUS in the detection of CCA. Our study suggests that EUS-FNA contributes to the diagnosis of CCA in patients with negative cytology and in patients in whom cross-sectional imaging does not reveal any mass lesion.	Endosc

Methodical Notes

Funding Sources: The study was supported by a research grant to Udayakumar Navaneethan from the American College of Gastroenterology.

COI: none declared

Study Quality: The methodological quality of the included studies was asassessed by the QUADAS-2 criteria. - In most studies, there was a low risk of bias regarding the selection of patients and we had included only patients who were positive for cancer.
There were no bias issues or concerns regarding validity of the selection of patients.
There was no bias in any of the studies.

Heterogeneity: not addressed

Publication Bias: not addressed

Notes:
evidence level 1: SR and MA
no heterogeneity analysis

Zhang, H. et al. Radiological Imaging for Assessing the Respectability of Hilar Cholangiocarcinoma: A Systematic Review and Meta-Analysis. Biomed Res Int. 2015. 497942. 2015

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 **Study type:** Systematic Review and Meta Analysis **Databases:** MEDLINE, EMBASE, CancerLit and the Cochrane Library **Search period:** January 1980 to March 2015 **Inclusion Criteria:** The following inclusion criteria were applied: (1) articles were published in English; (2) CT, MRI or PET/CT was used to evaluate the resectability of HCC; (3) for per-patient statistics, sufficient data were presented to calculate the true-positive (TP), false-negative (FN), false-positive (FP), and true-negative (TN) values; (4) 10 or more patients were included; (5) when data or subsets of data were presented in more than one article, the article with the most detail or the most recent article was chosen. Authors of abstracts and studies that did not report sufficient data were contacted to request additional information **Exclusion Criteria:** All review articles, letters, comments, and case reports were eliminated.	**Population:** no specification **Intervention:** CT, MRI,or PET/CT was used to evaluate the resectability of hilar cholangiocarcinoma **Comparison:** not mentioned	**Primary:** Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy **Secondary:** **Results:** - a total of 16 studies including 651 patients were eligible for the meta-analysis, of which 11 were CT studies, 5 were MRI studies and 3 were PET/CT studies. sensitivity - pooled sensitivities for CT, MRI and PET/CT were 95% (95% CI: 91–97), 94% (95% CI: 90–97) and 91% (95% CI: 84–96), respectively - no statistically significant difference was found between CT and MRI (**Author's Conclusion:** In summary, CT is the most frequently used imaging modality to assess HCC resectability with a good sensitivity and specificity. MRI was generally comparable with that of CT and can be used as an alternative imaging technique. PET/CT appears to be the best technique in detecting lymph node and distant metastasis in HCC but has no clear role in helping to evaluate issues of local resectability.	Cha et al. 2000, Abdominal Imaging Lee et al. 2006, Radiology Aloia et al. 2007, The American Journal of Surgery Endo et al. 2007, Surgery Unno et al. 2007, Journal of Hepato-Biliary-Pancreatic Surgery Yin et al. 2007, Chinese Medical Journal Masselli et al. 2008, European Radiology Park et al. 2008, The American Journal of Roentgenology Li et al. 2008, Journal of Surgical Oncology Kim et al. 2008, American Journal of Gastroenterology Chen et al. 2009, Hepato-Gastroenterology Yu et al. 2010, Hepatobiliary and Pancreatic Diseases International Ryoo et al. 2010, Investigative Radiology Cannon et al. 2012, HPB Gu et al. 2012, Zhonghua Yi Xue Za Zhi Nagakawa et al 2014, Journal of Hepato-Biliary-Pancreatic Sciences
Methodical Notes			

Funding Sources: This work was supported by Introductory Funding project from Shanghai Science and Technology Bureau (124119a-0600).

COI: The authors declare that they have no conflict of interests.

Study Quality: The quality assessment scores of 16 studies showed high quality ranging from 10 to 12, with a mean study quality score of 11. The imaging findings were probably known during surgery and therefore the reference standard was generally not blinded to the results of the index test (QUADAS item 11). The time period between imaging and the reference standard was mentioned in only 7 studies and was 14 days or less in 6 studies. Inclusion and exclusion criteria were clearly mentioned in all studies.

Heterogeneity: No significant heterogeneity of diagnostic performance was found for the CT and MRI studies

Publication Bias: The results of funnel plots did not suggest a publication bias

Notes:
evidence level 1: SR and MA

OXFORD (2011) Appraisal Sheet: Diagnostic Studies: *2 Bewertung(en)*

Kalaitzakis, E. et al. Endoscopic retrograde cholangiography does not reliably distinguish IgG4-associated cholangitis from primary sclerosing cholangitis or cholangiocarcinoma. Clin Gastroenterol Hepatol. 9. 800-803 e2. 2011

Evidence level/Study Types	Population	Outcomes/Results
Evidence level: 3 **Study type:** retrospective diagnostic study	**Number of patients / samples:** 20 patients with IgG4-associated cholangitis (IAC) 10 patients with primary sclerosing cholangitis (PSC) 10 patients with cholangiocarcinoma representative study collective not assumed. From 104 ERCs, a final set of 48 good quality ERCs were selected. **Reference standard:** Yes, ERCs were histologically and/or clinically confirmed. **Validation:** sensitivity, specificity and kappa statistic for inter- and intra-observer agreement for the diagnosis IAC **Blinding:** Yes. Readers of ERC images were not aware of any clinical data, underlying diagnoses or the relative frequency of each diagnosis within the image set. **Inclusion of clinical information:** no **Dealing with ambiguous clinical findings:** During this retrospective review of images, physicians were asked to provide the most probable diagnoses based on ERC findings.	**Results:** - Sensitivity (95%): 45% (36–54%) - Specificity (95%): 88% (83–93%) - intra-observer agreement for IAC (kappa): 0.74 - inter-observer agreeement for IAC (kappa): 0.18 - no significant differences between centers **Author conclusions:** In conclusion, this multicenter study shows that the performance of ERC alone for the diagnosis of IAC is uniformly poor. Additional diagnostic strategies, including aggressive attempts to achieve a pathological diagnosis, are likely to be vital in distinguishing these diseases and so defining optimal management.

	Up to 3 diagnoses could be listed by percentage confidence. The sum of the confidences had to add up to 100%. To be considered a correct interpretation a given ERC had to be read with at least 75% confidence for that condition.	

Methodical Notes

Funding Sources: Funding sources: None

COI: Conflicts of interest: No conflicts of interest exist for any of the authors

Notes: - evidence level 3: Retrospective study with reference standard and blinding
- study does not fit to PICO question: wrong population

Osanai, M. et al. Peroral video cholangioscopy to evaluate indeterminate bile duct lesions and preoperative mucosal cancerous extension: a prospective multicenter study. Endoscopy. 45. 635-42. 2013

Evidence level/Study Types	Population	Outcomes/Results
Evidence level: 3 **Study type:** prospective multicenter single-arm study (Japan)	**Number of patients / samples:** A total of 87 patients were eligible for the study **Reference standard:** The final diagnoses were made on the basis of surgical findings and pathology results or clinical follow-up of more than 12 months. **Validation:** The diagnostic accuracy, sensitivity, and specificity of endoscopic retrograde cholangiography (ERC)/tissue sampling, with or with-out PVCS, were calculated and compared with those in the final diagnosis. **Blinding:** No statement regarding blinding **Inclusion of clinical information:** - **Dealing with ambiguous clinical findings:** -	**Results:** <u>overall</u> - A total of 87 patients were eligible for the study. 38 had indeterminate biliary disease and 49 suspected bile duct cancers. PVCS observation revealed malignant lesions in 77 patients and benign lesions in 10. Biopsy of the primary lesions was performed in 84 patients. <u>indeterminate biliary disease</u> - In indeterminate biliary disease, PVCS correctly identified 27 of 28 malignant lesions, and 8 of 10 benign lesions (accuracy 92.1%; sensitivity 96.4%; specificity 80.0%) - Endobiliary forceps biopsy via PVCS or the transpapillary route was conducted in 35 of the 38 patients (92.1%). Endobiliary forceps biopsy correctly identified 22 of 27 malignant lesions and 8 of 8 benign lesions (accuracy 85.7%; sensitivity 81.5%; specificity 100%) <u>bile duct cancers</u> - Of the 49 patients with extrahepatic bile duct cancers, mucosal extension of the tumor of ≥20mm was observed in 17 (34.7%), and this was observed more frequently in the localized and papillary gross types. The cholangioscopes were successfully advanced from the papilla to the bile duct in 100% (49/49) of patients, and insertion to the proximal tumor site was achieved in 91.8% (45/49) of patients. - The accuracy rates for the diagnosis of the presence or absence of mucosal cancerous extension were for ERC with PVCS 83.7% (sensitivity 88.2%; specificity 83.9%) and ERC with PVCS+mapping biopsy were 92.9% (sensitivity 93.8%; specificity 92.3%) - The accuracy rate for ERC alone for the diagnosis

		of the presence or absence of mucosal cancerous extension was 73.5% (sensitivity 35.3%; specificity 96.8%) **Author conclusions:** In conclusion, PVCS enables accurate diagnosis by providing excellent resolution in combination with biopsy. Prospective multi-center clinical trials are currently in progress to evaluate the clinical use of PVCS for the diagnosis of biliary tract diseases.

Methodical Notes

Funding Sources: no statement

COI: Drs Osanai and Itoi have given lectures and serve as consultants for Olympus Medical Systems. The other authors have no competing interests

Notes: Evidence level 3: Prospective study without blinding

Schlüsselfrage:

CCA 07 Diagnostik - 2
Mit welchem Verfahren lässt sich die Diagnose eines CCA histologisch sichern

Inhalt: *4 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
De Moura, D. T. H. 2018	1	systematic review and meta analysis
Lee, Y. N. 2019	2	Single-center, prospective, observational study (Korea)
Navaneethan, U. 2015	1	systematic review and meta analysis
Slivka, A. 2015	2	Prospective, multicenter study (USA, Italy, France)

OXFORD (2011) Appraisal Sheet: Systematic Reviews: *2 Bewertung(en)*

De Moura, D. T. H. et al. Endoscopic retrograde cholangiopancreatography versus endoscopic ultrasound for tissue diagnosis of malignant biliary stricture: Systematic review and meta-analysis. Endosc Ultrasound. 7. 10-19. 2018

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 **Study type:** systematic review and meta analysis **Databases:** Medline, EMBASE, The Cochrane, LILACS (via BVS), Scopus and CINAHL (via EBSCO) databases **Search period:** No search period defined. The last search was performed on November 10, 2014.	**Population:** Any patient with suspicion of cholangiocarcinoma **Intervention:** endoscopic retrograde cholangiopancreatography (ERCP) endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) **Comparison:** gold standard: histopathology (surgery or the index test) and follow-up	**Primary:** sensitivity, specificity, pretest probability, positive and negative predictive values, and accuracy of EUS-FNA and ERCP for detection of a malignant lesion **Secondary:** none **Results:** - sensitivity: EUS-FNA 75% (SD=19.87) versus ERCP 49% (SD=2.64) - specificity: EUS-FNA 100% (SD=0) versus ERCP 96.33% (SD=6.35) - positive predictive value: EUS-FNA 100% (SD=0) versus ERCP 98.33% (SD=2.22) - negative predictive value: EUS-FNA 47% (SD=14.73)	DeWitt J 2005, Gastrointest Endosc Eloubeide MA 2004, Clin Gastroenterol Hepatol Fritscher-Ravens A 2004, Am J Gastroenterol Nayar MK 2011, Hepatogastroenterology Novis M 2010, Rev Col Bras Cir Ohshima Y 2011, J Gastroenterol Rösch T 2004, Gastrointest Endosc Weilert 2014, Gastrointest Endosc

Inclusion Criteria: *Types of studies* — Clinical trials and observational studies were searched and targeted for a posterior selection process. *Types of participants* — We chose studies with patients who had indeterminate malignant biliary strictures and with similar population characteristics (age, sex, abnormal liver function tests and evidence of biliary obstruction). *Types of intervention* — We chose trials that used either ERCP or EUS-FNA in diagnostics. There were no restrictions regarding the modality of diagnosis in each. *Types of outcome measures* — The main outcomes were accuracy, sensitivity, specificity, positive predictive value and negative predictive value. **Exclusion Criteria:** no specification		versus ERCP 34% (SD=24.63) - accuracy: EUS-FNA 79% (SD=13.07) versus ERCP 60.66% (SD=8.62) - pretest probability: 76.66% (SD=19.218) **Author's Conclusion:** This study demonstrates that EUS-FNA is better than ERCP for the detection of suspected malignant biliary stricture as it has superior sensitivity, specificity, positive posttest probability and accuracy. A negative test using EUS-FNA or ERCP does not exclude a malignant biliary stricture because both have low negative posttest probabilities.	

Methodical Notes

Funding Sources: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

COI: There are no conflicts of interest

Study Quality: Risk of bias within studies
Using QUADAS-2, we found that most studies did not impose bias

Heterogeneity: not assessed

Publication Bias: Risk of bias across studies
The risks of bias were minimal because the articles followed the same patterns. The greatest bias was related to the lesion size and secondarily to the lesion location. The size of the trials varied, facilitating the chance of suitable material for pathological studies, which could introduce bias.

Notes:
- evidence level 1: systematic review and mata analysis
- no heterogeneity assessed

Navaneethan, U. et al. Single-operator cholangioscopy and targeted biopsies in the diagnosis of indeterminate biliary strictures: a systematic review. Gastrointest Endosc. 82. 608-14.e2. 2015

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 **Study type:** systematic review and meta analysis **Databases:** PubMed and Embase **Search period:** January 1980 to October 2014 **Inclusion Criteria:** Only studies involving both cholangioscopy using SpyGlass and SpyBite biopsies in the identification of biliary strictures with availability of data for the construction of 2x2 contingency tables were included. **Exclusion Criteria:** We removed studies with insufficient data and those with a sample size of<10.	**Population:** patients with biliary strictures **Intervention:** SpyGlass and SpyBite biopsy **Comparison:** surgical pathology or autopsy and long-term clinical follow-up.	**Primary:** estimates of sensitivity, specificity, likelihood ratios and diagnostic odds ratio. **Secondary:** none **Results:** <u>overall</u> - 10 studies (n=456) met the inclusion criteria and were included in the analysis. - sensitivity: 60.1% (95% confidence interval [CI], 54.9%-65.2%) - specificity: 98.0% (95% CI, 96.0%-99.0%) - Diagnostic odds ratio: 66.4 (95% CI, 32.1-137.5). - positive LR: 21.0 (95% CI, 11.0-40.1); negative LR: 0.38 (95% CI, 0.29-0.49) <u>subgroup analyses</u> - 4 studies included patients who had previous negative imaging and brushings and/or intraductal biopsies.The pooled sensitivity and specificity for diagnosis of malignant biliary strictures was 74.7% (95% CI, 63.3%-84.0%) and 93.3% (95% CI, 85.1%-97.8%), respectively. The pooled DOR was 46.0 (95% CI,15.4-138.1). - Only 1 study directly compared the yield of SpyBite biopsies with standard brushings and biopsies. SpyBite biopsies had a sensitivity of 76.5% compared with brushings (5.8%) and biopsies (29.4%). - Six studies specifically reported the role of cholangioscopy with targeted biopsies in the diagnosis of CCA. The pooled sensitivity and specificity to detect CCA was 66.2% (95% CI,	Chen 2007, Gastrointest Endosc Chen 2011, Gastrointest Endosc Draganov 2012, Gastrointest Endosc Hartman 2012, Clin Gastroenterol Hepatol Kalaitzakis 2012, Eur J Gastroenterol Hepatol Manta 2012, Surg Endosc Nishikawa 2013, Gastrointest Endosc Ramchandani 2011, Gastrointest Endosc Siddiqui 2012, Clin Gastroenterol Hepatol Woo 2014, Dig Dis Sci

		59.7%-72.3%) and 97.0% (95% CI, 94.0%-99.0%), respectively. The pooled DOR to detect CCA was 79.7 (95% CI, 32.7-194.7) **Author's Conclusion:** To conclude, our study suggests that SpyGlass cholangioscopy with SpyBite biopsies have moderate sensitivity for the diagnosis of malignant biliary strictures. Future trials should develop algorithmic approaches incorporating cholangioscopy targeted biopsies and validate them in diagnosing patients with indeterminate biliary strictures.	

Methodical Notes

Funding Sources: no statement

COI: U. Navaneethan is a consultant for AbbVie. R. Hawes and S.Varadarajulu are consultants for Olympus and Boston Scientific. All other authors disclosed no financial relationships relevant to this publication.

Study Quality: QUADAS-2
- In most studies low risk of bias regarding the selection of patients
- no bias issues or concerns regarding applicability of the selection of patients
- no risk of bias issues of the index test in any of the studies
- In most studies low risk of bias to determine whether an appropriate reference standard was used or its applicability

Heterogeneity: not assessed

Publication Bias: The Begg-Mazumdar indicator for bias gave a Kendall tau b of 0.23; P value=.11, and the Egger test, another indicator for publication bias, was -0.15 (95% CI, -0.51 to 0.19;P=.42). These tests did not suggest any evidence of publication bias; however, power was low with our small sample size of only 10 studies.

Notes:
evidence level 1: systematic review and meta analysis
heterogeneity not assessed

OXFORD (2011) Appraisal Sheet: Diagnostic Studies: *2 Bewertung(en)*

Lee, Y. N. et al. Tissue acquisition for diagnosis of biliary strictures using peroral cholangioscopy or endoscopic ultrasound-guided fine-needle aspiration. Endoscopy. 51. 50-59. 2019

Evidence level/Study Types	Population	Outcomes/Results
Evidence level: 2 **Study type:** Single-center,	**Number of patients / samples:** Yes. 181 patients from 188 screened patients (Consecutive patients with suspected MBS	**Results:** accuracy - the diagnostic accuracy of initial TPB was 71.8% (95% confidence interval [CI] 65.3%–78.4 %].

prospective, observational study (Korea)	that required tissue sampling) were included **Reference standard:** Final diagnosis was confirmed using one of the following criteria: 1) definite result of malignancy in a surgical specimen or biopsy of a metastatic lesion; 2)malignant diagnosis by TPB or EUS-FNAB or POC-FB, and clinical/imaging follow-up compatible with malignant disease; 3) malignancy not found on TPB and EUS-FNAB or POC-FB, and clinical/imaging follow-up compatible with benign disease for at least 12 months. **Validation:** Sensitivity, specificity and accuracy analyses were performed **Blinding:** final diagnosis was confirmed after diagnostic tests **Inclusion of clinical information:** - **Dealing with ambiguous clinical findings:** -	- The accuracy of malignancy detection using POC-FB for proximal biliary strictures and EUS-FNAB for distal biliary strictures was 93.6% (95%CI 84.9%−100%) and 96.3% (95%CI 89.2%−100 %), respectively. - The overall diagnostic accuracy for the combination of TPB with either POC-FB for proximal strictures and EUS-FNAB for distal strictures was 98.3%(95 %CI 95.9%−100%) and 98.4% (95%CI 95.3%−100%),respectively. sensitivity - The sensitivity of malignancy detection using POC-FB for proximal biliary strictures and EUS-FNAB for distal biliary strictures was 92.3% (95%CI 74.9%−99.1%) and 96.0% (95%CI 79.7%−99.9 %), respectively. - The overall sensitivity for the combination of TPB with either POC-FB for proximal strictures and EUS-FNAB for distal strictures was 98.2%(95 %CI 93.7%−99.8%) and 98.4% (95%CI 91.2%−99.9%),respectively. specificity The specificity of malignancy detection using POC-FB for proximal biliary strictures and EUS-FNAB for distal biliary strictures was 100% (47.8−100) and 100% (15.8−100), respectively - The overall specificity for the combination of TPB with either POC-FB for proximal strictures and EUS-FNAB for distal strictures was 100% (47.8−100) and 100% (15.8−100), respectively **Author conclusions:** In conclusion, an approach using POC-FB or EUS-FNAB according to the stricture location may be useful for the diagnosis of suspected MBS.

Methodical Notes

Funding Sources: This work was supported in part by the SoonChunHyang University Research Fund.

COI: none

Notes: evidence level 2: Individual prospective studies with consistently applied reference standard and blinding.

Slivka, A. et al. Validation of the diagnostic accuracy of probe-based confocal laser endomicroscopy for the characterization of indeterminate biliary strictures: results of a prospective multicenter international study. Gastrointest Endosc. 81. 282-90. 2015

Evidence level/Study Types	Population	Outcomes/Results
Evidence level: 2 **Study type:** Prospective,	**Number of patients / samples:** A total of 136 patients with indeterminate biliary strictures were screened for eligibility, 128	**Results:** Investigators provided a presumptive diagnosis based on the patient history, ERCP impression,and pCLE during the procedure before and after tissue sampling results were available. A presumptive diagnosis also was made separately by a blinded investigator during ERCP

multicenter study (USA, Italy, France)	were enrolled and 112 were finally evaluated. **Reference standard:** By having an independent second physician blinded to the pCLE findings, make a presumptive diagnosis based on an electronic review of clinical data and ERCP images before and after tissue sampling, we estimated the standard of care without pCLE. **Validation:** Accuracy, sensitivity, and specificity during ERCP alone, ERCP with pCLE, and ERCP with pCLE and tissue sampling. **Blinding:** pCLE was not blinded but reference standard was applied in a blinded fashion. **Inclusion of clinical information:** yes **Dealing with ambiguous clinical findings:** -	and after tissue sampling to estimate care without pCLE. - ERCP impression: sensitivity (CI 95%)=84% (73-92); specificity (CI 95%)=76% (60-88); Accuracy(CI 95%)=81% (72-88) - ERCP impression + pCLE: sensitivity (CI 95%)=89% (79-95); specificity (CI 95%)=71% (54-84); Accuracy(CI 95%)=82% (74-89) - ERCP impression + pCLE + tissue sampling: sensitivity (CI 95%)=89% (79-95); specificity (CI 95%)=88% (74-96); Accuracy(CI 95%)=88% (81-94) - tissue sampling (cytology&histology): sensitivity (CI 95%)=56% (44-68); specificity (CI 95%)=100% (91-100); Accuracy(CI 95%)=72% (63-80) - ERCP impression + tissue sampling: sensitivity (CI 95%)=85% (75-93); specificity (CI 95%)=69% (52-83); Accuracy(CI 95%)=79% (71-87) **Author conclusions:** Overall, this study confirms the high performance of pCLE performed in real time when combined with tissue sampling in providing more accurate and more sensitive diagnosis of cholangiocarcinoma compared with standard procedures. pCLE has the potential to overcome some of the inherent limitations of tissue sampling techniques in establishing a pathologic confirmation of the stricture and offering the ability to objectify patient management decision making. The high sensitivity and accuracy brought by the addition of pCLE may improve the management of patients with indeterminate biliary strictures and expedite treatment, saving unnecessary repeat ERCPs and precious time for the patients.

Methodical Notes

Funding Sources: This study was funded by a research grant from Mauna Kea Technologies.

COI: - A. Slivka does research for Mauna Kea Technologies, research and consulting for Boston Scientific, and research for Wilson-Cook.
- I. Gan is a speaker for Mauna Kea Technologies. P. Jamidar does research for Mauna Kea Technologies and is a consultant and speaker for Boston Scientific.
- M. Giovannini does research for Mauna Kea Technologies and Wilson-Cook.
- M.Kahaleh does research for Mauna Kea Technologies, research and consulting for Boston Scientific, and research for MI Tech, Apollo, Emcision, and Pinnacle.
- No other financial relationships relevant to this article were disclosed.

Notes: evidence level 2: Individual prospective studies with consistently applied reference standard and blinding.

Schlüsselfrage:

CCA 09 Operation/ Transplantation
Profitieren Patienten mit einem lokal begrenzten Cholangiozellulären Karzinom von einer Operation oder Transplantation?

Inhalt: *4 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Becker, N. S. 2008	3	retrospective follow-up study
Darwish Murad, S. 2012	3	retrospective, multi-center, follow-up study (USA)
Mavros, M. N. 2014	2	systematic review and meta-analysis
Tang, H. 2016	1	systematic review and meta analysis

OXFORD (2011) Appraisal Sheet: Systematic Reviews: *2 Bewertung(en)*

Mavros, M. N. et al. Treatment and Prognosis for Patients With Intrahepatic Cholangiocarcinoma: Systematic Review and Meta-analysis. JAMA Surg. 149. 565-74. 2014

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 2 **Study type:** systematic review and meta-analysis **Databases:** Pubmed **Search period:** studies published on or after January 1, 2000. **Inclusion Criteria:** studies reporting on factors prognostic of survival or recurrence in patients undergoing curative-intent surgical treatment of ICC. Prognostic factors included preoperative, intraoperative, and postoperative variables. **Exclusion Criteria:** - Small series assessing fewer than 20 patients - studies not assessing	**Population:** patients undergoing curative-intent surgical treatment of ICC **Intervention:** surgical treatment of ICC **Comparison:** none	**Primary:** overall survival and recurrence-free survival prognostic factors **Secondary:** none **Results:** - 57 Articles included in the systematic review - 7 included in Meta Analysis <u>overall survival</u> - Median, 3-year, and 5-year over-all survival (OS) ranged from 9 to 53 months, 16% to 65%, and 5% to 56%, respectively. - In a subset analysis of the 5 largest studies, the median, 3-year, and 5-year OS ranged from 18 to 33 months, 32% to 47%, and 21% to 35%, respectively. <u>recurrence-free survival</u> - median, 3-year, and 5-year recurrence-free survival (RFS) ranged from 7 to 34 months, 6% to 47%, and 2% to 39%, respectively	for meta analysis: de Jong et al. 2011, J Clin Oncol. Ribero et al. 2012, Arch Surg. Wang et al. 2013, J Clin Oncol. Tamandl et al. 2008, Ann Surg Oncol. Bunsiripaiboon et al. 2010, J Med Assoc Thai. Clark et al. 2011, HPB (Oxford) Fisher et al. 2012, HPB (Oxford)

factors prognostic of clinical outcome or not reporting - studies reporting on mixed series of patients with intrahepatic and other types of cholangiocarcinoma (eg, hilarcholangiocarcinoma) - series of patients with exclusively hepatolithiasis-associated ICC or recurrent ICC - Conference abstracts that did not proceed to publication in peer-reviewed journals were not included in the present review		prognostic factors: meta analysis - Factors associated with shorter OS included older age (pooled hazard ratio, 1.10; 95% CI, 1.03-1.17), larger tumor size (1.09; 1.02-1.16), presence of multiple tumors (1.70; 1.43-2.02), lymph node metastasis (2.09; 1.80-2.43), vascular invasion(1.87; 1.44-2.42), and poor tumor differentiation (1.41; 1.17-1.71), - none of the factors were significantly associated with shorter RFS **Author's Conclusion:** The prognosis of ICC remains grave, with less than one-third of the patients who undergo curative-intent surgical treatment surviving beyond 5 years after resection. Prognosis is dictated primarily by tumor factors, such as tumor size, lymphnode invasion, and vascular invasion, which underlines the necessity for earlier diagnosis. Furthermore, the high incidence of recurrence and its association with certain tumor-specific factors highlight the need for more effective adjuvant therapies. Future research should therefore target the identification of novel agents with more activity toward ICC so as to increase the goal of prolonging survival among this challenging group of patients.	

Methodical Notes

Funding Sources: no statement

COI: None reported

Study Quality: no quality assessment

Heterogeneity: - Statistical heterogeneity between studies was assessed with a $\chi 2$-test and I^2; P< .10 for the $\chi 2$-test or I^2 greater than 50% indicated significant heterogeneity.
- hetereogeneity can be assumed for the factors "large tumor size" and "positive surgical margin"

Publication Bias: There was no publication bias, as evidenced in the funnel plot of all combined risk factors

Notes:
evidence level 2: SR and MA, downgraded due to missing quality assessment

Tang, H. et al. Influence of surgical margins on overall survival after resection of intrahepatic cholangiocarcinoma: A meta-analysis. Medicine (Baltimore). 95. e4621. 2016

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References

Evidence level: 1 **Study type:** systematic review and meta analysis **Databases:** PubMed, Web of Science, EMBASE, and the Cochrane Library **Search period:** from the initiation of the databases to February 2016 **Inclusion Criteria:** - ICC (confirmed by pathological examination) patients primarily undergoing potentially curative resections - inclusion of surgical margins as a variable in the outcome analysis; - stratification of negative surgical margins into less than 10mm (with or without additional subgroups) and 10mm or more groups; - a survival hazard ratio (HR) for a less than 10mm group compared with a 10mm or more group, either directly available in the article or possible to calculate **Exclusion Criteria:** - articles with the types of abstracts, reviews, case reports, editorials, and expertopinions - articles grouping the patients by other cut off values of margin length; - overlapping or duplicate reports; - articles including	**Population:** ICC patients primarily undergoing potentially curative resections. Only patients with negative margins (R0 resection) were eligible to be included. **Intervention:** surgical resection with negative resection margin of ≥10mm **Comparison:** surgical resection with negative resection margin of <10mm	**Primary:** hazard ratios for survival **Secondary:** Subgroup analyses were performed according to the following four predefined parameters: cohorts with all MF subtype, cohorts without lymph node involvement and cohort sample size (size≥50 or size<50). **Results:** - 6 studies (8 cohorts) involving 712 patients were included in the final synthesis - 269 (37.80%) were in the ≥10mm group, 443 (62.20%) were in <10mm group <u>survival hazard ratios</u> - pooled HR for the <10mm negative margin group was 1.59 (95% CI: 1.09–2.32) when compared with the HR for the ≥10mm group (reference), - a statistically significant survival benefit was identified in patients with negative margins ≥10mm <u>Subgroup analyses</u> - pooled HR for the <10mm negative margin group was 2.19 (95% CI: 0.23–20.52) when compared with the HR for the ≥10mm group (reference) in the subgroup of cohorts with a sample size <50 - no significant differences for other 3 parameters **Author's Conclusion:** In summary, the result of this meta-analysis suggests a survival advantage for negative margins of 10mm or more in comparison with negative margins less than 10mm for patients undergoing surgical resection of ICC. However, because such a wide surgical margin may not be feasible in every case, a resection margin less than 10mm should not be recognized as a contraindication to surgery. Taken together, the findings suggest that surgeons ought to strive to achieve a negative margin of 10mm or more in surgical resection of ICC to obtain a long-term survival (OS) benefit. Further multicenter and high-quality randomized controlled trials will be required to support this conclusion.	Spolverato G, 2015, Ann Surg Oncol Farges O, 2011, Ann Surg Cho SY, 2010, Ann Surg Oncol Tamandl D, 2008, Ann Surg Oncol Shimada K, 2007, J Surg Oncol Cherqui D, 1995, Arch Surg

patients mainly undergoing repeated hepatectomy for recurrent ICC - articles including patients with extrahepatic metastases (metastases in the lung, bone, or brain)			

Methodical Notes

Funding Sources: The work is supported by the National Key Technology R&D Program of China (No. 2012BAI06B01) and the National S&T Major Project for Infectious Diseases of China (No.2012ZX10002-017).

COI: The authors have no funding and conflicts of interest to disclose.

Study Quality: "A quality assessment of each included article was conducted using the Newcastle–Ottawa Scale, which is mainly concerned withthree aspects (selection of patients, comparability of groups, andassessment of outcomes). Studies scored with 6 or more were considered to be of high quality."
- However only 2 Scores were stated: Spolverato et al, 2015: NOS-Score=8; Farges et al, 2011: NOS-Score=7

Heterogeneity: - overall between-study hetereogeneity was moderate (I^2=45.30%, P=0.07)
- moderate to high between-study hetereogeneity in subgroups of sample size (≥50: I^2=44.70%, P=0.11; <50: I^2=68.90, P=0.07)

Publication Bias: no obvious publication bias was detected by Egger test (P=0.99), with symmetry in Begg funnel plot

Notes:
- evidence level 1: Systematic Review and Meta Analysis
- NOS-Score for quality assessment, however scores were stated for only 2 out of 6 studies

NEWCASTLE - OTTAWA Checklist: Cohort: *2 Bewertung(en)*

Becker, N. S. et al. Outcomes analysis for 280 patients with cholangiocarcinoma treated with liver transplantation over an 18-year period. J Gastrointest Surg. 12. 117-22. 2008

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 3 **Study type:** retrospective follow-up study	**Funding sources:** no statement **Conflict of Interests:** no statement **Randomization:** none **Blinding:** none	**Total no. patients:** 302 analyzed transplants in 280 study patients **Recruiting Phase:** April 1987 and December 2005 **Inclusion criteria:** - patient information in UNOS/OPTN database	**Interventions:** orthotopic liver transplantation **Comparison:** none

	Dropout rates: none	- diagnosis of cholangiocarcinoma at listing (n=102) or at discharge (n=245) **Exclusion criteria:** no statement	
Notes:	evidence level 3: retrospective follow-up study **Author's conclusion:** This multi-institutional analysis of the US experience with liver transplantation for cholangiocarcinoma determined that outcomes following OLT for cholangiocarcinoma have improved over time with a 5-year survival rate of 45% during the most recent era of transplantation. Compared to outcomes in similar patients treated with medical therapy alone, patients with known cholangiocarcinoma that presents at an early, but unresectable, stage appear to benefit from OLT. However, patients incidentally found to have cholangiocarcinoma at the time of transplant, independent of the presence or absence of PSC, have a poorer prognosis.		
Outcome Measures/results	**Primary** 1- and 5-year patient survival **Secondary** prognostic value of multiple clinicopathologic variables	**Results:** - median follow-up interval of 452 days (range: 0–6,166 days), patient survival - 1- and 5-year patient survivals were 74 and 38%, respectively, with 49 actual 5-year survivors and 21 actual 10-year survivors. - Posttransplant 1- and 5-year allograft survivals were 69 and 36%, respectively. prognostic value of multiple clinicopathologic variables - Study variables associated with improved survivals included diagnosis of cholangiocarcinoma pre-OLT [5-year OS: 68 vs. 20% for patients with incidental diagnoses at the time of OLT, p<0.001] and OLT after 1993 (5-year OS: 45 vs. 30% pre-1994,p<0.01).	

Darwish Murad, S. et al. Efficacy of neoadjuvant chemoradiation, followed by liver transplantation, for perihilar cholangiocarcinoma at 12 US centers. Gastroenterology. 143. 88-98.e3; quiz e14. 2012

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 3 **Study type:** retrospective, multi-center, follow-up study (USA)	**Funding sources:** Sarwa Darwish Murad is a recipient of the 2010/2011 AASLD/LIFER Clinical and Translational ResearchFellowship in Liver Diseases Award **Conflict of Interests:** all authors declare no conflict of interest **Randomization:** none **Blinding:** none **Dropout rates:** In total, 71 patients (25%) dropped out after a median of 4.6 months (1.1–17.1) from presentation.	**Total no. patients:** In total, 12 participating centers reported 319 patients. 26 patients were excluded, thus 287 eligible patients were included in this study. **Recruiting Phase:** January 1993 to July 2010 **Inclusion criteria:** 1) perihilar cholangiocarcinoma; 2) diagnosis by a malignant-appearing stricture on cholangiography with malignant endoluminal brushing/biopsy, CA 19-9 greater than 100 U/ml, mass on cross-sectional imaging and/or polysomy on Fluorescent In-Situ Hybridization (FISH));	**Interventions:** Neoadjuvant therapy followed by liver transplantation **Comparison:** none

		3) unresectable disease or arising in Primary Sclerosing Cholangitis; 4) completion of neoadjuvant therapy before LT; and 5)medical suitability for transplantation **Exclusion criteria:** Patients with intrahepatic or distal cholangiocarcinoma were excluded	
Notes:	evidence level 3: retrospective follow-up study **Author's conclusion:** In conclusion, this study confirms excellent outcomes of neoadjuvant chemoradiotherapy followed by LT for patients with perihilar cholangiocarcinoma across 12 U.S. institutions with variable neoadjuvant protocols.		
Outcome Measures/results	**Primary** recurrence-free survival overall survival (intent-to-treat) **Secondary** none	**Results:** basic results - patients completed external radiation (99%), brachytherapy (75%), radio-sensitizing (98%), and/or maintenance chemotherapy (65%). - Median follow-up time 2.5 years (range 0.1–17.8) from time of listing for transplantation. - 122 patients died (43%) after a median of 1.2 years from presentation (0.1–17.5), of whom 60 (49%) died pre-transplant - Post-transplant, 43 patients (20%) developed recurrence, and 62 patients died (22%) from either recurrence (N=40), sepsis (N=8), multiorgan failure (N=3), liver failure (N=3), post-transplant lymphoproliferative disease (N=2), or other causes (N=6). recurrence-free survival - at 2 years: 78% (95% CI 72–84) - at 5 years: 65% (95% CI 57–73) - at 10 years: 59% (95% 49–69) overall survival (intent-to-treat) - at 2 years: 68% (95% CI 62–70) - at 5 years: 53% (95% CI 46–60) - at 10 years: 42% (95% 33–51)	

Schlüsselfrage:

CCA 11 lokoregionäre Verfahren
Profitieren Patienten mit nicht-operablen Cholangiozellulärem Karzinom von lokoregionären Verfahren?

Inhalt: *5 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Al-Adra, D. P. 2015	2	Systematic review and pooled analysis
Boehm, L. M. 2015	1	systematic review and meta analysis
Cucchetti, A. 2017	1	systematic review and meta-regression analysis
Han, K. 2015	2	systematic review and meta analysis
Moole, H. 2017	2	systematic review and meta analysis

OXFORD (2011) Appraisal Sheet: Systematic Reviews: *5 Bewertung(en)*

Al-Adra, D. P. et al. Treatment of unresectable intrahepatic cholangiocarcinoma with yttrium-90 radioembolization: a systematic review and pooled analysis. Eur J Surg Oncol. 41. 120-7. 2015

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 2 **Study type:** Systematic review and pooled analysis **Databases:** A comprehensive search of electronic databases (e.g., MED-LINE, EMBASE, SCOPUS, BIOSIS Previews and the Cochrane Library) **Search period:** 2000 to 2013 **Inclusion Criteria:** - studies with greater than one patient were included in order to ensure the	**Population:** adult (>18 years old) male or female patients with unresectable ICC **Intervention:** radioembolization therapy with yttrium-90 microspheres, treatment may be performed before, synchronously, or after systemic chemotherapy **Comparison:** none	**Primary:** overall survival and radiological response to radioembolization **Secondary:** ability of yttrium-90 treatment to convert unresectable cholangiocarcinoma to resectable, mortality, and morbidity **Results:** basics - 12 primary studies meeting the inclusion criteria, these included 7 prospective case series and 5 retrospective cohort studies with a total of 298 patients overall survival - weighted median survival was 15.5 months (range: 7-22.2), based on 11 included studies radiological response - data of studies reporting RECIST,	Bower and Little, 2013, Intern Med J Camacho et al., 2013, J Clin Oncol Camacho et al., 2013, J Vasc Interv Radiol Chaiteerakij et al., 2011, Gastroenterology Hoffmann et al., 2012, Cardiovasc Intervent Radiol Hyder et al., 2013, Ann Surg Oncol Martinez et al., 2013, J Vasc Interv Radiol

comprehensive capture of the available clinical experience. This included human case-series (>1 case), randomized controlled trials, non-randomized controlled trials, prospective cohort series - adult (>18 years old) male or female patients with unresectable ICC - intervention under study is radioembolization therapy with yttrium-90 microspheres **Exclusion Criteria:** none		modified (m)RECIST and Positron emission tomography response evaluation criteria in solid tumour (PERCIST) were pooled for analysis (=6 studies) - A weighted mean partial response was seen in 28% and stable disease was seen in 54% of patients at three months. secondary outcomes - Combined, 3 studies with a total 73 patients, reported on surgical resection to previously unresectable disease and surgery was performed on seven patients post-radioembolization - Mortality data was specifically reported in three included studies, and of these, there was one treatment-related death. - Overall morbidity was reported in eight included studies. The most common types of morbidity following radioembolization therapy with yttrium-90 microspheres were fatigue (33%), abdominal pain (28%) and nausea (25%). **Author's Conclusion:** Therefore, the use of yttrium-90 microspheres should be considered in the list of available treatment options for ICC. However, future randomized trials comparing systemic chemotherapy, TACE and local radiation will be required to identify the optimal treatment modality for unresectable cholangiocarcinoma. In addition, the creation of a treatment registry with standardized criteria has been recommended by the Brachytherapy Oncology Consortium. Report standardization may also allow any synergistic effects from the concomitant use of chemotherapy and Yittrium-90 radiation microspheres to be identified.	Mouli et al., 2013, J Vasc Interv Radiol Prajapati et al., 2012, J Vasc Interv Radiol Saxena et al., 2010, Ann Surg Oncol Shridhar et al., 2012, J Vasc Interv Radiol Turkmen et al., 2013, Cancer Biother Radiopharm

Methodical Notes

Funding Sources: The authors of this manuscript have no conflicts of interest to disclose and there has been no financial support for this research study.

COI: The authors of this manuscript have no conflicts of interest to disclose and there has been no financial support for this research study.

Study Quality: not assessed

Heterogeneity: not assessed

Publication Bias: not assessed

Notes:
- evidence level 2: SR with pooled analysis, downgraded due to missing quality assessment, heterogeneity and publication bias assessment
- 7 of the 12 included studies are abstracts only

Boehm, L. M. et al. Comparative effectiveness of hepatic artery based therapies for unresectable intrahepatic cholangiocarcinoma. J Surg Oncol. 111. 213-20. 2015

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 **Study type:** systematic review and meta analysis **Databases:** Pubmed **Search period:** January 1990 to April 2013 **Inclusion Criteria:** - clinical trials, prospective cohort studies, and retrospective studies of human subjects - published in PubMed in English language between January, 1990 and April, 2013. - Studies reporting the primary outcome of interest on patients with unresectable ICC receiving HAT were included. **Exclusion Criteria:** - Case reports or case series (<10 patients) - studies including patients receiving concomitant systemic chemotherapy and patients receiving concomitant radiotherapy - studies on patients with resectable tumor and studies reporting outcomes of patients with mixed histology such as ICC with HCC	**Population:** patients with unresectable ICC **Intervention:** HAI, TACE, DEB−TACE or Y−90 in the treatment of unresectable ICC **Comparison:** none	**Primary:** overall survival (OS) **Secondary:** - tumor response using Response Evaluation Criteria in Solid Tumors (RECIST) - treatment related toxicity assessed with the National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE) or World Health Organization (WHO) criteria **Results:** basics - Of 793 total articles, 20 were selected for analysis HAI: 3 articles with 62 patients, TACE: 11 articles with 431 patients, DEB-TACE: 2 articles with 37 patients, Y-90: 5 articles with 127 patients survival - The median OS across the entire cohort was 14.5 months (95% CI 12.48–16.43) - The median OS across the four strategies: HAI 22.8 months (95%CI 9.8–35.8) versus Y−90 13.9 months (9.5–18.3) versus TACE 12.4 months (10.9–13.9) versus DEB−TACE 12.3 months (11.0–13.5) Tumor Response to Therapy - Overall, partial or complete response was observed in 28.5% (95% CI 18.0–39.1, n=390) of evaluable subjects - Response rates (complete or partial) stratified according to treatment strategy: HAI group 56.9% (95% CI 41.0–72.8) versus Y−90 27.4% (17.4–37.5) versus TACE 17.3% (6.8–27.8) - The rate of stable disease was highest in the DEB−TACE group 61.5% (95% CI 42.8–80.2) versus Y−90 54.8% (95% CI 45.2–56.7) versus TACE 46.9% (95% CI 5.5–58.4) versus HAI 42.2% (95% CI 17.1–67.2) Toxicity - rate of grade III/IV complications (events per patient) was highest for HAI 0.35 (95% CI 0.22–0.48) versus TACE 0.26 (95% CI 0.21–0.32) versus DEB−	HAI Tanaka et al. (2002), Eur J Radiol Jarnagin et al. (2009), Ann Oncol Inaba et al. (2011) , Am J Clin Oncol Burger et al. (2005), J Vasc Interv Radiol TACE Herber et al. (2007), Cardiovasc Intervent Radiol Gusani et al. (2008), J Gastrointest Surg Shitara et al. (2008), Clin Oncol (R Coll of Radiol) Andrasina et al. (2010), Gut liver Park et al. (2011), Clin Radiol Kiefer et al. (2011), Cancer Kuhlman et al. (2012), Eur J Gastroenterol Hepatol Halappa et al. (2012), Radiology Vogl et al. (2012), Int J Cancer Scheuermann et al. (2013), Eur J Surg

		TACE 0.32 (95% CI 0.17–0.48) - organ specific (hepatic) toxicity was highest for HAI 0.75 (95% CI 0.65–0.86) versus Y-90 0.64 (95% CI 0.55–0.72) versus TACE 0.09 (95% CI 0.06–0.12) versus DEB-TACE 0.08 (95% CI 0.0–0.17). - None of the studies using Y-90 reported complications according to NCI/WHO criteria and could not be used for quantitative synthesis of complications for comparison. **Author's Conclusion:** Hepatic artery based therapies offer a promising strategy for improving outcomes for patients with unresectable ICC. Hepatic arterial infusion (HAI) offers the best outcomes in terms of tumor response and OS but was associated with increased toxicity. Individualization of strategy based on patient-disease characteristics and patient preferences are a focus for future research.	Oncol DEB-TACE Aliberti et al. (2008), Cardiovasc Intervent Radiol Kuhlman et al. (2012), Eur J Gastroenterol Hepatol Y-90 Ibrahim et al. (2008), Cancer Saxena et al. (2010), Ann Surg Oncol Haug et al. (2011), Eur J Nucl Med MolImaging Hoffmann et al. (2012), Cardiovasc Intervent Radiol Rafi et al. (2013), Cardiovasc Intervent Radiol

Methodical Notes

Funding Sources: There was no source of funding for this study

COI: all authors have no disclosures to make

Study Quality: Of the studies included in our analysis, the majority (60%) was prospective cohort studies and the rest were retrospective studies. When analyzed in accordance with Centre for Evidence-based Medicine (CEBM, Oxford) guidelines, 70% were assigned as level 2b and 30% were level 4. The confounding factors were described adequately only in 24% of the articles, and therefore could not be utilized for analysis.

Heterogeneity: high heterogeneity assumed for all survival analysis

- overall: I^2=99.3%, P=0.000
- HAI: I^2=99.8%, P=0.000
- TACE: I^2=98.4%, P=0.000
- DEB-TACE: I^2=70.8%, P=0.064
- Y-90: I^2=96.3%, P=0.000

low-to-high heterogeneity assumed for all complete/partial response analysis

- overall: I^2=85.9%, P=0.000
- HAI: I^2=0.0%, P=0.576
- TACE: I^2=83.1%, P=0.000
- Y-90: I^2=11.8%, P=0.322

Publication Bias: in methods section, note that publication bias was explored using funnel plots, but no reporting of results

Notes:
evidence level 1: systematic review and meta analysis
- hetereogeneity high across survival analysis

Cucchetti, A. et al. Improving patient selection for selective internal radiation therapy of intra-hepatic cholangiocarcinoma: A meta-regression study. Liver Int. 37. 1056-1064. 2017

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 **Study type:** systematic review and meta-regression analysis **Databases:** PubMed and Scopus **Search period:** until 1 September 2016 **Inclusion Criteria:** (i) a study population formed by patients treated for cholangiocarcinoma or extractable from studies in which SIRT was performed also for other clinical malignancies; (ii) a sufficient description of this study population; (iii) a description of patient survival rates for at least 1 year after SIRT. **Exclusion Criteria:** none	**Population:** patients treated for cholangiocarcinoma treated with SIRT **Intervention:** Selective internal radiation therapy (SIRT) **Comparison:** none	**Primary:** patient survival **Secondary:** tumour overall response rate **Results:** <u>basics</u> - The final list of included studies consisted of 9 reports. 6 of these were a prospective (n=151), whereas the remainder were retrospective (n=73) <u>survival</u> - The pooled 1- , 2- and 3- year survival estimates were 55.7%, 33.1% and 20.2%, respectively, with a median survival of 14.9 months. (I^2=17%, 48.9% and 0%, respectively) <u>Variables significantly related to survival</u> - infiltrative iCCAs have a 1- year survival of 36.0% vs. mass-forming type with 65.8% - 2-year survival of naïve iCCAs 50.4% vs. iCCAs treated after failure/recurrence of a previous treatment 23.6% - 2-year survival of patients receiving concurrent chemotherapy 42.5% vs. patients not receiving chemotherapy <10% <u>tumour overall response rate</u> - The overall response rate was 24.1% (95% CI: 16.4-34.0; I^2= 27.7%), and 68.1% of patients experienced some clinical adverse events (95% CI: 53.4-80.0; I^2=70.3%). - Metaregression did not find any significant relationship between clinical and tumour features and overall response rate or occurrence of clinical adverse events **Author's Conclusion:** In conclusion, this study tries to provide an	Mosconi (2016), Br J Cancer Soydal (2016), Ann Nucl Med Edeline (2015), Clin Nucl Med Filippi (2015), Nucl Med Biol Camacho (2014), J Vasc Interv Radiol Mouli (2013), J Vasc Interv Radiol Rafi (2013), Cardiovasc Intervent Radiol Hoffmann (2012), Cardiovasc Intervent Radiol Saxena (2010), Ann Surg Oncol

		assessment of survival that can be expected following SIRT in various clinical scenarios through a meta-analytic approach. Best survival outcomes can be suggested in mass-forming, naïve iCCAs patients and concomitant chemotherapy is advisable. Even if larger trial are surely needed to draw any more evidence-based conclusions, the present results can be useful for planning such prospective trials such as providing some indications for patient selection and study planning.	

Methodical Notes

Funding Sources: no statement

COI: The authors do not have any disclosures to report.

Study Quality: - The quality of each selected study was assessed by means of the quality appraisal tool for case series studies using a modified Delphi technique.
- max. score was 20 points. All studies scored at least 15 points. These studies were regarded as high quality.

Heterogeneity: Statistical heterogeneity was explored by inconsistency (I^2) statistics.
- Clinical and tumour characteristics showed medium-to-considerable heterogeneity (I^2>50%).
- see results section for further I^2 values

Publication Bias: not assessed

Notes:
evidence level 1: SR and MR

Han, K. et al. Radiofrequency ablation in the treatment of unresectable intrahepatic cholangiocarcinoma: systematic review and meta-analysis. J Vasc Interv Radiol. 26. 943-8. 2015

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 2 **Study type:** systematic review and meta analysis **Databases:** MEDLINE and EMBASE databases **Search period:** The last search was done on September 5, 2014 **Inclusion Criteria:** - Population: Patients with biopsy-proven, primary or recurrent ICC (in this review, ICC refers to tumors that are	**Population:** Patients with biopsy-proven, primary or recurrent ICC **Intervention:** RF ablation **Comparison:** none	**Primary:** - survival rates (1-year, 3-year, and 5-year survival rates) - local tumor progression rates **Secondary:** none **Results:** survival - The pooled 1-year, 3-year, and 5-year survival rates were 82% (95% CI, 72%–90%), 47% (95% CI, 28%–65%), and 24% (95% CI, 11%–40%) - no substantial heterogeneity was found in the 1-year and 5-year survival rates. Borderline heterogeneity was noted in the	Butros et al, 2014, Clin Imaging Fu et al, 2012, J Vasc Interv Radiol Haidu et al, 2012, Cardiovasc Intervent Radiol Kim et al, 2011, Eur J Radiol Kim et al, 2011 AJR Am J Roentgenol Carrafiello et al,

confined to the liver with or without evidence of extrahepatic disease) - Intervention: RF ablation - Outcome: Technical success, technical effectiveness, median overall survival, 5 year-survival rate, local tumor progression and complications - Study designs: All observational studies (retrospective or prospective) **Exclusion Criteria:** - case reports; - review articles, letters, comments and conference proceedings - studies on topics other than the efficacy and safety of RF ablation in the management of ICC - studies with overlapping patients and data		pooled 3-year survival rate (I^2=57%) Local Tumor Progression - The pooled rate was 21% (95% CI, 13%–30%) - no substantial heterogeneity was noted **Author's Conclusion:** Our results suggest that RF ablation is a locoregional treatment option that prolongs survival rates in patients with ICC who are ineligible for surgery.	2010, Cardiovasc Intervent Radiol Chiou et al, 2005, J Med Sci

Methodical Notes

Funding Sources: The authors acknowledge support for this work by the Korea Research Foundation grant (NRF-2014R1A1A1003475).

COI: None of the authors have identified a conflict of interest.

Study Quality: not assessed

Heterogeneity: Heterogeneity of the pooled data was assessed using the CochraneQ test and quantified with I^2 statistics. An I^2 value ≥50% was considered to indicate substantial heterogeneity.

Publication Bias: The publication bias was not evaluated using the funnel plot because fewer than 10 studies were included in this meta-analysis.

Notes:
evidence level 2: SR and MA, downgraded due to missing quality assessment

Moole, H. et al. Success of photodynamic therapy in palliating patients with nonresectable cholangiocarcinoma: A systematic review and meta-analysis. World J Gastroenterol. 23. 1278-1288. 2017

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 2 **Study type:** systematic review and meta analysis **Databases:** Medline, PubMed, Ovid journals, EMBASE, Cumulative Index for Nursing and Allied	**Population:** patients with advanced non-resectable cholangiocarcinoma **Intervention:** photodynamic	**Primary:** surival change in Karnofsky performance scores **Secondary:** Biliary drainage outcomes Adverse events	Ortner et al, 2003, Gastroenterology Dumoulin et al, 2003, Gastrointest Endosc Cheon et al,

Health Literature, ACP journal club, DARE, International Pharmaceutical Abstracts, old Medline, Medline nonindexed citations, OVID Healthstar, and Cochrane Central Register of Controlled Trials (CENTRAL) **Search period:** 1966 to May 2016 **Inclusion Criteria:** - Studies evaluating the role of PDT as a palliative option in patients with advanced non-resectable cholangiocarcinoma, - Prospective studies, retrospective studies and randomized controlled trials (RCTs) - Only full text articles, peer reviewed and published in international journals **Exclusion Criteria:** - Studies that used PDT as a neo-adjuvant therapy in patients with resectable cholangiocarcinoma - Studies that used chemotherapy or radiation therapy along with PDT in patients with resectable or unresectable cholangiocarcinoma - Studies without original data, perspective articles review articles, and expert opinions	therapy along with biliary stenting (PDT group) **Comparison:** biliary stenting alone (BS group)	**Results:** <u>basics</u> - Data was extracted from 10 studies (n=402) which met the inclusion criterion. - Studies evaluating survival of patients followed up with the patients till death. - Studies describing the adverse events and quality of life had a median follow up period of three months. - All except 3 studies used Photofrin 2 mg/kg as the PDT agent. Photogem, Photosan-3 and Temoporfin were the three other PDT agents <u>Survival benefit and Quality of life with photodynamic therapy</u> - survival periods in PDT group and BS group were 413.04 d (95%CI: 349.54-476.54) and 183.41 days (95%CI: 136.81 to 230.02) respectively. I^2 (inconsistency) = 85.1% (95%CI: 73.5%-90.2%), Egger: bias = 5.09 (95%CI: 2.12-8.07), P = 0.0043. - The change in Karnofsky performance scores after intervention in PDT and BS groups were +6.99 (95%CI: 4.15-9.82) and -3.93 (95%CI: -8.63-0.77) respectively. I^2 (inconsistency)= 97.6% (95%CI: 96.7%-98.1%), Egger: bias = 7.66 (95%CI: -0.22-15.53) P = 0.054 <u>Biliary drainage outcomes</u> - Pooled odds ratio for successful biliary drainage in PDT group vs BS group was 4.39 (95%CI: 2.35-8.19). I^2 (inconsistency) = 28.8% (95%CI: 0%-79.9%), Horbold-Egger: bias = -1.19 (92.5%CI: -20.32-17.94) P = 0.69. - pre-treatment bilirubin levels (mg/dL) in PDT and BS group were 6.36 (95%CI: 5.86-6.87) and 7.83 (95%CI: 7.08-8.58) respectively. - after intervention (after 3 months), the bilirubin levels decreased by 4.23 (95%CI: 3.86-4.60) and 2.45 (95%CI: 2.08-2.81) in PDT and BS group respectively; I^2 (inconsistency) = 97.1% (95%CI: 96.4%-97.7%), Egger: bias = 11.38 (95%CI: 5.28-17.48), P = 0.0026.	2004, Korean J Gastroenterol Wiedmann et al, 2004, Gastrointest Endosc Shim et al, 2005, Endoscopy Zoepf et al, 2005, Am J Gastroenterol Witzigmann et al, 2006, Ann Surg Prasad et al, 2007, Clin Gastroenterol Hepatol Lee et al, 2012, World J Gastroenterol Wagner et al, 2013, Photochem Photobiol Sci

		Adverse events - Pooled odds ratio for post-intervention cholangitis episodes in PDT group vs BS group was 0.57 (95%CI: 0.35-0.94). I² (inconsistency) = 48.3% (95%CI: 0%-73.4%), Egger: bias = -0.70 (95%CI: -2.44-1.03), P = 0.38 - In the pooled proportion of patients in PDT group, 10.51% (95%CI: 6.94-14.72) had photosensitivity reactions that were self-limiting. I² (inconsistency)= 61.2% (95%CI: 0%-79.5%), Egger: bias = 2.81 (95%CI: 0.38-5.23) P = 0.02. Subgroup analysis of prospective studies showed similar results, except the incidence of cholangitis was comparable in both groups. **Author's Conclusion:** Overall, PDT combined with biliary stenting improves the success of biliary drainage and has a significant benefit in improving the survival period and quality of life. PDT is beneficial, minimally invasive, and well tolerated with a favorable side effect profile. We conclude that PDT with biliary stenting could be offered to all patients with nonresectable cholangiocarcinoma as a palliative option.	

Methodical Notes

Funding Sources: no statement

COI: The authors deny any conflict of interest.

Study Quality: description of quality assessment in methods section but no reporting of results of such an assessment

Heterogeneity: - The heterogeneity among studies was tested using I^2 statistic and Cochran's Q test based upon inverse variance weights. I^2 of 0%-39% was considered as non-significant heterogeneity, 40%-75% as moderate heterogeneity, and 76%-100% as considerable heterogeneity

- See results section for individual I^2 values

Publication Bias: - The effect of publication and selection bias on the summary estimates was tested by both Harbord-Egger bias indicator and Begg bias indicator. Also, funnel plots were constructed to evaluate potential publication bias

- See results section for individual Egger bias scores

Notes:
evidence level 2: systematic review and meta analysis, downgraded due to missing quality assessment (described in method section, but no reporting of results)

Schlüsselfrage:

CCA 15 Systemtherapie
Von welchen Systemtherapien profitieren Patienten mit fortgeschrittenem biliären Karzinom?

Inhalt: *4 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Andre, T. 2008	3	single-arm, interventional, phase II study
Park, J. O. 2015	2	systematic review
Primrose, John N. 2019	2	randomized controlled study, open-label
Valle, Juan 2010	2	randomized controlled study

OXFORD (2011) Appraisal Sheet: Systematic Reviews: *1 Bewertung(en)*

Park, J. O. et al. Gemcitabine Plus Cisplatin for Advanced Biliary Tract Cancer: A Systematic Review. Cancer Res Treat. 47. 343-61. 2015

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 2 **Study type:** systematic review **Databases:** MEDLINE via PubMed (1946-search date); EMBASE (1966-search date); ClinicalTrials.gov results database (2008-search date); and abstracts from American Society of Clinical Oncology, European Society for Medical Oncology (ESMO),ESMO Gastrointestinal Cancer, and European CanCer Organisation conferences (2009-2013). **Search period:** searched on 5 December 2013 - for search period for each database see section	**Population:** patients with advanced and/or metastatic BTC **Intervention:** gemcitabine-cisplatin combination therapy as first-line theray **Comparison:** none	**Primary:** - Efficacy outcome data were extracted from prospective studies only and included among others OS, PFS, overall response rate (complete response [CR]+partial response [PR]), **Secondary:** - Safety outcome data were extracted from all prospective and retrospective studies and included the type, frequency, and severity of toxicities, deaths and discontinuations related to toxicity, and any other reported safety outcomes. **Results:** 16 fulltext publications and 4 abstracts met the eligibility criteria for inclusion efficacy - median OS ranged from 4.6 months (reported as 20 weeks) to 11.7 months - overall response rates ranged from 17.1% to 36.6% - Disease control rates ranged from 45.7% to 81.4%	Mizuno et al. (2013), J Clin Oncol Kang et al. (2012), Acta Oncol Okusaka et al. (2010), Br J Cancer Valle et al. (2009), Br J Cancer Valle et al. (2010), N Engl J Med Charoentum et al. (2013), J Clin Oncol Doval et al. (2004), Br J Cancer Giuliani et al. (2006), Ann Oncol Goldstein et

"databases" **Inclusion Criteria:** - patients who received gemcitabine-cisplatin combination therapy, at any dose or regimen, as first-line treatment for advanced and/or metastatic BTC. - meta analyses, systematic reviews, randomized and nonrandomized clinical trials, and both prospective and retrospective observational studies - Full-text publications, abstracts, and ClinicalTrial.gov trials with posted results **Exclusion Criteria:** - studies not conducted in humans - studies of patients with cancers other than BTC - studies of therapies other than gemcitabine-cisplatin (including gemcitabine alone or combined with other agents); - studies of gemcitabine-cisplatin used as second-line therapy, as part of chemoradiotherapy, or administered intra-arterially; - studies in which data for gemcitabine-cisplatin therapy were pooled with data for other therapies; - studies that did not report relevant outcomes (e.g., retrospective studies that did not report safety outcomes); - and conference abstracts of retrospective studies - Narrative reviews, systematic reviews that did not report original data, case reports, case series, nonclinical letters, editorials, and commentaries were also excluded.		- In the ABC-02 trial, significantly greater OS, PFS and disease control rate were observed ($p < 0.001$ for OS and PFS; $p=0.049$ for disease control rate) in the gemcitabine-cisplatin group compared with the gemcitabine only group - Subgroup analyses of efficacy based on primary tumor site were performed in three studies; however, no statistical comparison between tumor site groups was performed. - In the three included studies in which subgroup analyses were performed, response rates tended to be higher, and OS shorter in participants with gallbladder cancer than in those with other primary tumor sites safety - Most publications reported grade 3/4 hematologic, nonhematologic toxicities, - lower grade toxicities and/or treatment-related deaths and discontinuations are also reported - incidence of the most commonly reported grade 3/4 hematologic toxicities varied widely (anemia, 2.4%-36%; neutropenia, 1.73%-56.1%; thrombocytopenia, 0%-39.0%). - most commonly reported grade 3/4 nonhematologic toxicities were nausea and vomiting, with incidence ranging from 0% to approximately 30%. - Few treatment-related deaths (n=5 of 526 participants in studies reporting deaths; 1.0%) or discontinuations due to toxicities (n=55 of 427 participants in studies reporting treatment-related discontinuations; 12.9%) were reported. - no apparent relationship between gemcitabine dose (1,000 mg/m^2 vs. 1,200-1,250 mg/m^2) and the incidence of grade 3/4 anemia, neutropenia, and thrombocytopenia or between the incidence of nausea, vomiting, or other nonhematologic toxicities. **Author's Conclusion:** In conclusion, this systematic review presents collective evidence from a range of study designs that supports the use of gemcitabine-cisplatin combination therapy as standard treatment for advanced or metastatic BTC. However, detailed information regarding the effectiveness of gemcitabine-cisplatin in different types of BTC, or toxicities associated with different regimens, is lacking, in part because of the difficulty of conducting studies of sufficient sample size. Of particular importance, despite heterogeneity in the study designs, no substantial difference in toxicity was	al. (2011), Cancer Chemother Pharmacol Kim et al. (2006), Cancer Lee et al. (2006), Am J Clin Oncol Lee et al. (2008), Cancer Chemother Pharmacol Mahfouf et al. (2010), J Clin Oncol Meyerhardt et al. (2008), Dig Dis Sci Park et al. (2006), J Gastroenterol Hepatol Singh et al. (2011), Ann Oncol Thongprasert et al. (2005), Ann Oncol Charoentum et al. (2007), World J Gastroenterol Eckmann et al. (2011), Gastrointest Cancer Res Wu et al. (2012), Chang Gung Med J

		observed among the different dosing schedules of gemcitabine and cisplatin. In lieu of a large, multinational, collaborative RCT powered to enable subgroup analyses, a meta-analysis of patient-level data could help to address these questions. Alternatively, individual research teams conducting smaller studies should report subgroup-level data, which could facilitate future pooled analyses.	

Methodical Notes

Funding Sources: Eli Lilly and Company, manufacturer/licensee of gemicitabine (Gemzar), was involved in the study design, data collection, data analysis, and preparation of the manuscript.

COI: - Do-Youn Oh has received research funding from Eli Lilly.
- Jen-Shi Chen has received consultancy fees and honoraria from Eli Lilly, Roche, and Novartis.
- Li-Tzong Chen has received honoraria from Eli Lilly, Novartis, TTY Biopharm, and PharmaEngine, and support for investigator-initiated trials from Merck Serono, Novartis, Sanofi-Aventis, and TTY.
- Jong Seok Kim is an employee of and owns stock in Eli Lilly Korea Ltd., Republic of Korea.
- Mauro Orlando is an employee of and owns stock in Eli Lilly Interamerica, Argentina.
- Joon Oh Park, Chiun Hsu, and Ho Yeong Lim have no conflicts of interest to declare.

Study Quality: not methodically assessed, few comments only:
Only four RCTs on the use of gemcitabine-cisplatin in advanced BTC have been published, and only one of these was a large, phase 3 trial. All RCTs were open-label by necessity, given the different treatment regimens involved. Most of the other included studies were nonrandomized and uncontrolled, with small sample sizes, reflecting the relative rarity of BTC.
- Of the 17 publications of prospective studies, four described open-label RCTs . The ABC-01, ABC-02, and BT-22 trials compared gemcitabine-cisplatin with gemcitabine monotherapy, whereas the fourth RCT compared gemcitabine-cisplatin with S-1 plus cisplatin. All RCTs used the intention-to-treat population for efficacy analyses; however, only the ABC-02 trial publication specified the allocation method used for randomization (centralized telephone system).
- The 12 remaining publications described nonrandomized, prospective studies, of which none were comparative and most included fewer than 50 participants. Of the three retrospective studies that reported safety outcomes, one compared gemcitabine-cisplatin with all other treatments, whereas two studies were not comparative

Heterogeneity: assumed high across all studies, therefore no meta analysis was performed

Publication Bias: not assessed

Notes:
evidence level 2: systematic review, downgraded due to missing bias assessment

OXFORD (2011) Appraisal Sheet: RCT: *3 Bewertung(en)*

Andre, T. et al. Gemcitabine and oxaliplatin in advanced biliary tract carcinoma: a phase II study. Br J Cancer. 99. 862-7. 2008

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 3 **Study type:** single-arm,	**Intervention:** - gemcitabine 1000 mg m^{-2} as a 100-min	**Primary:** efficacy (based on RR): progression-free survival, overall survival, tumor response

interventional, phase II study **Number of Patient:** - 70 patients were enroled (ITT population) - Three patients did not receive study treatment. The exposed population therefore, comprised 67 patients. **Recruitung Phase:** Between April 2003 and April 2005 **Inclusion Criteria:** - aged >18 years - histologically proven, locally advanced or metastatic carcinoma of the biliary tract (gallbladder, intrahepatic bile ducts, extrahepatic bile ducts and ampulla of Vater) - Eastern Cooperative Oncology Group performance status ≥2 - unidimensionally measurable disease - no prior chemotherapy for advanced disease; - adequate haematological (absolute neutrophil count >1.5x10^{9}l^{-1}, platelets >100x10^{9}l^{-1}), renal (creatinine <1.5x the upper limit of normal; ULN), and hepatic function (alanine aminotransferase <5xULN; bilirubin <2.5xULN). - Patients with jaundice or evidence of bile duct obstruction and in whom the biliary tree could be decompressed by endoscopic percutaneous endoprosthesis, with a subsequent reduction in bilirubin to <2.5xULN **Exclusion Criteria:** - Patients with prior malignancy or prior chemotherapy for advanced disease, central nervous system metastases or peripheral neuropathy grade ≥2 - Prior radiation therapy	i.v. infusion on day 1 followed by oxaliplatin 100 mg m^{-2} as a 2-h i.v. infusion on day 2. - Cycles were repeated every 2 weeks. **Comparison:** none	**Secondary:** safety **Results:** <u>tumor response</u> - 10 partial responses (PR) (14.9%; 95% CI, 7.4–25.7%) in the exposed population - A further five unconfirmed PRs in the exposed population (three GBCs and three CCs). - The majority of responses were observed in patients with CC: PRs were observed for 9/44 patients (20.5%) with CC and 1/23 patients (4.3%) with GBC. <u>progression-free survival</u> - Median PFS was 3.4 months (95% CI, 2.5 – 4.6 months) for both the ITT and exposed populations - Median PFS was 2.5 months for patients with GBC (95% CI, 1.6–4.3 months) and 3.8 months for patients with CC (95% CI, 2.7–5.6 months). <u>overall survival</u> - Median OS was 8.8 months (95% CI, 6.9–11.1 months) in the ITT population and 9.3 months (95% CI, 6.9–11.4 months) in the exposed population - For both populations, median OS was 11.0 months for patients with non-GBC and 6.1 months for patients with GBC <u>adverse events</u> - Overall, nausea (82.1%) and vomiting (56.7%) of all grades were frequent side effects - Grade 3 nausea and vomiting occurred in 4.5% and 10.4% of patients, respectively, - Overall, grade 3/4 AEs occurred in 47 patients (70.1%). - Peripheral sensory neuropathies were observed in 67.2% of patients, with grade 3 neuropathy in 6.0% - Other frequently reported AEs included anaemia (77.6%), fatigue (73.1%), thrombocytopenia (68.7%), liver enzyme increase (62.7%), and weight loss (61.2%), although the majority of these events were grade 1/2 in severity **Author's Conclusion:** In conclusion, this multinational study provides further evidence for the activity of GEMOX as a treatment for non-GBC, but also demonstrates the poor activity of this agent in GBCs. The combination of gemcitabine and oxaliplatin is well tolerated and provides a treatment option for patients with advanced BTCs, and inparticular non-GBCs. A phase III study comparing GEMOX to gemcitabine is necessary to further establish the role of GEMOX inadvanced BTCs. The design of such a study should include stratification for the location of the carcinoma (non-GBCs vs GBCs).

within 4 weeks of the first gemcitabine administration was not permitted - Women of childbearing potential were required to be neither pregnant nor breastfeeding and to be under active contraception.		

Methodical Notes

Funding Sources: The study was sponsored by sanofi-aventis.

COI: no statement

Randomization: none

Blinding: none

Dropout Rate/ITT-Analysis: Three patients did not receive study treatment: two died before starting treatment (one with GBC, one with CC) and one patient with CC had hyperbilirubinaemia.

Notes:
evidence level 3: single-arm, interventional, phase II study

Primrose, John N. et al. Capecitabine compared with observation in resected biliary tract cancer (BILCAP): a randomised, controlled, multicentre, phase 3 study. The Lancet Oncology. 20. 663-673. 2019

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** randomized controlled study, open-label **Number of Patient:** - 447 patients (intention-to-treat population) were enrolled and randomly assigned to the capecitabine group (n=223) or the observation group (n=224) - The per-protocol population comprised 430 patients (210 in capecitabine group) and 220 in the observation group) following the exclusion of 17 patients - The safety population comprised any patient receiving at least one dose of capecitabine. **Recruitung Phase:** Between March 15, 2006 and Dec 4, 2014	**Intervention:** Oral capecitabine (1250 mg/m²) was given post-operatively twice a day on days 1 to 14 of a 3-weekly cycle for 24 weeks (eight cycles) **Comparison:** observation	**Primary:** overall survival **Secondary:** per-protocol analysis of outcomes, recurrence-free survival, toxicity, health economics, and quality of life. **Results:** <u>overall survival</u> - In the intention-to-treat analysis, median overall survival was 51.1 months (95% CI 34.6–59.1) in the capecitabine group and 36.4 months (29.7–44.5) in the observation group (HR 0.81, 95% CI 0.63–1.04; p=0.097), when adjusted for minimisation factors other than surgical centre - In the per-protocol analysis, median overall survival was 53 months (95% CI 40 to not reached) in the capecitabine group and 36 months (30–44) in the observation group (adjusted HR 0.75, 95% CI 0.58–0.97; p=0.028) <u>recurrence-free survival</u> - In the intention-to-treat analysis, median recurrence-free survival was 24.4 months (95% CI 18.6–35.9) in the capecitabine group and 17.5 months (12.0–23.8) in the observation group. - The adjusted recurrence-free survival HR was 0.75 (95% CI 0.58–0.98; p=0.033) in the first 24 months from randomisation, with no evidence of a difference in the period from 24 to 60 months

Inclusion Criteria: - Patients aged 18 years or older - with histologically confirmed cholangiocarcinoma or muscle-invasive gallbladder cancer who had a macroscopically complete resection with curative intent - should have had radical surgical treatment, which includes liver resection, pancreatic resection or both. - The Eastern Cooperative Oncology Group (ECOG) performance status had to be less than 2, - adequate renal, haematological, and liver function was required. **Exclusion Criteria:** - Patients with pancreatic or ampullary cancer, mucosal gallbladder cancer, or unresolved biliary tree obstruction - Patients who had not completely recovered from previous surgery or who had previous chemotherapy or radiotherapy for biliary tract cancer		(recurrence-free survival HR 1.48, 95% CI 0.80–2.77; p=0.21). - In the per-protocol analysis, median recurrence-free survival was 25.9 months (95% CI 19.8–46.3) in the capecitabine group and 17.4 months (12.0–23.7) in the observation group - The adjusted recurrence-free survival HR from 0 to 24 months was 0.70 (95% CI 0.54–0.92; p=0.0093), and there was no evidence of a difference beyond 24 months (recurrence-free survival HR 1.55, 95% CI 0.82–2.93; p=0.18) safety - 122 (55%) patients completed eight cycles of capecitabine. - of the 69 (32%) who discontinued treatment because of toxicity, the most common complaints were hand-foot syndrome in ten patients (14%), diarrhoea in nine patients (13%) and other (patients could cite more than one toxicity type) in 21 (31%) patients - Of the 213 patients who strted treatment, 94 (44%) had at least one grade 3 toxicity, and one patient (<1%) had grade 4 cardiac ischaemia or infarction. - The most frequent grade 3 events were hand-foot syndrome in 43 (20%), diarrhoea in 16 (8%) patients and fatigue in 16 (8%) patients. - Serious adverse events were observed in 47 (21%) of 223 patients (64 events, 33 of them treatment-related) in the capecitabine group and 22 (10%) of 224 patients (29 events) in the observation group. quality of life - significant differences were observed in the social functioning scale of the QLQ-C30, with a median standardised area under the curve of 76.2 (IQR 56.9–91.7) in the capecitabine group and 83.3 (64.6–95.8) in the observation group (p=0.0060). **Author's Conclusion:** In summary, although the BILCAP study did not meet its primary endpoint of improving overall survival in the intention-to-treat population, the sensitivity and secondary analyses suggest that capecitabine can improve overall survival in resected biliary tract cancer when used as adjuvant chemotherapy following surgery and could be considered as standard of care. Furthermore, the safety profile is manageable and the quality of life data favourable, supporting the use of capecitabine in this setting.

Methodical Notes

Funding Sources: - This study is supported by Cancer Research UK and an unrestricted educational grant to support recruitment and translational sample collection from Roche. JB is supported by the University College London Hospitals and University College London Biomedical Research Centre (London, UK). DC is funded by the Royal Marsden National Institute for Health Biomedical Research Centre (London, UK).
- The funder of the study had an advisory role in study design but no role in the running of the study, data collection, data analysis, data interpretation, or writing of the report. Upon completion of patient follow-up, JNP, RPF, CS, and JB had full access to all the data and the corresponding authors had final responsibility

for the decision to submit for publication

COI: - JB has received honoraria, speakers' fees, and travel support from Roche, Amgen, Merck Serono, Servier, Celgene, and Merck Sharp & Dohme.
- DC has received research funding from Amgen, AstraZeneca, Bayer, Celgene, Merrimack/Medimmune, and Merck Serono.
- JTRE has received research funding and honoraria from Eisai, Clovis, Karus, Baxalta, Bayer, Celgene, GlaxoSmithKline, Otsuka, Roche, TC Biopharm, Immunova, Basilea, e-Therapeutics, Immunocore, Vertex, Verastem, Daiichi, Merck, and Bristol-Myers Squibb.
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- JWV reports personal fees from Lilly, AstraZeneca, Merck, Delcath, Agios, and Celgene; and personal fees and non-financial support from Ipsen, Novartis, Celgene, Eisai, Bayer, Sanofi-Genzyme, Sobi, Baxalta, Lilly, and AstraZeneca.
- All potential conflicts of interests were outside of the submitted work.
- All other authors declare no competing interests.

Randomization: Patients were randomly assigned 1:1 to the capecitabine group or the observation group.
- Allocation concealment was achieved using a computerised minimisation algorithm that stratified patients by surgical centre, site of disease, resection status, and performance status. Concealment remained until the interventions were assigned by a central telephone-based randomisation service hosted by the Cancer Research UK Clinical Trials Unit

Blinding: - Treatment was not masked

Dropout Rate/ITT-Analysis: - 447 patients (intention-to-treat population) were enrolled.
- The per-protocol population comprised 430 patients following the exclusion of 17 patients: seven (2%) patients who were found to be ineligible after randomisation, nine (2%) patients who did not receive capecitabine and one (<1%) patient was ineligible and also received no drug

Notes:
- evidence level 2: randomized controlled study
- this study was not included in the initial literature search

Valle, Juan et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N. Engl. J. Med. 362. 1273-81. 2010

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** randomized controlled study **Number of Patient:** 410 patients, 204 patients received cisplatin plus gemcitabine, and 206 received gemcitabine alone **Recruitung Phase:** February 2002 and October 2008 **Inclusion Criteria:** - 18 years of age or older - received a histopathological or cytologic	**Intervention:** cisplatin plus gemcitabine or gemcitabine alone for up to 24 weeks. - In the cisplatin–gemcitabine group, each cycle comprised cisplatin (25 mg per square meter of body-surface area) followed by gemcitabine (1000 mg per square meter), each administered on days 1 and 8 every 3 weeks, initially for four cycles.	**Primary:** overall survival **Secondary:** progression-free survival tumor response adverse events **Results:** <u>basics</u> - median follow-up time was 8.2 months. At the time of the final analysis, 327 deaths had occurred, and 362 patients (88.3%) had tumor progression. - median duration of treatment 14 weeks in the gemcitabine-only group vs. 21 weeks in the

diagnosis of nonresectable, recurrent, or metastatic biliary tract carcinoma (intrahepatic or extrahepatic cholangiocarcinoma, gallbladder cancer, or ampullary carcinoma) - an Eastern Cooperative Oncolog y Group (ECOG) performance status of 0, 1, or 2 - and an estimated life expectancy of more than 3 months. - adequate hematologic and biochemical function, in particular a total bilirubin level of 1.5 times the upper limit of the normal range or less, liver-enzyme levels that were five times the upper limit of the normal range or less, renal function with levels of serum urea and serum creatinine that were less than 1.5 times the upper limit of the normal range, and a calculated glomerular filtration rate of 45 ml per minute or higher **Exclusion Criteria:** none	**Comparison:** gemcitabine alone at a dose of 1000 mg per square meter on days 1, 8, and 15 every 4 weeks, initially for three cycles.	cisplatin–gemcitabine group, P=0.003 overall survival - median survival in the cisplatin–gemcitabine group was 11.7 months (95% confidence interval [CI], 9.5 to 14.3), as compared with 8.1 months (95% CI, 7.1 to 8.7) for the gemcitabine-only group (P<0.001). - Patients who received cisplatin plus gemcitabine were 36% less likely to die at any time than those who received gemcitabine alone (hazard ratio, 0.64; 95% CI, 0.52 to 0.80). - Adjustment for the randomization stratification factors did not significantly alter this outcome (hazard ratio, 0.67; 95% CI, 0.54 to 0.84). progression-free survival - Cisplatin plus gemcitabine significantly improved progression-free survival, with a median of 8.0 months (95% CI, 6.6 to 8.6) in the cisplatin–gemcitabine group as compared with 5.0 months (95% CI, 4.0 to 5.9) in the gemcitabine-only group (P<0.001). - The hazard ratio for disease progression was 0.63 (95% CI, 0.51 to 0.77) tumor response - Tumor control (complete or partial response or stable disease) was achieved in 131 of 161 patients who received cisplatin plus gemcitabine (81.4%), as compared with 102 of 142 patients who received gemcitabine alone (71.8%) (P=0.049) adverse events - Liver function was significantly worse in the gemcitabine-only group (27.1%) than in the cisplatin–gemcitabine group (16.7%) - 7 suspected, unexpected serious adverse reactions all of whom were reported in the gemcitabine-only group **Author's Conclusion:** In summary, this study shows a significant survival advantage for cisplatin plus gemcitabine over gemcitabine alone in patients with advanced biliary cancer. Cisplatin

		plus gemcitabine is an appropriate option for the treatment of these patients.

Methodical Notes

Funding Sources: Supported by the University College London Hospitals and University College London Comprehensive Biomedical Research Centre, University College London, Cancer Research United Kingdom, and an unrestricted educational grant from Lilly Oncology.
Lilly Oncology provided the investigators with gemcitabine at no cost but was not involved in the accrual or analysis of the data, the interpretation of the results, or the preparation of the manuscript.

COI: Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

Randomization: Patients were randomly assigned by telephone by the Cancer Research United Kingdom and University College London Cancer Trials Centre, which coordinated the trial. Randomization was conducted with the use of a minimization algorithm stratified according to the primary tumor site, extent of disease (locally advanced vs. metastatic), performance status, previous therapy, and recruiting center.

Blinding: - none (open-label)
- Investigators were unaware of the overall survival analysis in the ABC-01 trial (preceding phase II trial), as mandated by the independent data and safety monitoring committee.

Dropout Rate/ITT-Analysis: All analyses were performed on an intention-to-treat basis

Notes:
evidence level 2: randomized, controlled trial (open-label)

Schlüsselfrage:

HCC 03
Welche Vorsorgeuntersuchung bei Patienten mit Leberzirrhose soll zur Früherkennung eines Hepatozelluläre Karzinoms durchgeführt werden?

Inhalt: *3 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Pocha, C. 2013	2	RCT
Trinchet, J. C. 2011	2	Multicenter, randomized trial; included were patients from 43 specialist liver disease centers in French and Belgium.
Zhang, B. H. 2004	2	RCT

OXFORD (2011) Appraisal Sheet: RCT: *3 Bewertung(en)*

Pocha, C. et al. Surveillance for hepatocellular cancer with ultrasonography vs. computed tomography -- a randomised study. Aliment Pharmacol Ther. 38. 303-12. 2013

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** RCT **Number of Patient:** 163 subjects (American veterans; the mean age was 59.3, 83.6% were Caucasian and 99.4% were male). 106 subjects were actively being screened (50 followed in the CT-arm and 56 followed in the ultrasonography-arm). **Recruitung Phase:** June 6, 2002 and February 8, 2011. **Inclusion Criteria:** 1) aged 18–70 years, 2) had Child's A cirrhosis and 3) were potential candidates for treatment of HCC. All patients were required to have no evidence of any liver mass by abdominal imaging within 12 months prior to enrollment.	**Intervention:** AFP was obtained in every patient for every 6 months. Ultrasonography was performed by designated technicians using a standardized protocol for scanning the liver and documenting findings. **Comparison:** The triple-phase contrast CT was performed per institutional protocol to assure correct timing of arterial, venous and late contrast phase.	**Primary:** The endpoint of the study was a lesion consistent with HCC histologically or by imaging criteria according to Barcelona Clinic Liver Cancer (BCLC) guidelines. **Secondary:** Total costs. **Results: Hepatocellular cancer incidence rate** was 6.6% per year. Sensitivity and specificity of **ultrasonography for HCC** detection were 71.4% and 97.5%, respectively, with a positive predictive value (PPV) of 83.3% and a negative predictive value (NPV) of 95.1%. Sensitivity and specificity of **CT for HCC detection** were 66.7% and 94.4%, respectively, with a PPV of 50.0% and NPV of 97.1%. The mean survival of all subjects with HCC after diagnosis was 19.9 months. There was no difference in number and

Exclusion Criteria: Key exclusion criteria were active malignancy other than non melanoma skin cancer and not being an acceptable candidate for treatment of HCC secondary to advanced medical conditions (severe cardiovascular or pulmonary disease, Child C cirrhosis). We excluded patients who were unable to receive IV contrast secondary to advanced renal insufficiency or allergy and patients with a history of a hepatic mass identified on imaging study.		size of lesions detected by either ultrasonography or CT regardless of the different screening interval in each screening arm. **An elevated baseline AFP** (mean 30 ng/mL in the CTarm – 55 ng/mL in the ultrasonography-arm) compared with normal AFP using a cut-off level of 20 ng/mL was the only significant predictor in all patients who developed HCC (P = 0.02; OR: 1.78; 95% CI: 1.08–2.93). Sensitivity and specificity of AFP using cut-off level of 20 ng/mL were 70.6% and 86.3%, respectively, which confirms data reported in the literature. **The cost** to detect one HCC with ultrasonography ranges from $12 069 in the VHA system to $17 041 in non-VHA care setting. If CT is used as the preferred screening tool, the cost estimates range from $18 768 for patients in VHA care to $57 383 in non-VHA care. **Author's Conclusion:** Biannual ultrasonography was marginally more sensitive and less costly for detection of early HCC compared with annual CT. Despite early detection, HCC-related mortality was high. These data support the use of biannual ultrasonography for HCC surveillance in a US patient population.

Methodical Notes

Funding Sources: The study was supported in part by the Department of Veterans Affairs Hepatitis C Resource Centers and the Research Service of the Minneapolis VA Health Care System.

COI: None.

Randomization: A computer-generated random number list was used to allocate and randomize subjects to ultrasonography every 6 months or triple-phase contrast CT every 12 months.

Blinding: n.a.

Dropout Rate/ITT-Analysis: Two subjects did not receive an imaging study after enrollment and were excluded from this analysis.
A total of 57 (34.9%) subjects, 30 assigned to the CT-arm and 27 to the ultrasonography-arm were no longer receiving their initially assigned screening test for the following reasons: non-adherence to the protocol 12/57; withdrawal active participation in assigned screening arm 8/57; contrast allergy 4/57; followed by transplant centre 10/57; non liver-related death 6/57; patient moved 9/57; other 8/57.

In the intention-to-treat analysis including all 163 study patients, a total of 17 HCC with 9/83 (10.8%) in the ultrasonography-arm and 8/80 (10.0%) in the CT arm were found. Pearson chi-square testing was not significant (chi-quadrat (1) = 1.27, P = 0.86].

Notes:
Limitations:

Our study has several limitations, including long enrolment period, relatively small sample size, predominance of Caucasian race and performance of the study in an all-male veteran' population, making generalisability to other US populations difficult.

Trinchet, J. C. et al. Ultrasonographic surveillance of hepatocellular carcinoma in cirrhosis: a randomized trial comparing 3- and 6-month periodicities. Hepatology. 54. 1987-97. 2011

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** Multicenter, randomized trial; included were patients from 43 specialist liver disease centers in French and Belgium. **Number of Patient:** 1,340 patients. 62 were subsequently excluded from analysis (see drop-out rates). Consequently, the final analyses were performed on 1,278 patients. **Recruitung Phase:** June 2000 until March 2006. **Inclusion Criteria:** (1) age older than 18 years; (2) histologically proven cirrhosis, whatever the time of biopsy; (3) cirrhosis related to either excessive alcohol consumption (80 g per day in males and 60 g per day in females for at least 10 years), chronic infection with hepatitis C virus (HCV) (serum anti-HCV antibodies-positive) or hepatitis B virus (HBV) (serum hepatitis B surface antigen (HBsAg)-positive), or hereditary hemochromatosis (liver-iron overload and C282Y homozygosity); (4) absence of previous complications of cirrhosis (particularly ascites, gastrointestinal hemorrhage or HCC); (5) patients belonging to Child-Pugh class A or B and without a focal liver lesion at inclusion; and (6) written informed consent. **Exclusion Criteria:** (1) patients belonging to Child-Pugh class C; (2) severe uncontrolled	**Intervention:** 1) US plus an AFP assay every 6 months (n = 326), 2) US every 3 months plus an AFP assay every 6 months (n = 328), 3) US every 6 months but no AFP assay (n = 312), and 4) US every 3 months but no AFP assay (n = 312). After data analyses, high rates of serum AFP assays were actually observed in groups 3 and 4 (60.5% and 54.8%, respectively), which precluded reliable interpretation based on serum AFP assay randomization. Consequently, the steering committee decided to restrict the final analysis to US randomization only. Accordingly, the final analysis considered only US randomization as follows: US every 3 months (n = 640, Gr3M) or US every 6 months (n = 638, Gr6M). **Comparison:** see Intervention	**Primary:** The prevalence of Hepatocellular carcinoma (HCC)≤ 30 mm in diameter. **Secondary:** Focal-lesion incidence, survival. **Results: Focal-lesion inicidence:** Focal-lesion incidence was not different between Gr3M and Gr6M groups (2-year estimates, 20.4% versus 13.2%, P = 0.067) but incidence of lesions ≤10 mm was increased (41% in Gr3M versus 28% in Gr6M, P = 0.002). **Hepatocellular Carcinoma:** HCC was diagnosed in 123 patients (9.6%) during the trial: 53 in Gr3M and 70 in Gr6M. The prevalence of HCC ≤ 30 mm in diameter was estimated at 79% (95% CI: 69- 90%) in Gr3M and 70% in Gr6M (95% CI: 59- 81%) (P = 0.30). Three variables remained associated with the outcome: age, platelet count, and serum bilirubin. Adjusted HR, stratified according to the etiology of cirrhosis, in the Gr6M versus Gr3M groups, was estimated at 1.18 (95% CI: 0.82-1.72; P = 0.37). **Survival**: 154 patients (12%) died during the trial: 72 (11.3%) in the Gr3M group and 82 (12.1%) in the Gr6M group. No evidence of difference in survival between the randomized groups was observed regarding 5-year estimated survival at 84.9% versus 85.8% for the Gr3M and Gr6M groups, respectively (P = 0.38). **Author's Conclusion:** In conclusion, US surveillance performed every 3 months in patients with cirrhosis, mainly caused by HCV or alcohol abuse, fails to improve the detection rate of HCCs ≤ 30 mm in diameter that are eligible for curative treatment,

extrahepatic disease resulting in estimated life expectancy of less than 1 year; and (3) coinfection with human immunodeficiency virus (HIV), even if controlled by an antiviral treatment.		although it detects more focal lesions than US performed every 6 months. This negative result is probably linked to the limitations of the recommended diagnostic procedures for small focal lesions in current practice.

Methodical Notes

Funding Sources: Grants from the French Ministry of Health (PHRC P980902 and P03009) and from the Ligue Nationale Contre le Cancer (Paris, France).

COI: Dr. Bronowicki received grants from Gore and Schering-Plough.

Randomization: Study design based on a two-by-two factorial design with balanced randomization, to compare two US periodicities (3 months versus 6 months). Randomization was computer-generated, with allocation concealed using a centralized phone procedure to the data-management center.

Blinding: n.a.

Dropout Rate/ITT-Analysis: Based on a 5% expected yearly incidence of HCC, within 3 years of follow-up, a sample size of at least 1,200 patients was computed to be needed. The minimal number of patients to include in the trial (n = 1,200) was reached in May 2005) the steering committee decided to stop further inclusions into
the trial by March 2006. At that time, 1,340 patients were included.
62 were subsequently excluded from analysis after revision of individual data due to either immediate loss to followup (n = 12) or to the presence of a focal liver lesion at inclusion (n =50).

Notes:

Zhang, B. H. et al. Randomized controlled trial of screening for hepatocellular carcinoma. J Cancer Res Clin Oncol. 130. 417-22. 2004

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** RCT **Number of Patient:** 19.200 individuals of urban Shanghai (China), Screening group (n= 9,757) or no screening (control, n= 9,443) group. In the screening group, 384 subjects refused to participate to the program. **Recruitung Phase:** January 1993 to December 1995 **Inclusion Criteria:** People aged 35 years to 59 years and with serum evidence of hepatitis B virus (HBV) infection or a	**Intervention:** Serum AFP test and a screening ultrasonography examination every 6 months. Screening-group participants who were found to have HCC were treated and transferred to follow-up programs. Individuals with negative screening tests were invited to repeat screening every 6 months. **Comparison:** Controls were identified but received no intervention, and continued to use health-care facilities as usual	**Primary:** Mortality from HCC. **Secondary:** - **Results:** During study period: 153 HCCs, with 86 deaths from HCC among the 18,816 participants. Although the total incidence of HCC was virtually identical in two groups, the total mortality rate from HCC was lower in the screened group (83.2 per 100,000) than in the control group (131.5 per 100,000). The **rate ratio for mortality** from HCC was 0.633 (95 percent confidence interval, 0.41–0.98). These results reveal a significant reduction in mortality at 5-year follow-up in the screened group compared to the control group. **Stage distribution:** Screening group (sg)(n= 86), Control group (cg) n= 67. Stage I sg: 52(60.5%); cg: 0(0%) Stage II sg: 12(13.9%); cg: 25(37.3%)

history of chronic hepatitis)(and due to that have an increased risk for HCC). **Exclusion Criteria:** Individuals with a known history of HCC, or other malignant diseases, or serious illness.		Stage III sg: 22(25.6%); cg: 42(62.7%) Small HCC sg: 39(45.3%); cg: 0 . There was a significant survival advantage for HCC patients in the screening group over those in the control group (P<0.01). Log-rank v2 =35.50, p<0.01. Subclinical cancers had the best prognosis, the 5-year survival reaching 67.8%, while this was only around 30% for stage II cancers, and 0% 5-year survival for stage III cancers. The survival rates of stage II and stage III cancers in the screened group and control were similar. **Staging:** stage I (subclinical stage or early stage) refers to HCC patients without obvious cancer symptoms and signs; stage II (moderate stage) refers to those between stage I and stage III, i.e., patients with symptoms or signs of HCC, such as palpatable mass in the abdomen; stage III (late stage) refers to those HCC patients with obvious cachexia, jaundice, ascites or distant metastases. small HCC: The diameter of a tumor less than 5 cm is empirically defined as small HCC. **Author's Conclusion:** In conclusion, biannual screening with combined AFP and ultrasound in individuals aged 35–59 years reduced HCC mortality after 5-year follow-up. Our findings suggest that consideration should be given to a program of screening using AFP and ultrasound to reduce HCC mortality in an increased risk population in the developed areas of China.

Methodical Notes

Funding Sources: n.s.

COI: n.s.

Randomization: Simple cluster sampling was carried out. Every ‘factor’, ‘enterprise’, or ‘school’ was regarded as a unit. This ensured that all eligible members of the unit were allocated to the same group. These units were randomly allocated to a screening (9,757) or no screening (control, 9,443) group.

Blinding: n.a.

Dropout Rate/ITT-Analysis: -

Notes:
Unklar ob Population der Studie für Fragestellung geeignet (HBV and chron. Hepatitis).

Schlüsselfrage:

HCC 08
Welche Untersuchungsmethoden sollen bei Patienten mit Verdacht auf ein hepatozelluläres Karzinom zur Sicherung auf Diagnose angewendet werden?

Inhalt: *17 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Bolondi, L. 2005	3	Prospective diagnostic study, Italy.
Burrel, M. 2003	2	Prospective diagnostic study.
de Sio, I. 2014	3	Retrospective diagnostic study, Italy.
Di Martino, M. 2013	2	Prospective diagnostic study.
Forner, A. 2015	3	Prospective diagnostic study.
Furlan, A. 2012	4	Retrospective diagnostic study.
Granito, A. 2013	3	Prospective diagnostic study
Haradome, H. 2011	3	Retrospective diagnostic study.
Inoue, T. 2012	3	Retrospective diagnostic study.
Khalili, K. 2011	4	Retrospective diagnostic study.
Liu, G. J. 2015	4	Retrospective diagnostic study, China
Manini, M. A. 2014	4	Prospective diagnostic study. Italy.
Mueller, C. 2018	4	Retrospective diagnostic study.
Sun, H. Y. 2010	4	Retrospective diagnostic study.
Tsurusaki, M. 2016	2	prospective diagnostic study
Wildner, D. 2015	4	Retrospective diagnostic study.
Wildner, D. 2014	4	Prospective diagnostic study.

OXFORD (2011) Appraisal Sheet: Diagnostic Studies: *17 Bewertung(en)*

Bolondi, L. et al. Characterization of small nodules in cirrhosis by assessment of vascularity: the problem of hypovascular hepatocellular carcinoma. Hepatology. 42. 27-34. 2005

Evidence level/Study Types	Population	Outcomes/Results
Evidence level: 3 **Study type:** Prospective diagnostic study, Italy.	**Number of patients / samples:** **Population:** 72 nodules in 59 patients. **Recruitment:** 2002-2004. **Inclusion:** All patients in Child-Turcotte-Pugh class A or B19 with a definite diagnosis of cirrhosis who were undergoing the surveillance program at 6-month intervals in our liver unit or who were referred from other institutions, as well as patients submitted to periodic controls after curative treatment for HCC, who had one to three distinct new nodules with a maximum diameter between 1 and 3 cm detected by conventional US examination were consecutively enrolled. **Exclusion:** (1) presence of four or more nodules, (2) a nodule exceeding 3 cm in diameter, (3) local recurrence at the same site as previously treated HCC, (4) thrombosis in the main portal branches, (5) extrahepatic metastases, or (6) previous diagnosis of HCC submitted to noncurative treatment **Reference standard:** "Impact of arterial hypervascularity, as established by the (EASL) recommendations, as a criterion for characterizing small (1-3 cm) nodules in cirrhosis." Comparison of perfusional ultrasonography and helical computed tomography. Gold standard ultrasound-guided biopsy was performed when one or both techniques (perfusional ultrasonography, helical computed tomography) showed negative results. **Validation:** perfusional ultrasonography and helical computed tomography were performed. In case both lead to a finding of arterial vascularization a definite diagnosis of HCC was established according EASL criteria. If one or both methods had negative results, a US-guided biopsy was performed. Sensitivity, Specificity, Positive Predictive Value, Negative Predictive Value not investigated. **Blinding:** "In each case, a diagnosis of hypervascularity was made by a consensus read by the physician performing the study and two blinded and independent readers when the nodule became hyperechoic during the early arterial phase and it was distinctly detected before enhancement of the surrounding liver parenchyma." **Inclusion of clinical information:** No.	**Results:** Coincidental hypervascularity was found in 44 of 72 nodules (61%);44% of 1-2-cm nodules and 84% of 2-3-cm nodules). 14 nodules (19.4%) had negative results with both techniques (hypovascular nodules). Biopsy showed HCC in 5 hypovascular nodules and in 11 of 14 nodules with hypervascularity using only one technique. All nodules larger than 2 cmfinally resulted to be HCC. Not satisfying the EASL imaging criteria for diagnosis were 38% of HCCs 1 to 2 cm (17% hypovascular) and 16% of those 2 to 3 cm (none hypovascular). **Author conclusions:** "The noninvasive EASL criteria for diagnosis of HCC are satisfied in only 61% of small nodules in cirrhosis; thus, biopsy frequently is required in this setting. Relying on imaging techniques in nodules of 1 to 2 cmwould miss the diagnosis of HCC in up to 38% of cases.."

	Dealing with ambiguous clinical findings: -	

Methodical Notes

Funding Sources: not described

COI: none declared.

Notes: Evidence level 3: Prospective studies without consistently applied reference standard or Prospective studies without blinding or Retrospective studies (non-consecutive studies) with reference standard and blinding
Notes: Gold standard was not applied to all participants
"Non-consecutive studies, or studies without consistently applied reference standards"

Burrel, M. et al. MRI angiography is superior to helical CT for detection of HCC prior to liver transplantation: an explant correlation. Hepatology. 38. 1034-42. 2003

Evidence level/Study Types	Population	Outcomes/Results
Evidence level: 2 **Study type:** Prospective diagnostic study.	**Number of patients / samples:** Fifty cirrhotic patients waiting for cadaveric LT (48) or LDLT applying expanded criteria (2). MRA and pathological examinations were conducted in all 50 patients. Helical CT was performed in 26 of 29 HCC patients. **Reference standard:** Pathologic examination was considered the gold standard. **Validation:** Accuracy of MRA and Triphasic Helical CT on a Per-Nodule Basis for Characterization of HCC Disease Extension in 29 Patients With Known HCC: Sensitivity MRA (%) 58/76 (76), Helical-CT (%) 43/70 (61) Specificity MRA (%) 18/24 (75), Helical-CT (%) 12/18 (66) Positive predictive value MRA (%) 58/64 (90), Helical-CT (%) 43/49 (87)	**Results:** Sensitivity: Overall detection of HCC was significantly better with MRA than CT (58/76 vs. 43/70, respectively, P = .OOl), particularly for HCC of 10 to 20 mm (24/27 vs. 15/25, respectively, P = .03). There were no significant differences in detection of nodules >20 mm or <10 mm. Overall, there was agreement between both techniques (K statistic = 0.64, P = .OOl). Accuracy: The likelihood ratio for a positive result by MRA was better than for helical CT (3.04 vs. 1.79, respectively). HCC Staging and Treatment Decisions. MRA established an accurate staging in 59% of the cases, underestimation in 3 1%, and overestimation in lo%, without differences with helical CT. **Author conclusions:** Our data provide the rationale to propose 3-D MRA as the best radiologic technology for HCC staging. This technology detects all nodules above 20 mm in size and a high proportion of nodules between 10 and 20 mm and is significantly better than triphasic helical CT. However, its deficiency lies in the inability to detect HCC nodules of less than 1 cm in size. New advancements in radiology, such as double-contrast MRI or multidetector row CT scan, may allow to increase the current 32% detection rate of these nodules, but, as stated before, this will have to be tested again using explant livers as the gold standard.

	False-positive results MRA (%) 6/64 (10), Helical-CT (%) 6/49 (13) Negative predictive value MRA (%) 18/36 (50), Helical-CT (%) 12/39 (30) LR for a positive result$ MRA (%) 3.04, Helical-CT (%) 1.79 **Blinding:** The observers were unaware of the results of the pathologic examination. **Inclusion of clinical information:** **Dealing with ambiguous clinical findings:**	

Methodical Notes

Funding Sources: Supported by a contract from Programa “Ramon y Cajal”(IDIBAPS, Ministerio de Ciencia y Tecnologia to J.M.L.) and supported in part by a grant of Instituto de Salud Carlos III (C03/02).

COI:

Notes: Evidence level 2: Individual prospective studies with consistently applied reference standard and blinding.

de Sio, I. et al. Optimized contrast-enhanced ultrasonography for characterization of focal liver lesions in cirrhosis: A single-center retrospective study. United European Gastroenterol J. 2. 279-87. 2014

Evidence level/Study Types	Population	Outcomes/Results
Evidence level: 3 **Study type:** Retrospective diagnostic study, Italy.	**Number of patients / samples:** We enrolled a total of 282 patients (197 M, 85 F; mean age, 67±7 years; range, 28–79 years) with a ‘de novo’ diagnosis of single (n=165; 58%) and multiple (n=117) focal liver lesions (FLLs). The underlying etiology of cirrhosis was: hepatitis C (n=220; 78%), hepatitis B (n=31; 11%), alcoholic cirrhosis (n=11; 4%), alcoholic plus hepatitis C (n=7; 2.5%), hepatitis C plus hepatitis B (n=10; 3.5%), cryptogenetic cirrhosis (n=2) and primary biliary cirrhosis (n=1). **Reference standard:** For all leasions a confirmation of diagnosis was obtained by US-guided percutaneous biopsy. **Validation:** CEUS capability of discriminating	**Results:** Histological diagnosis of FLLs: 34 benign lesions (i.e. 25 regenerative nodules and 9 dysplastic nodules) and 248 malignant lesions (223 well-to-moderately differentiated HCCs; 7 poorly-differentiated HCCs; 5 intrahepatic colangiocellular carcinomas (ICCs); 5 primary non-Hodgkin B-cell lymphomas (NHBLs); and 8 metastatic liver tumors). A time to wash-out>55 s identified patients with HCC with the highest level of accuracy (92.7%). Similarly, a time to washout ≥55 s correctly identified the vast majority of the non-HCC malignancies (100%

	between HCC and non-HCC malignancies in cirrhotic patients. **Blinding:** Yes. "The imaging review was performed by three operators, with at least 5 years' experience in liver CEUS, all blinded to the patients' clinical histories and final histopathological diagnoses." **Inclusion of clinical information:** Yes. **Dealing with ambiguous clinical findings:** -	sensitivity, 98.2% specificity and diagnostic accuracy of 98.3%). **Author conclusions:** "CEUS is an accurate and safe procedure for discriminating FLLs in cirrhotic patients, especially when a cut-off time to wash-out of 55 s is chosen as a reference value."

Methodical Notes

Funding Sources: "This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors."

COI: "The authors declare that there are no conflicts of interest."

Notes: Evidence level 3: Prospective studies without consistently applied reference standard or Prospective studies without blinding or Retrospective studies (non-consecutive studies) with reference standard and blinding.

Di Martino, M. et al. Hepatocellular carcinoma in cirrhotic patients: prospective comparison of US, CT and MR imaging. Eur Radiol. 23. 887-96. 2013

Evidence level/Study Types	Population	Outcomes/Results
Evidence level: 2 **Study type:** Prospective diagnostic study.	**Number of patients / samples:** 250 **Inclusion:**consective with chronic liver disease patients between 2007 and July 2010 were evaluated regarding liver transplantation with available imaging data (US, MDCT and MRI) within 1 month and had histologically proven cirrhosis at liver biopsy. **Exclusion:** Younger than 18 years of age, pregnant or lactating females, were contraindicated for MRI **Reference standard: Aim:** Prospective Comparison of the diagnostic performance of state-of-the-art US, MDCT and contrast-enhanced MRI in a population of cirrhotic patients who were candidates for liver transplantation. **Reference standard:** "A composite reference standard was used to diagnose or rule out HCC. A diagnosis of HCC required one or more of the following criteria: histological confirmation (liver biopsy, resection and transplantation) or demonstration of substantial growth at a minimum imaging follow-up of 12 months,	**Results:** *Population:* Out of 250 60 were not considered suitable for liver transplant surgery and were excluded (history of previous neoplasia, n=6; severe cardiopulmonary disease, n=20; end-stage liver disease, n=5; diffuse metastatic disease, n016; active drug/alcohol abuse, n=13). A total of 254 confirmed lesions comprising 163 diagnosed HCC nodules and 91 benign lesions were present in 106 of the 140 patients in our population. In the remaining 34 patients no lesions were identified either at initial imagingor at follow-up after a minimum of 12 months. Sixteen out of the 34 patients with no lesions underwent liver transplantation. *Diagnostic performance:* Significantly higher diagnostic accuracy, sensitivity 0.87 (0.81, 0.92) and NPV 0.80 (0.70, 87) was achieved on dynamic + hepatobiliary phase MRI compared with US, MDCT and dynamic phase MRI alone (data for lesions of all sizes, rest see article). The specificity 0.62 (0.5, 0.68) and PPV 0.71 (0.68, 0.82) of US was significantly lower than that of MDCT, dynamic phase MRI and dynamic + hepatobiliary phase MRI(data for lesions of all sizes, rest see article).

	defined as an increase in the longest lesion diameter of >5 mm at either CT or MRI." **Validation:** Four different image datasets were evaluated: (1) US, (2) MDCT, (3) MRI unenhanced + enhanced dynamic phase, (4) MRI unenhanced + enhanced dynamic phase + enhanced hepatobiliary phase. **Blinding:** Partial blinding. "Readers were aware of the imaging phase and that all patients had cirrhosis, but they were unaware of the results of other imaging exams, and AFP levels and were blinded to all other patient radiological and clinical information." **Inclusion of clinical information:** see blinding section. **Dealing with ambiguous clinical findings:** -	**Author conclusions:** "In summary, our study suggests that while US, MDCT and dynamic phase MRI may be appropriate for detection and characterisation of large (>2 cm) HCC nodules in patients with cirrhosis, significantly better sensitivity and diagnostic accuracy is achieved on dynamic + hepatobiliary phase MRI after the administration of gadobenate dimeglumine. A particular benefit of this latter technique may be in the evaluation of liver nodules between 1 and 2 cm in size, since the diagnostic performance achieved may obviate the need for lesion biopsy in certain patients with suspicious nodules."

Methodical Notes

Funding Sources: not declared.

COI: not declared.

Notes: Evidence level 2: Individual prospective studies with consistently applied reference standard and blinding.

Forner, A. et al. Lack of arterial hypervascularity at contrast-enhanced ultrasound should not define the priority for diagnostic work-up of nodules <2 cm. J Hepatol. 62. 150-5. 2015

Evidence level/Study Types	Population	Outcomes/Results
Evidence level: 3 **Study type:** Prospective diagnostic study.	**Number of patients / samples:** **Number of patients:** 168 patients: **Inclusion:** Prospectively included asymptomatic patients with Child-Pugh class A-B cirrhosis with no history of HCC, in whom a new, solitary, well-defined, solid nodule between 10 and 20 mm was detected by screening ultrasonography (US) **Reference standard:** Fine needle biopsy (FNB) was considered the gold standard and was applied in all patients. **Validation:** "Upon initial detection of hepatic nodule at screening ultrasound (US)... we registered all clinical data.	**Results:** In 119 nodules the final diagnosis was HCC (70.8%). In fourteen of these patients, HCC diagnosis was established only by non-invasive criteria. Regarding the 49 non-HCC nodules, threenodules were intrahepatic cholangiocarcinoma (ICC) (1.8%), 1 lesion corresponded to a metastasis of a poor-differentiated neuroendocrine tumour (0.6%), and the remaining forty-five lesions were classified as benign nodules (26.8%). CEUS did not detect contrast hyperenhancement in the arterial phase in 55 cases (34%). 18 out of these 55 nodules were diagnosed as HCC. Non-CEUS hyper-enhanced HCCs were more frequently well-differentiated than CEUS-hyper-enhanced

	Patients were examined by dynamic MRI and CEUS with a second-generation contrast agent (SonoVue, Bracco, Italy), and finally submitted to fine-needle biopsy (FNB)." **Blinding:** No blinding described. **Inclusion of clinical information:** "Upon initial detection of hepatic nodule at screening ultrasound (US) and after signing informed consent, we registered all clinical data." **Dealing with ambiguous clinical findings:** -	HCCs (p <0.004). 14 patients were treated with ablation and 4 with resection. 10 (55.6%) patients experienced tumour recurrence after treatment, mostly distant, confirming their overt malignant profile. **Author conclusions:** "Absence of contrast hyperenhancement on CEUS during the arterial phase in nodules <2 cm in a cirrhotic liver does not predict a less malignant profile. Accordingly, priority for diagnostic work-up and treatment should not differ according to contrast profiles on CEUS."

Methodical Notes

Funding Sources: "The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript."

COI: "The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript."

Notes: Evidence level 3: Prospective studies without consistently applied reference standard or Prospective studies without blinding or Retrospective studies (non-consecutive studies) with reference standard and blinding.
Notes: No blinding was performed.

Furlan, A. et al. Enhancement pattern of small hepatocellular carcinoma (HCC) at contrast-enhanced US (CEUS), MDCT, and MRI: intermodality agreement and comparison of diagnostic sensitivity between 2005 and 2010 American Association for the Study of Liver Diseases (AASLD) g. Eur J Radiol. 81. 2099-105. 2012

Evidence level/Study Types	Population	Outcomes/Results
Evidence level: 4 **Study type:** Retrospective diagnostic study.	**Number of patients / samples:** **Inclusion:** (i) cirrhotic patients with new lesions 10–20 mm in maximum transverse diameter detected at routine US-surveillance between January 2008 and December 2009; (ii) lesion's diagnostic work-up using a combination of two contrast-enhanced imaging techniques among CEUS, MDCT, and MRI performed within 15 days; and (iii) conclusive diagnosis of HCC. **Exclusion:**(i) tumors at advanced stage (portal vein neoplastic thrombosis; infiltrative tumor); (ii) multifocal HCC (>3 nodules); and (iii) lesions receiving loco-regional treatment prior to imaging. **Population:** 91 patients (mean age, 68 years; range, 43–86 years) were included in the final study population. 69 men and 22 women.	**Results:** 91 patients (69 M; 22 F; mean age, 68 years) with 96 HCCs, studied with a combination of CEUS and MDCT (n = 59), CEUS and MRI (n = 26), or MDCT and MRI (n = 11). Intermodality agreement for assessment of tumor enhancement pattern was 67% (k = 0.294, P = 0.001). Typical enhancement pattern was detected coincidentally at two imaging modalities in 50 (52%) HCCs. Sensitivity for the diagnosis of HCC increased significantly using the 2010 AASLD (81/96 (84%) vs. 50/96 (52%), P < 0.001). **Author conclusions:** "Agreement between two imaging modalities for the detection of typical tumor enhancement pattern was reached in 52% of cases. The 2010 AASLD guidelines significantly

	The underlying cause of cirrhosis was hepatitis C in 73 cases, and hepatitis B in the remaining 18 patients. There was a total of 96 HCCs, Mean ± standard deviation (SD) of tumor maximum transverse diameter was 15.2±3.8mm (range, 10–20 mm). **Reference standard:** No reference standard is used. Instead different imaging techniques for HCC are compared contrast-enhanced CEUS, MDCT, and MRI. **Validation:** All 96 lesions were studied with two contrast enhanced imaging techniques: 59/96 (61%) HCCs (mean size, 15.5±3.6mm) in 57 patients were studied at both CEUS and MDCT; 26/96 (27%) HCCs (mean size, 15.6±4.1mm) in 25 patients were studied at both CEUS and MRI; 11/96 (12%) HCCs (mean size, 12.0±2.2mm) in 9 patients were studied at both MDCT and MRI. **Blinding:** no blinding was performed. **Inclusion of clinical information:** "Demographic and clinical characteristics, including age, gender, etiology of cirrhosis, and level of serum alpha-fetoprotein were documented for each patient." **Dealing with ambiguous clinical findings:** -	increased the sensitivity for the diagnosis of HCC."

Methodical Notes

Funding Sources: none disclosed.

COI: none.

Notes: Evidence level: 4 Prospective studies without blinding and reference standard, Retrospective studies without reference standard or without blinding; Small study groups
Notes: No reference standard is used and no blinding performed. Very small n overall and for certain imaging technique comparisons (n=11).

Granito, A. et al. Impact of gadoxetic acid (Gd-EOB-DTPA)-enhanced magnetic resonance on the non-invasive diagnosis of small hepatocellular carcinoma: a prospective study. Aliment Pharmacol Ther. 37. 355-63. 2013

Evidence level/Study Types	Population	Outcomes/Results
Evidence level: 3	**Number of patients / samples:** From December 2008 to January 2011, all	**Results:** Of the 48 nodules, 38 (79%) were diagnosed as HCC, 24 of them (63%) based

Study type: Prospective diagnostic study	cirrhotics with a de novo liver nodule found during the US surveillance program at the Department of Clinical Medicine of University of Bologna, and at the Diagnostic Imaging Department, Spedali Civili di Brescia, were recruited. A total of 33 patients with 48 newly detected liver lesions were enrolled, 26 patients with 41 nodules at the Department of Clinical Medicine of University of Bologna, and 7 patients with 7 nodules at the Diagnostic Imaging Department of Brescia. **The inclusion criteria** were the following: (i) patients over 18 years of age. (ii) the absence of a previous HCC diagnosis or, in case of previous HCC, a maximum of two small nodules treated with curative treatment (resection, local ablation) and only if free from recurrence for at least 2 years. (iii) size of nodules between 1 and 3 cm. (iv) total number of liver nodules between 1 and 3. (v) satisfactory visibility of nodules at conventional US. (vi) absence of contraindications for performing imaging techniques. (vii) no evidence of extrahepatic metastasis or vascular invasion. Sixty-nine patients with newly diagnosed nodules were excluded because they did not meet the inclusion criteria. **Reference standard:** The diagnosis of cirrhosis was established by either histology or a combination of physical examination, biochemical tests and imaging features. **Validation:** The diagnostic accuracy of the hepatobiliary phase for the diagnosis of HCC was 94%, with a - sensitivity of 100% (95% CI: 90–100), - specificity 70% (95% CI: 35–93), - positive predictive value of 93% (95% CI: 80– 98), - negative predictive value of 100% (95% CI: 59–100), - positive likelihood ratio of 3.33 (95% CI: 1.2–8.4) and - negative likelihood ratio of 0 (95% CI: 0–0.2). **Blinding:** All patients underwent contrast-enhanced ultrasound (CEUS), helical computed tomography (CT), and Gd-EOB-DTPAenhanced MR. The	on the AASLD noninvasive criteria and 14 diagnosed at histology (n = 11) or follow-up (n = 3). Thirty-one HCCs had a typical vascular pattern (arterial hypervascularity and portal/delayed washout) in at least one imaging technique. It was detected in 30 (79%) HCC nodules by MR, in 22 (58%) by CT and in 17 (45%) by CEUS. **Magnetic resonance was significantly more sensitive** in detecting this typical vascular pattern **than CEUS**, considering both the 38 HCC nodules (P = 0.004, Fisher's exact test) and the nodules between 1 and 2 cm (P = 0.008, Fisher's exact test). In nodules greater than 2 cm, these differences were not statistically significant, although MR had a higher sensitivity than CT and CEUS. The MR pattern of washout in the venous phase followed by hypointensity in the hepatobiliary phase, without hyperenhancement in the arterial phase, corresponded in 8 of 8 cases to a final diagnosis of HCC (PPV 100%). **Author conclusions:** In conclusion, our study showed that Gd-EOB-DTPA MR might significantly impact the surveillance strategy of cirrhotic patients and emphasised the importance of the combination of the vascular and the hepatobiliary phases in the characterisation of small nodules.

	interpretation of each of these imaging modalities was carried out in a blinded fashion by each operator. In all cases, the operators were aware of the presence, location and size of the new nodule detected by US. **Inclusion of clinical information:** Before referring patients to imaging methods and performing a liver biopsy, written informed consent was obtained. **Dealing with ambiguous clinical findings:** -	

Methodical Notes

Funding Sources: None

COI: Luigi Bolondi, Rita Golfieri and Fabio Piscaglia have received fees as speakers and for participation in advisory boards from Bayer. Luigi Bolondi and Fabio Piscaglia have acted as consultants for Bracco.

Notes: Evidence level: 3 Prospective studies without consistently applied reference standard or Prospective studies without blinding or Retrospective studies (non-consecutive studies) with reference standard and blinding.
Notes: No independent reference standard applied in all patients.

Haradome, H. et al. Additional value of gadoxetic acid-DTPA-enhanced hepatobiliary phase MR imaging in the diagnosis of early-stage hepatocellular carcinoma: comparison with dynamic triple-phase multidetector CT imaging. J Magn Reson Imaging. 34. 69-78. 2011

Evidence level/Study Types	Population	Outcomes/Results
Evidence level: 3 **Study type:** Retrospective diagnostic study.	**Number of patients / samples:** We found 176 consecutive patients suspected of having HCC. Among these patients, 46 patients were excluded from the study because of a lack of satisfactory confirmation (ie, if both pathological proof and sufficient follow-up examinations were not available). Fifty-five patients were considered ineligible for the study because of 1) a long interval between MDCT and MRI (more than 21 days) (n = 26); 2) the presence of more than 10 HCC lesions (n = 18); or 3) inadequate MDCT examination (n = 6) (extravasation of contrast agent or equipment failure) or MRI examination (n = 5) (nondiagnostic image quality due to severe motion artifacts). Finally, 75 patients (60 men and 15 women; age range 42–67 years; mean age 54.7 years) with a total of	**Results:** ROC Analysis: The two readers had comparable (not significantly different) Az values for all lesions between MDCT and dynamic MRI. However, both readers achieved significantly higher Az values for all lesions with combined MRI than with dynamic MRI (P = 0.0083 for reader 1, and P = 0.0162 for reader 2). Reader agreement for the diagnosis of HCC using MDCT, dynamic MRI, and combined MRI was good to excellent, given the k values of 0.921 (95% confidence interval [CI]: 0.881–0.961), 0.921 (95% CI: 0.882–0.960), and 0.789 (95% CI: 0.727–0.850), respectively. For both readers, Az and sensitivity of combined MRI for smaller lesions (<1.5 cm) were significantly higher than that of dynamic MRI and MDCT (P < 0.0166). The majority of false-negative nodules on dynamic MRI or MDCT (75% and 62%, respectively) were due to a lack of identified washout findings. **Author conclusions:** In conclusion, the

	86 nodules were enrolled in this study. **Reference standard:** The diagnosis of all 60 HCC nodules was achieved based on pathologic specimens: surgical resection (n = 19) or fine needle biopsy (n = 41). **Validation:** All lesions (n = 60) 5 (numbers for analysis) Reader 1 - MDCT - Dynamic MRI - combined MRI Sensitivity 68.3 (41/60) 75.0 (45/60) 86.7 (52/60)*,y Specificity 94.9 (37/39) 92.3 (36/39) 89.7 (35/39) Reader 2 Sensitivity 71.7 (43/60) 78.3 (47/60) 86.7 (52/60)* Specificity 94.9 (37/39) 94.9 (37/39) 92.3 (36/39) **Blinding:** Two abdominal radiologists with 21 and 15 years of experience, respectively, in the interpretation of hepatic MR images independently, blindly, and randomly evaluated three imaging modalities: 1) triphase dynamic MDCT (arterial, portal, and equilibrium phases); 2) dynamic MRI: unenhanced (precontrast T1WI and T2WI) and EOB-enhanced dynamic images (arterial, portal, and late phases); 3) combined MRI: dynamic + hepatobiliary phase images on a lesion-by lesion basis. The readers were aware of the image phase and that all patients had cirrhosis and suspected HCC, but were unaware of the results of tumor histopathology, US findings, tumor marker levels (eg, AFP, PIVKA II), and the opinions of other readers. **Inclusion of clinical information:** Among the 86 nodules, 60 nodules were HCCs, 10 nodules were hemangiomas, and the remaining 16 nodules were arterioportal (A-P) shunts. In all, 38 patients had only HCC, 14 had HCC accompanied with hemangioma or A-P shunt, and seven had only hemangioma or A-P shunt. **Dealing with ambiguous clinical findings:**	performance of dynamic EOB-enhanced MRI for the diagnosis of early stage HCC is equivalent to that of triple-phase dynamic MDCT. The diagnostic performance of dynamic EOB-enhanced MRI can significantly be improved by adding hepatobiliary phase images, in particular in small lesions showing isointensity during portal or equilibrium phases. The sensitivity and accuracy of EOB-enhanced MRI with hepatobiliary phase imaging were significantly superior to MDCT for the diagnosis of lesions less than 1.5 cm in diameter. EOB-enhanced MRI has the potential to replace dynamic MDCT imaging and could become a promising modality for the noninvasive management of patients with HCC.
Methodical Notes		

Funding Sources: n.s.

COI: n.s.

Notes: **Evidence level 3:** Prospective studies without consistently applied reference standard or Prospective studies without blinding or Retrospective studies (non-consecutive studies) with reference standard and blinding.

Inoue, T. et al. Assessment of Gd-EOB-DTPA-enhanced MRI for HCC and dysplastic nodules and comparison of detection sensitivity versus MDCT. J Gastroenterol. 47. 1036-47. 2012

Evidence level/Study Types	Population	Outcomes/Results
Evidence level: 3 **Study type:** Retrospective diagnostic study.	**Number of patients / samples:** 66 patients with 86 nodules pathologically diagnosed as HCCs or DNs. **Reference standard:** All 86 nodules were diagnosed pathologically as HCC (77 nodules) or DN (9 nodules). **Validation:** see results **Blinding:** Dynamic MDCT studies were evaluated by blinded reviewers who were unaware of the findings of the other imaging techniques and of the pathologic and clinical data. MRI scans were interpreted by 3 experienced radiologists who were unaware of the findings of the other imaging techniques or of the pathologic and clinical data. **Inclusion of clinical information:** Baseline characteristics of the patients are shown. Written informed consent was obtained from all patients. **Dealing with ambiguous clinical findings:** In cases of discrepancy, the reviewers assessed the saved images together and reevaluated their findings to reach an agreement.	**Results:** diagnostic sensitivity of Gd-EOBDTPA-enhanced MRI versus dynamic MDCT for hypervascular HCCs: Gd-EOB-DTPA-enhanced MRI was 91% (41/45) versus 76% (34/45) with dynamic MDCT (p = 0.0103, McNemar's v2 test). -based on the size of the tumors (2 or > 2 cm): diagnostic sensitivity of Gd-EOB-DTPA-enhanced MRI was significantly higher than that of MDCT for lesions of 2 cm or less (p = 0.048, McNemar's v2 test). Comparison of the detection sensitivity of Gd-EOB-DTPA-enhanced MRI versus dynamic MDCT for HCCs and DNs: There was no difference in the detection of hypervascular HCCs between hepatobiliary phase images of Gd-EOBDTPA-enhanced MRI (43/45: 96%) and dynamic MDCT (40/45: 89%). The detection sensitivity of hepatobiliary phase images for hypovascular HCCs and DNs [32/32 for hypovascular HCCs and 7/9 for DNs, total 39/41 (95%)] was significantly higher than that achieved by dynamic MDCT [20/ 32 for hypovascular HCCs and 5/9 for DNs, total 25/41 (61%)] (p = 0.003, McNemar's v2 test). **Author conclusions:** In conclusion, the diagnostic ability of Gd-EOB-DTPAenhanced MRI for small hypervascular HCCs less than 2 cm was significantly higher than that of MDCT. For hypovascular HCCs and DNs, the detection sensitivity of hepatobiliary phase images of Gd-EOB-DTPA-enhanced MRI was significantly higher than that of dynamic MDCT. It was difficult to distinguish between DNs and hypovascular well-differentiated HCCs based on the EOB ER. Further study with additional resected specimens is needed to more accurately determine the diagnostic ability of GdEOB-DTPA-enhanced MRI for DNs and hypovascular well-differentiated HCCs.

Methodical Notes

Funding Sources: n.s.

COI: The authors declare that they have no conflict of interest.

Notes: **Evidence level:** 3 Prospective studies without consistently applied reference standard or Prospective studies without blinding or Retrospective studies (non-consecutive studies) with reference standard and blinding.

Khalili, K. et al. Optimization of imaging diagnosis of 1-2 cm hepatocellular carcinoma: an analysis of diagnostic performance and resource utilization. J Hepatol. 54. 723-8. 2011

Evidence level/Study Types	Population	Outcomes/Results
Evidence level: 4 **Study type:** Retrospective diagnostic study.	**Number of patients / samples:** 101 nodules were found in 84 patients (1.2 nodules/patient). **Reference standard:** All patients have histologic (48, 57%) or imaging (36, 43%) evidence of cirrhosis. **Validation:** Scan - Sensitivity - Specificity - Positive predictive value - Negative predictive value - Accuracy (=95% CI) CEUS - 53% (37-69)- 91% (82-96)- 75% (58-87)- 79% (74-83) - 78% CT - 53% (37-69) - 99% (92-100) - 95% (78-99) - 80% (77-82) - 83% MRI - 62% (45-76) - 100% (95-100) - 100% (96-100) - 84% (80-84) - 87%. **Blinding:** Both readers were blinded to the final diagnosis of the nodule and were only given the size and hepatic segment of the nodule in question. **Inclusion of clinical**	**Results:** Maasuring diagnostic performance (3 strategies): **Strategy 1**: Single imaging scan only (CEUS, CT, or MRI) **Strategy 2**, Coincidental scanning: Combining 2 contrast enhanced imaging scans, requiring both to be positive for a positive diagnosis (AASLD strategy) **Strategy 3**, Sequential scanning: Performing one imaging scan on all nodules, and performing the second scan only on nodules deemed indeterminate on the first scan. **Diagnostic performance of single imaging scans:** There was no statistically significant difference in the sensitivities of individual imaging modalities (p = 0.6). MRI was significantly more specific than CEUS (p = 0.04), but not CT. **Strategy 2:** There was no significant difference in the differences of sensitivity (p≤ P 0.34) and specificity (p ≥ 0.31) between the combinations of imaging modalities. **Strategy 3:** There was no significant difference in the sensitivity (p ≥P 0.61) or specificity (p ≥P 0.07) between the modality combinations. For Details see publication. General: Sensitivities/specificities for single scans is already high (53–62% and 91–100%). When two scans were combined requiring both to be positive, sensitivities/specificities ranged between 29–41% and 99–100%. When two scans were combined sequentially, requiring only one to be positive, sensitivities/specificities ranged between 74–89% and 91–99%. **Author conclusions:** In summary our results show that for imaging work-up of 1– 2 cm nodules found on surveillance for HCC, sequential imaging (obtaining a second imaging scan only when the first is negative) improves sensitivity and with it reduces the number of potential biopsies or follow-up scans but is subject to lower specificity. We have also shown that single imaging modalities have a very high specificity for diagnosis of 1–2 cm nodules; similar to what is reported for nodules greater than 2 cm. The addition of a second coincident imaging scan does not

	information: - **Dealing with ambiguous clinical findings:** -	significantly improve specificity but has a greater detrimental effect on malignancy detection and resource usage. Our conclusions have been considered in the latest (2010) revision of the AASLD guidelines which now advocate sequential imaging work-up of 1–2 cm nodules instead of a second coincident imaging scan.

Methodical Notes

Funding Sources: n.s.

COI: The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

Notes: EL 4: Retrospective studies without consistently applied reference standard

Liu, G. J. et al. Contrast-Enhanced Ultrasound for the Characterization of Hepatocellular Carcinoma and Intrahepatic Cholangiocarcinoma. Liver Cancer. 4. 241-52. 2015

Evidence level/Study Types	Population	Outcomes/Results
Evidence level: 4 **Study type:** Retrospective diagnostic study, China	**Number of patients / samples:** 819 patients (HCC=546, ICC=273) **Reference standard:** No reference standard was used. **Validation:** Differenatioan of HCC and ICC by CEUS. **Blinding:** Yes. "The reviews were performed by consensus by two readers who each had at least five years of experience in liver CEUS; the readers were not involved in the imaging acquisition and they were blinded to the clinical histories,.." **Inclusion of clinical information:** Yes. "The clinical data showed that compared with ICC, HCC occurred mostly in younger predominantly male patients, and in those with chronic hepatitis infections and/or cirrhosis (p<0.05). Regarding the tumor markers, elevated alpha-fetoprotein (AFP) was more common in the patients with HCC, whereas CA19-9 and CA125 were more common in the patients with ICC (all p<0.05). Elevated AFP levels (>20 ng/ml) were present in 67.8% (370/546) of the patients with HCC but only in 7.3%	**Results:** Arterial hyperenhancement followed by washout was observed in 92.3% (504/546) of the HCC lesions and 85.7% (234/273) of the ICC lesions on CEUS (p<0.05). Additionally, the ICCs presented contrast washout much earlier than the HCCs, with an average time of 27.5 seconds after injecting the contrast agent compared with 70.1 seconds for the HCCs (p<0.05). Peripheral rim-like enhancement was observed in 68.5% (187/273) of the ICCs, which was significantly more common than that in the HCCs (2.0%, 11/546) (p<0.05). When using arterial hyperenhancement with a washout phase later than 43 seconds after injecting the contrast agent and with no peripheral rim-like enhancement as the diagnostic criteria for HCC ≤5 cm in diameter, the area under the curve was 0.808, with 64.1% sensitivity, 97.4% specificity and 73.6% accuracy. **Author conclusions:** "In summary, the majority of HCCs and ICCs may show typical patterns of arterial hyperenhancement, with portal or late phase contrast washout on CEUS. The differentiation between these two entities is difficult, but peripheral rim-like enhancement and quick contrast washout may be useful features in this regard. CEUS should have a proper position in the noninvasive diagnostic algorithm of HCC, with the benefits of safety, absence of radiation, good tolerability, cost effectiveness and high efficiency."

	(20/273) of the patients with ICC, respectively. **Dealing with ambiguous clinical findings:** -	

Methodical Notes

Funding Sources: not stated.

COI: none.

Notes: Evidence level 4: Prospective studies without blinding and reference standard, Retrospective studies without reference standard or without blinding; Small study groups
Notes: No reference standard was applied. Differenatioan of HCC and ICC by CEUS.

Manini, M. A. et al. Clinical and economical impact of 2010 AASLD guidelines for the diagnosis of hepatocellular carcinoma. J Hepatol. 60. 995-1001. 2014

Evidence level/Study Types	Population	Outcomes/Results
Evidence level: 4 **Study type:** Prospective diagnostic study. Italy.	**Number of patients / samples: Number of patients:** 119 **Recruitment:** 2009-2012 **Inclusion:** all patients with a Child–Pugh A-B cirrhosis and a de novo liver nodule detected during US surveillance were consecutively recruited in four referral Italian centers for liver disease. **Exclusion:** Patients with a pre-existing liver nodule, a previous HCC or ICC diagnosis, and those with poor liver function (Child–Pugh C) were excluded. **Reference standard:** "study designed to assess the diagnostic performance of the 2010 vs. 2005 AASLD recommendations for the diagnosis of de novo liver nodules detected in cirrhotic patients with compensated cirrhosis under surveillance with ultrasounds (US)." "The gold standard for the diagnosis of HCC was the concordance of 2005 and 2010 AASLD radiological criteria [2,7] and histology in the remaining cases". "A FNB was performed when required to meet both 2005 and 2010 AASLD criteria." The gold standard was not applied to all participants. **Validation:** "The gold standard for the diagnosis of HCC was the concordance of 2005 and 2010 AASLD radiological criteria [2,7] and histology in the remaining cases. An at least	**Results:** 84 (70%) nodules were HCC: the radiological diagnosis was done in 38 (88%) of those 1–2 cm and in 38 (95%) for those >2 cm HCCs according to 2010 AASLD criteria. CT or MRI detected 13 HCC nodules that were missed by unenhanced US. Despite an absolute specificity, CEUS failed to identify any HCC uncharacterized by CT or MRI. By updated AASLD criteria 6 (17%) FNB procedures were spared in patients with 1–2 cm nodules (p = 0.025), as compared to 2005 criteria. The 2010 vs. 2005 AASLD per patient cost was similar in 1–2 cm nodules, 432 € vs. 451 € (p = 0.46), but lower in >2 cm nodules, 248 € vs. 321 € (p <0.001). **Author conclusions:** "..sequential application of imaging techniques and FNB for the diagnosis of HCC as suggested by the updated AASLD and EASL recommendations, results in a significant spare of FNB procedures to evaluate 1–2 cm nodules and in significant cost saving for the characterization of >2 cm nodules."

	6 month enhanced follow-up was required to confirm histological non-malignancy." "All patients were sequentially examined by CEUS and CT, using MRI as a rescue approach in patients lacking a typical vascular pattern for HCC by one or both contrast techniques in the 1–2 cm nodules and by CT in the >2 cm nodules. **Blinding:** No blinding was performed. **Inclusion of clinical information:** "After giving an informed consent in the presence of an independent witness, patients were assessed following the collection of a detailed medical history, a physical examination, complete blood count and biochemical tests, including serum alpha-fetoprotein (AFP), and viral hepatitis and autoimmunity serum markers, and finally enrolled." **Dealing with ambiguous clinical findings:** -	

Methodical Notes

Funding Sources: none described

COI: "Massimo Colombo: Grant and research support: Merck, Roche, BMS, Gilead Science; Advisory committees: Merck, Roche, Novartis, Bayer, BMS, Gilead Science, Tibotec, Vertex, Janssen Cilag, Achillion, Lundbeck, Abbott, Boehringer Ingelheim;
Speaking and teaching: Tibotec, Roche, Novartis, Bayer, BMS, Gilead Science, Vertex.
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Antonio Grieco: speaking and travel support: Janssen, BMS, Merck, Roche, Bayer.

Notes: Evidence level 4: Prospective studies without blinding and reference standard, Retrospective studies without reference standard or without blinding; Small study groups
Notes: No blinding was performed. Reference standard was not applied to all patients.

Mueller, C. et al. Non-invasive diagnosis of hepatocellular carcinoma revisited. Gut. 67. 991-993. 2018

Evidence level/Study Types	Population	Outcomes/Results
Evidence level: 4 **Study type:** Retrospective diagnostic study.	**Number of patients / samples:** 94 biopsies of 92 patients (after exclusion of 88 biopsies). **Reference standard:** Unclear. **Validation:** The full diagnostic power of Liver Imaging Reporting and Data System (LI-RADS) became evident, when applied on late arterial images. Under this	**Results:** HCC development was associated with the presence of cirrhosis (n=51/65, p<0.001), which was also found in 27% (3/11) of ICC and 33% (1/3) of combined hepatocellular–cholangiocarcinoma (HCC– CC) patients. The number of false-positive non-invasive HCC diagnosis was higher in

	condition, the performance of non-invasive HCC diagnosis in daily routine practice was as reported from carefully controlled and supervised studies sensitivity: 96% vs 64%, p<0.001; accuracy: 80% vs 61%, p=0.017. **Blinding:** - **Inclusion of clinical information:** **Dealing with ambiguous clinical findings:**	patients without cirrhosis (n=13/19), while most false-negative diagnoses (n=19/22) occurred in patients with cirrhosis. Thus, the imaging features of HCC are characteristic but neither specific nor pathognomonic. A particular challenge represents the identification of HCC–CC and ICC. According to a recent study, about 70% of HCC–CCs were misclassified by both CT and MRI. **Author conclusions:** In summary, we encourage the use of LI-RADS in clinical practice, as the distinction of HCC, ICC and HCC-CC has profound clinical implications and LI-RADS seems to separate these entities better than classical algorithms. To prevent mistreatment a biopsy should be performed whenever there is doubt on the typing of an observation or the patient is low risk for HCC development. Our findings should be validated in a prospective randomised controlled trial.

Methodical Notes

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Deutsche Krebshilfe (110881).

COI: None declared.

Notes: Evidence level 4: Prospective studies without blinding and reference standard, Retrospective studies without reference standard or without blinding; Small study groups
Notes: Retrospective studiy without reference standard and without blinding.

Sun, H. Y. et al. Gadoxetic acid-enhanced magnetic resonance imaging for differentiating small hepatocellular carcinomas (< or =2 cm in diameter) from arterial enhancing pseudolesions: special emphasis on hepatobiliary phase imaging. Invest Radiol. 45. 96-103. 2010

Evidence level/Study Types	Population	Outcomes/Results
Evidence level: 4 **Study type:** Retrospective diagnostic study.	**Number of patients / samples:** 351 patients with liver cirrhosis were referred to the Radiology Department for Gadoxetic acid-enhanced MRI of suspected focal hepatic lesions detected on ultrasound examination or because of the clinical suspicion for HCC. Among these 146 patients with small, arterial, enhancing, hepatic lesions (2 cm in diameter) were detected. 77 were	**Results: Morphological characteristics of HCCs and AEPs:** The mean diameters of the HCCs and AEPs were 1.37 ± 0.41 and 1.09 ± 0.26, respectively. There was a tendency for AEPs to be more often located adjacent to the surface compared with HCCs (P= 0.0268). **Enhancement Characteristics of HCCs and AEPs:** Among 44 HCCs, 42 (95.4%) demonstrated

	excluded for one or more of the following reasons: (a) lack of confirming proof of the diagnosis of HCC or AEP (n =63); (b) more than 5 hepatic lesions (n =6); and (c) the presence of both HCC and AEP in the same hepatic lobe (n =8). The remaining 69 patients with 97 arterial enhancing hepatic lesions (56 men and 13 women; age range, 39–73 years; mean, 55.8 years) were included. **Reference standard:** In all patients, the diagnosis of liver cirrhosis was made according to the pathology findings (n =18) or a combination of the radiologic findings, clinical findings, and the results of laboratory examinations including blood chemistry tests (n = 51). **Validation:** Diagnostic Performance of Gadoxetic Acid-Enhanced Dynamic MRI Sensitivities for HCC characterization were 96.2% for reviewers 1 and 93.2% for reviewer 2, respectively. Specificities were 96.2% for both reviewers. Positive and negative predictive values were 95.5% and 96.2% for reviewer 1 and 95.3% and 94.4% for reviewer 2, respectively. Interobserver agreement was good (kappa = 0.80). For gadoxetic acid-enhanced dynamic MRI and multiphasic CT, the k values for the 2 observers were 0.80 and 0.639, respectively, thus indicating good interobserver agreement. **Blinding:** Using the extracted enhancement characteristics as the diagnostic criteria, 2 other radiologists with 12 and 5 years, respectively, of clinical experience and who were blinded to the final diagnosis of arterial enhancing lesions, independently reviewed the MR images in random order and recorded the confidence level of each lesion on a 5-point scale where “1” was defined as “definitely AEP,” “2” as “probably AEP,” “3” as “indeterminate,” “4” as “probably HCC,” and “5” as “definitely HCC.” **Inclusion of clinical information:** Among the 69 included patients, 13	low signal intensity (SI) and only 2 showed iso- or high SI on the hepatobiliary phase of gadoxetic acid-enhanced MRI. Alternatively, most AEPs showed iso SI on the hepatobiliary (n = 50, 94.3%) phase, and only 2 AEPs showed low SI. Comparison of the Diagnostic Performance of Liver MRI and MDCT: For both reviewers, MR imaging showed a tendency toward higher Az values than those of CT imaging although the differences were not statistically significant (P=0.069 for reviewer 1 and 0.106 for reviewer 2). However, the MR sensitivities of each reviewer for the differentiation of HCC and AEP, were greater than 90% and were significantly higher than the CT sensitivities of 54.5%. Specificity with CT was slightly higher than that with MR, but both were greater than 90% and there was no statistical difference. **Author conclusions:** In conclusion, small (2 cm in diameter) HCC and AEP show different enhancing features on the hepatobiliary phase of gadoxetate disodium-enhanced MRI. Using the hepatobiliary phase of gadoxetic disodium-enhanced MRI, these pseudolesions may be differentiated from HCCs, thus preventing additional, unnecessary treatment, which can result in further decreased hepatic functioning in patients with liver cirrhosis.

	had 2 arterial enhancing lesions, 4 had 3 lesions, 1 had 4 lesions, and 1 had 5 lesions. Furthermore, of these 69 patients, in 42 patients with 60 arterial enhancing lesions detected on MRI, quadruple-phase CT studies performed within 4 weeks before or after the MRI, were available for direct comparison of the MR and CT imaging on a lesion-by-lesion basis. **Dealing with ambiguous clinical findings:**	

Methodical Notes

Funding Sources: n.s.

COI: n.s.

Notes: **Evidence level:** 4 Prospective studies without blinding and reference standard, Retrospective studies without reference standard or without blinding;
Small study groups

Tsurusaki, M. et al. Comparison of gadoxetic acid-enhanced magnetic resonance imaging and contrast-enhanced computed tomography with histopathological examinations for the identification of hepatocellular carcinoma: a multicenter phase III study. J Gastroenterol. 51. 71-9. 2016

Evidence level/Study Types	Population	Outcomes/Results
Evidence level: 2 **Study type:** prospective diagnostic study	**Number of patients / samples:** Patients were eligible for enrollment if they had ≤10 known focal liver lesions that were strongly suspected of being HCCs on the basis of ultrasound and tumor marker results, had undergone multiphasic MDCT within 4 weeks before undergoing gadoxetic acid-enhanced MRI, and were scheduled for a defined standard of reference (SOR) surgical procedure for verification of the presence of lesions and characterization. The final study cohort consisted of 54 non-consecutive patients (mean age 63 years; range 35–84 years) with 83 confirmed liver lesions and included 39 men (mean age 66 years; range 41–79 years) and 15 women (mean age 65 years; range 43–84 years). **Reference standard:** histopathological examinations (surgery) **Validation:** sensitivity and positive predictive value (PPV) of the CT and MRI sets for detection of HCC by each observer were assessed by using the number of	**Results:** Interobserver agreement Good-to-excellent (*kappa* =0.64–0.82) reader agreement for the detection of HCC lesions with each technique was obtained among the three readers. AFROC-analysis Regardless of lesion size, significantly higher diagnostic accuracy for the detection of HCC lesions was achieved by each reader for gadoxetic acid-enhanced MRI (mean Az=0.927 for all lesions) than for multiphasic MDCT image set (Az=0.864). Sensitivity For the subgroup of HCC lesions ≤1 cm in diameter and the subgroup of HCC lesions 1–2 cm in diameter, the mean sensitivity was significantly higher for gadoxetic acid-enhanced MRI than for multiphasic MDCT. The MR sensitivities of the two readers for detection of all HCCs were significantly higher than those of multiphasic MDCT (p=0.029 and 0.060). False-negative findings Nine lesions (>1–2 cm,n=2; ≤1 cm,n=7) in

	lesions that were assigned confidence scores of 3 or 4 (i.e., probably HCC or definitely HCC) of all HCCs. The McNemar test was used by each observer to compare the sensitivity and PPV for CT and MRI sets among the composite data. The alternative free-response receiver operating characteristics (AFROC) analysis for each reader and each image set was performed on a tumor-by-tumor basis by using a maximum-likelihood estimation program. The area under each AFROC curve (Az) indicated the overall diagnostic accuracy of each image set and each reader. Interobserver variability was assessed by calculating the *kappa* statistic for multiple observers and nonweighted *kappa* statistics, with binary data defined by the presence or absence of liver metastases. **Blinding:** image assessment The CT and MR images were independently and randomly assessed by three observers with at least 5 years of experience in the interpretation of liver MR images. All three observers were unaware of the study design; they were aware that the patients were at risk of HCC, but were unaware of the imaging findings or the final diagnosis. histopathological assessment 2 radiologists, who had not participated in the interpretation sessions, determined the presence or absence of HCCs on the basis of findings obtained at definitive surgery that involved intraoperative US. Hepatic resection and intraoperative US for the non-resected segments were performed by surgeons who were aware of the preoperative MRI findings. **Inclusion of clinical information:** HCC was suspected on the basis of the results of previous ultrasonographic (US) examination or elevation of alpha-fetoprotein levels (>400 ng/ml [400µlg/l]). **Dealing with ambiguous clinical findings:** The CT and MR images were independently and randomly assessed by three observers. Interobserver variability was calculated to ascertain agreement.	six patients, which were confirmed by histopathological inspection of the surgically resected specimen (n=6)were not detected with a high confidence score of 3 or 4 by any reader on any image set and were thus deemed false-negative lesions. False-positive findings and PPV There were no significant differences between the mean PPVs between gadoxetic acid-enhanced MRI and multi-phasic MDCT. **Author conclusions:** In summary, the sensitivity and accuracy for detection of HCCs were significantly higher for gadoxetic acid-enhanced 3T MRI than for multiphasic 64-sectional MDCT in this multicenter prospective study.

Methodical Notes

Funding Sources: There was no financial support or relationships that posed a conflict of interest.

COI: The authors declare that they have no conflict of interest.

Notes: Evidence level 2: Individual prospective study with consistently applied reference standard and blinding.

Wildner, D. et al. CEUS in hepatocellular carcinoma and intrahepatic cholangiocellular carcinoma in 320 patients - early or late washout matters: a subanalysis of the DEGUM multicenter trial. Ultraschall Med. 36. 132-9. 2015

Evidence level/Study Types	Population	Outcomes/Results
Evidence level: 4 **Study type:** Retrospective diagnostic study.	**Number of patients / samples:** Patients with histologically proven HCC (n = 278) and ICC (n = 42) from the DEGUM multicenter trial. **Inclusion:**Consecutive patients with a solid liver tumor visible at routine US were recruited for CEUS at the time of their US examination, after contraindications for US contrast agent were ruled out. **Exclusion:** Patients with liver lesions diagnosed from characteristic characteristic B-mode echomorphology, such as patients with cysts and typical hemangiomas, as well as lesions with clear signs of malignancy were not included. **Reference standard:** No reference standard was used. All samples were identified by biopsies. **Validation:** Comparison of tumor vascularization and CEUS for the characterization of HCC and ICC. **Blinding:** No blinding was performed. **Inclusion of clinical information:** No. **Dealing with ambiguous clinical findings:** -	**Results:** An underlying liver cirrhosis was found in 214/278 patients with HCC (76.9 %) and 7/42 patients with ICC (16.7 %). In CEUS, HCC showed a global arterial hyperenhancement compared to ICC (HCC: tumor center: 60.3 %; tumor periphery: 75 %; ICC: tumor center: 16.7 %; tumor periphery: 40.5 %). ICC showed an initial contrast enhancement primarily at the tumor periphery (ICC: 85.7 % vs. HCC: 61 %) followed by an early portalvenous contrast washout in the tumor center (ICC: 85.8 % vs. HCC: 49.8 %) and tumor periphery (ICC: 66.7 % vs. HCC: 32.6 %). HCC showed a delayed contrast washout (late phase hypoenhancement: HCC: 75 % vs. ICC: 92.9 %). **Author conclusions:** "Tumor-specific vascularization patterns in CEUS have a high diagnostic impact on the overall high diagnostic accuracy of CEUS for the differential diagnosis of hepatic tumors in clinical practice. ICC is a very rare differential diagnosis in cirrhotic patients. CEUS can demonstrate differences in the vascularization pattern in the comparison between HCC and ICC. The majority of HCCs showed intratumoral contrast hyperenhancement in the arterial phase, whereas contrast washout is delayed beginning in the portal-venous phase. Initial contrast enhancement at the tumor periphery with early hypoenhancement in the portal-venous and late phase is a characteristic pattern of ICC."

Methodical Notes

Funding Sources: not described.

COI: not described.

Notes: Evidence level: 4 Prospective studies without blinding and reference standard, Retrospective studies without reference standard or without blinding; Small study groups
Notes: No reference standard was applied. No blinding was performed.

Wildner, D. et al. Dynamic contrast-enhanced ultrasound (DCE-US) for the characterization of hepatocellular carcinoma and cholangiocellular carcinoma. Ultraschall Med. 35. 522-7. 2014

Evidence level/Study Types	Population	Outcomes/Results
Evidence level: 4 **Study type:** Prospective diagnostic study.	**Number of patients / samples: Inclusion criteria** :not described. **Population:** 43 patients, 23 with proven HCC, 16 with ICC. 30 men and 13 women; mean (range) age: 67 years (41 – 83). **Reference standard:** Comparison of perfusion kinetics of HCC and ICC using dynamic contrast-enhanced ultrasound (DCE-US). No reference standard was used. **Validation:** Not investigated. **Blinding:** no blinding was performed. **Inclusion of clinical information:** Not reported. **Dealing with ambiguous clinical findings:** -	**Results:** No statistical difference of the arterial DCEUS parameters was found between HCC and ICC. Contrast enhancement of the portal venous and late phases showed significantly lower values in the ICC group indicating early wash-out of the contrast agent: mTTI (p = 0.0209): HCC 118.4 s (SD± 88.4); ICC 64.8 s (SD± 49.7). FT (p = 0.0433): HCC 42.5 s (SD± 27.7); ICC 27.7 s (SD± 16.2). The percental loss of intensity at a definite time point after PEwas significantly higher in ICC than in HCC lesions. **Author conclusions:** "DCE-US is able to detect and quantify differences in perfusion kinetics between HCC and ICC. Whereas arterial contrast enhancement patterns may overlap between HCC and ICC, a timed characterization of wash-out kinetics may offer an additional tool to characterize HCC and ICC. The presence of a rapid loss of signal intensity in the early portal venous phase is significantly higher in ICC than in HCC lesions."

Methodical Notes

Funding Sources: not stated.

COI: not stated.

Notes: Evidence level: 4 Prospective studies without blinding and reference standard, Retrospective studies without reference standard or without blinding Small study groups
Notes: No clinical information is available. No blinding was performed. Different methods of diagnosis confirmation were applied (either histology, MRI, CEUS). No reference standard was used, instead the same method was used to distinguish between two tumor entities.

Schlüsselfrage:

HCC 09
Welche bildgebende Untersuchungsmethode soll bei Patienten mit HCC zur Ausbreitungsdiagnostik angewendet werden?

Inhalt: *2 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Davenport, M. S. 2013	3	prospective observational study (Cohort Study)
Song, K. D. 2015	4	retrospective,observational, prognostic study

OXFORD (2011) Appraisal Sheet: Prognostic Studies: *1 Bewertung(en)*

Song, K. D. et al. Subcentimeter hypervascular nodule with typical imaging findings of hepatocellular carcinoma in patients with history of hepatocellular carcinoma: natural course on serial gadoxetic acid-enhanced MRI and diffusion-weighted imaging. Eur Radiol. 25. 2789-96. 2015

Population	Intervention	Outcomes/Results
Evidence level: 4 **Study type:** retrospective,observational, prognostic study **Number of Patient:** a total of 39 patients (46 SHNHRs) with history of HCC were included in the study. **Recruitung Phase:** November 2012 and February 2013 **Inclusion Criteria:** patients who underwent liver MRI at this institution and have a history of previous treatment for HCC with a proven SHNHRs. **Exclusion Criteria:** Among the 204 patients with SHNHRs, patients who - had multiple (n≥4) SHNHRs (n=18), - coexistent overt HCC (n=107), - local tumour progression found at the site of previous treatment with TACE or RFA (n=16), - had SHNHRs which were already	**Intervention:** serial gadoxetic acid-enhanced MRI and DWI follow-up every 2-3 months for patients with a subcentimeter hypervascular nodule at high-risk for developing into HCC (SHNHR) **Comparison:** none	**Primary:** overall cumulative rate of progression to overt HCC Hazard ratio of risk factors of progression to overt HCC **Secondary:** Tumour volume doubling time (TVDT) **Results:** - overall cumulative rate of progression to overt HCC at 3,6, 9, and 12 months was 13.9 %, 61.7 %, 83.2 %, and 89.9 %,respectively. - Initial nodule size was the only significant predictor of progression to overt HCC in univariate (HR=1.494; 95 % CI:1.162, 1.920;P= 0.002) and multivariate analyses (HR=1.468; 95 % CI: 1.130, 1.906;P=0.004). - sensitivity and specificity of cut-off value of 5.5 mm for predicting progression to overt HCC at 12 months were 0.671 and 0.829, respectively. - The TVDT was 65.2±45.0 days (mean±standard deviation). **Author's Conclusion:** In

detected on previous MRIs before the study period (n=5), - and were treated immediately with TACE or RFA with no follow-up MRI due to patient preference (n=19) were excluded .		conclusion, the progression rate of SHNHR to overt HCC within 12 months was high (89.9 %) in patients with a history of HCC. The initial size of SHNHR was an important predictor for progression to overt HCC.

Methodical Notes

Funding Sources: The authors state that this work has not received any funding.

COI: The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

Randomization: none

Blinding: none

Dropout Rate/ITT-Analysis: none

Notes: Retrospective study without blinding

NEWCASTLE - OTTAWA Checklist: Cohort: *1 Bewertung(en)*

Davenport, M. S. et al. Comparison of acute transient dyspnea after intravenous administration of gadoxetate disodium and gadobenate dimeglumine: effect on arterial phase image quality. Radiology. 266. 452-61. 2013

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 3 **Study type:** prospective observational study (Cohort Study)	**Funding sources:** There was no industry support for this study. **Conflict of Interests:** No relevant conflicts of interest to disclose **Randomization:** - The choice of contrast material was physician-dependent, not randomized, and chosen when the examination was assigned an imaging protocol. - images of precontrast and dynamic postcontrast (arterial, venous, or late dynamic or extracellular) phases were anonymized and randomized for review. **Blinding:** - patients and physicians were not blinded to the type of GBCM administered. - images of precontrast and	**Total no. patients:** 99 administrations of gadoxetate disodium in 96 patients 99 administrations of gadobenate dimeglumine in 97 patients **Recruiting Phase:** March 19, 2011, to August 31, 2011 **Inclusion criteria:** **Exclusion criteria:**	**Interventions:** gadobenate dimeglumine (0.1 mmol per kilogram of body weight, maximum dose, 20 mL) as contrast material for MRI **Comparison:** gadoxetate disodium (10 mL, n = 97; 8 mL, n = 1; 16 mL, n = 1) as contrast material for MRI

	dynamic postcontrast (arterial, venous, or late dynamic or extracellular) phases were anonymized and randomized for review. The hepatobiliary phase images were not included to prevent inadvertent unblinding. **Dropout rates:**		
Notes:	The interview regarding adverse events did not include standardized questions. The paper does not comply with the PICO questions. **Author's conclusion:** Intravenous gadoxetate disodium can result in acute transient dyspnea that can have a deleterious effect on arterial phase MR image quality and occurs significantly more often than with intravenous gadobenate dimeglumine.		
Outcome Measures/results	**Primary** incidence of acute transient dyspnea effect of this adverse event on arterial phase image quality **Secondary**	**Results: Subjective Dyspnea (Self-reported, Transient after Injection)** Total no. of events: Gadoxetate Disodium 14 (14.1%) vs. gadobenate dimeglumine 5 (5.1%), p value 0.05 **New Severe Motion During Arterial Phase (Mean Motion Score ≥4, No Severe Motion before GMBC Administration)** Total no. of events: Gadoxetate Disodium 17 (17.1%) vs. gadobenate dimeglumine 1 (1.0%), p value >0.0001 This effect did not extend to venous (1% vs 2% , P=0.99) or late dynamic or extracellular (2% vs 0%, P=0.5) phases.	

Schlüsselfrage:

HCC 11
Welches bestehende Staging System soll bei Patienten mit HCC verwendet werdern?

Inhalt: *11 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Chan, A. C. 2013	2	Retrospective Prognostic study
Chevret, S. 1999	3	Prospective Prognostic study, F,BE,CA
Johnson, P. J. 2015	3	Multicenter prognostic study
Kitai, S. 2008	3	Retrospective prognostic study
Leung, T. W. 2002	3	Prospective prognostic study.
Marrero, J. A. 2005	3	Prognostic, prospective study.
Pinato, D. J. 2017	2	Retrospective diagnostic study, mutlicentric (USA, Asia, Europe)
Pinyol, R. 2018	2	Subgroup of Randomized controlled trial
Toso, C. 2015	2	Prospective prognostic study, multicentric
Vitale, A. 2009	3	Prognostic study.
Yau, T. 2014	3	Retrospective prognostic study

OXFORD (2011) Appraisal Sheet: RCT: *1 Bewertung(en)*

Pinyol, R. et al. Molecular predictors of prevention of recurrence in HCC with sorafenib as adjuvant treatment and prognostic factors in the phase 3 STORM trial. Gut. . . 2018

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** Subgroup of Randomized controlled trial **Number of Patient:** 202 collected samples, 188 were suitable for the study (hereinafter, BIOSTORM cohort) used were Formalin-fixed paraffin-embedded (FFPE) tissue	**Intervention:** Sorafenib **Comparison:** Placebo	**Primary:** Identify biomarkers predicting sorafenib efficacy in preventing HCC recurrence in terms of recurrence-free survival (RFS). RFS was defined as the time from randomisation to the first documented disease recurrence by independent radiological assessment or death by any cause, whichever happened first. **Secondary:** Define prognostic biomarkers of RFS and/or validate those previously reported. **Results:** None of the biomarkers tested (related to

blocks from patients with HCC. (Sorafenib n= 83, Placebo n=105). **Recruitung Phase:** STORM trial - 2008 and 2010 **Inclusion Criteria:** **Exclusion Criteria:** Patients who had undergone less than one treatment cycle (4 weeks) were excluded from the predictive biomarker analysis (sorafenib: n=9 out of 83; placebo: n=6 out of 105).		angiogenesis and proliferation) or previously proposed gene signatures, or mutations predicted sorafenib benefit or recurrence. A newly generated 146-gene signature identifying 30% of patients captured benefit to sorafenib in terms of RFS (p of interaction=0.04). These sorafenib RFS responders were significantly enriched in CD4+ T, B and cytolytic natural killer cells, and lacked activated adaptive immune components. Hepatocytic pERK (HR=2.41; p=0.012) and microvascular invasion (HR=2.09; p=0.017) were independent prognostic factors. **Author's Conclusion:** Overall, our biomarker BIOSTORM study (A) established lack of predictive value of sorafenib response for previously reported molecular biomarkers, (B) generated a predictive 146-gene signature to discriminate patients where sorafenib would prevent recurrence after resection, (C) established pERK and microvascular invasion as independent prognostic tools to identify recurrences in patients resected from early HCC tumours, and (D) did not validate previously reported signatures associated with recurrence. For any of these biomarkers to be used as surrogates of efficacy of sorafenib recurrence prevention, a validation study using an independent cohort and conducted by independent investigators would be required.

Methodical Notes

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COI: JML, JB, VM and AEC received research support and consultancy fees from Bayer. AV and SS received consultancy fees from Bayer. CP and GM are employees of Bayer HealthCare Pharmaceuticals.

Randomization: yes

Blinding: yes

Dropout Rate/ITT-Analysis: -

Notes:
Subgroup analysis of STORM phase 3 trial. No classical RCT but also no classical prognostic study type. Therefore the intervention (Sorafenib) isn't in line with the PICO question (intervention BCLC, TNM, Okuda, ...) and the relevance for the PICO question from methodological point of view unclear.

OXFORD (2011) Appraisal Sheet: Prognostic Studies: *10 Bewertung(en)*

Chan, A. C. et al. Evaluation of the seventh edition of the American Joint Committee on Cancer tumour-node-metastasis (TNM) staging system for patients undergoing curative resection of hepatocellular carcinoma: implications for the development of a refined staging system. HPB (Oxford). 15. 439-48. 2013

Population	Intervention	Outcomes/Results
Evidence level: 2 **Study type:** Retrospective Prognostic study **Number of Patient:** 516 **Recruitung Phase:** 1995-2004 **Inclusion Criteria:** Positive for HCV RNA for at least 2 time points with a>6 month interval, had no evidence of HBV infection, had no other potential causes of chronic liver disease (i.e. alcohol consumption<80 g/day, no history of hepatotoxic drug use and negativetests for autoimmune hepatitis, primary biliary cirrhosis, hemochromatosis and Wilson's disease), had a follow-upperiod>3 years, had no evidence of HCC at study entryand for at least 3 years from the start of the follow-up per-iod, had no antiviral therapy involving interferon and/ or ribavirin, had ALT measurements taken more than twice annually and had ALT values <40 IU/L. **Exclusion Criteria:** see inclusion	**Intervention: FIB4 index:** The FIB-4 index was calculated at the start of follow-upusing the following formula: FIB-4 index=AST [IU/L] X age [years]/platelet count [10^9/L] X ALT [IU/L]. atients were grouped according to theirFIB-4 index score as follows:≤2.0 (n=226),>2.0 and≤4.0 (n=169), and>4.0 (n=121) **FIB-4 and AFP composite score:** We established a new scoring system that combines the FIB-4 index and AFP. AFP was measured in 477 patients at the start of follow-up period. AFP levels categorized as ≤5.0 ng/mL,>5.0 and ≤10.0 ng/mL,and>10.0 ng/mL were scored as 1, 2 and 3, respectively.The FIB-4 index, categorized as ≤2.0,>2.0 and ≤4.0, and>4.0, were scored as 1, 2 and 3, respectively. The totalscore was the sum of the FIB-4 index and AFP scores. **Comparison:** -	**Primary:** HCC **Secondary:** - **Results: Population:** Median age was 66 years, Men (55.8%). The median FIB-4 index and serum AFP levels were 2.2 and 3.2 ng/mL. The median follow-up period was 11.3 years. HCC developed in 60 of 516 patients (11.6%). The incidence rate of HCC at 5 and 10 years were 2.6% and 17.6%. **Results:** Factors associated with the incidence of hepatocarcinogenesis Factors that were significantly associated with the incidence of HCC in the multivariate analysis were FIB-4 index>2.0 HR 7.690 (2.636,–22.438;P<0.001) and FIB-4 index>4.0 (HR, 8.991 (3.088–26.178;P<0.001), AFP>5 ng/mL (HR, 2.742 (1.497–5.023;P<0.001 and AFP>10 ng/mL (HR,4.915 (2.353–10.267;P<0.001) and total bili-rubin>1.2 mg/dL (HR, 2.142 1.115–4.117;P=0.022). Incidence of hepatocarcinogenesis based on the FIB-4 index and AFP: The FIB-4 index>2.0 and≤4.0 group had a significantlyhigher risk than the FIB-4 index≤2.0 group (P<0.001). The group with AFP>10.0 ng/mLwas at the highest risk for HCC development. Relationship between the FIB-4 index and AF: There were no significant correlation between the FIB-4index and AFP based on Spearman's rank correlation. Incidence of hepatocarcinogenesis based on the combinedFIB-4 index and AFP score: The incidence rate of HCC increased as the score increased (2vs3, P<0.001; 3vs4 points, P=0.070; 4vs5 points, P=0.011; and 5vs6 points;P=0.270). This scoringsystem reflected patient survival well. **Author's Conclusion:** "A scoring system for hepatocarcinogenesisthat combines the FIB-4 index and AFP

		predicted patientoutcomes with excellent discriminative ability. The FIB-4index is strongly associated with the risk of HCC in HCVcarriers with normal ALT levels."

Methodical Notes

Funding Sources: "There is no grant or other financial support for this study"

COI: "The authors declare no conflict of interests."

Randomization: -.

Blinding: -

Dropout Rate/ITT-Analysis: -

Notes: Evidence level 2: INception cohort study
Outcome criteria were not subjective to blinding

Chevret, S. et al. A new prognostic classification for predicting survival in patients with hepatocellular carcinoma. Groupe d'Etude et de Traitement du Carcinome Hepatocellulaire. J Hepatol. 31. 133-41. 1999

Population	Intervention	Outcomes/Results
Evidence level: 3 **Study type:** Prospective Prognostic study, F,BE,CA **Number of Patient:** 761 **Recruitung Phase:** 1990-1992 **Inclusion Criteria:** HCC paitents in 24 centers in France, Belgium and Canada. Diagnosis was confirmed by either histology, cytology, or the association of cirrhosis and liver tumor as observed at ultrasonography (US) or computed tomography scan (CT-scan). **Exclusion Criteria:** except 18 patients with liver transplantation who were excluded.	**Intervention: Aim:** Classification for prediction of survival in HCC patients. Predictors: Karnofsky index, Cirrhosis, serum bilirubin, albumin, phosphatase, prothrombin activity, alpha fetoprotein, US tumor type (uninodular, multinodular, diffuse, heterogeneous parenchyma), portal obstruction. **Comparison:** -	**Primary:** Survival **Secondary:** - **Results: Population:** 671 (88%) of the 761 patients were male and the median age was 64 (range 24-99). Cirrhosis was observed in 545 of the 598 patients with liver biopsy, and clinically presumed in 67 additional patients. Of the 612 patients with cirrhosis, 256 (42%) were classified in Child-Pugh class A, 220 (36%) in class B, and 136 (22%) in class C. **Results: Overall survival:** The overall survival rate was 30.9% at 1 year , 18.8% at 2 years, and 13.2% at 3 years. Cause of death, reported in 333 deceased patients (80%), was mostly liver failure (185 deaths), gastrointestinal hemorrhage (60 deaths) and/or sepsis (24 deaths). **Prognostic factors** 5 were selected at the 0.0001 level: Karnofsky index 50 pmoUl RR=2.1, (1.7-2.6), serum alkaline phosphatase at least twice the upper limit of normal range RR 1.6, (1.3-2.0), serum alpha-fetoprotein >35 pg/l RR=1.7, (l.4,2.1) and US portal obstruction RR=1.3,95% (1.1,1.7). Three risk groups with different l year survival rates (72%, 34%, 7%) were derived, and independently validated in the test sample (79%, 31%, 4%). **Author's Conclusion:** This classification could be useful in the assessment of

		prognosis from homogeneous groups of patients with respect to their expected outcome.

Methodical Notes

Funding Sources: This work was supported by grants from Assistance Publique-Hopitaux de Paris

COI: none stated.

Randomization: -

Blinding: All CT-scans were reviewed by two authors blinded to the clinical data:

Dropout Rate/ITT-Analysis: 24 patients (3.5%) were lost to follow-up, as a consequence of a move to another country.

Notes: Evidence level 3: Cohort study or control arm of randomized trial.

Johnson, P. J. et al. Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach-the ALBI grade. J Clin Oncol. 33. 550-8. 2015

Population	Intervention	Outcomes/Results
Evidence level: 3 **Study type:** Multicenter prognostic study **Number of Patient:** Japan: 2.599 patients from five centers (etiology was predominantly HCV) China: 1.112 patients (the etiology was predominantly hepatitis B virus) Europa: Spain: 843 patients (etiology was predominantly HCV or alcohol abuse). Europe: UK (Birmingham and Newcastle) 1.356 patients (various etiologies). United States (Boston): 509 patients (predominantly HCV or alcohol abuse). We had access to a data set including 1,132 patients receiving sorafenib for unresectable advanced HCC within the control groups of two international clinical trials. Of the 1,028 patients with complete data, 96% were classified as C-P grade A. 501 consecutive patients with cirrhosis but no HCC. The intent of this cohort is to	**Intervention:** - prognostic factors for the future model were undertaken on the entire Japanese cohort because this was the largest and most complete data set. The entire Japanese cohort (n = 2,599) was then randomly split into two groups, the training (n = 1,313) and validation sets (n =1,286). - The discriminatory performance of the ALBI model and C-P grade was analysed for each of the Japanese training and validation sets and for the European, Chinese, and US cohorts. **Comparison:**	**Primary:** Survival was measured from the date of diagnosis (first presentation with HCC) to date of death or last follow-up. **Secondary:** **Results:** Survival: Japanese patients had the highest median survival at 47.2 months, followed by the United States, Europe, and China at 18.6, 17.8, and 7.2 months (including patients undergoing liver transplantation), respectively. Visual inspection of the resulting KM curves showed equally good discrimination between the three ALBI prognostic groups and the C-P grade. This is reflected by the Harrell's C and Somers' D scores, which were similar. Applying the model to the other cohorts, visual inspection of the curves again indicated that the discrimination between the three ALBI groups was as good as that of the C-P grade. **Author's Conclusion:** The ALBI grade offers a simple, evidence-based, objective, and discriminatory method of assessing liver function in HCC that has been extensively tested in an international setting. This new model eliminates the need for subjective variables such as ascites and

provide evidence that the ALBI model is an actual measure of liver function, rather than, in some surrogate manner, a measure of tumor stage. **Recruitung Phase:** Sie paper. Recruition: data from major HCC centers and from international HCC clinical trials. The centers were chosen to ensure the inclusion of patients of all disease stages and representative of a broad range of etiologies and geographical regions. **Inclusion Criteria:** The patients from clinical trials all had advanced disease and were treated with the current standard of care, sorafenib. **Exclusion Criteria:** Patients undergoing liver transplantation (n= 125 and n = 168 in Spain and United Kingdom, (n 63 in Boston) were excluded, respectively.		encephalopathy, a requirement in the conventional C-P grade.

Methodical Notes

Funding Sources: see text

COI: see text

Randomization: n.s.

Blinding: n.s.

Dropout Rate/ITT-Analysis: -

Notes: Cohort study or control arm of randomized trial.

Note: Significance of the results unclear, because the results are collected by "visual inspection" of curves.

Kitai, S. et al. Validation of a new prognostic staging system for hepatocellular carcinoma: a comparison of the biomarker-combined Japan Integrated Staging Score, the conventional Japan Integrated Staging Score and the BALAD Score. Oncology. 75 Suppl 1. 83-90. 2008

Population	Intervention	Outcomes/Results
Evidence level: 3 **Study type:** Retrospective prognostic study **Number of Patient:** 1173	**Intervention: Score for tumor staging:** c-JIS Score(summation of the Child-Turcotte-	**Primary:** Overall survival. **Secondary:** - **Results:** **Population:**1,173

Recruitung Phase: 1990-2002 **Inclusion Criteria:** 4525 Consecutive HCC patients, diagnosed at 5 Japan Center; 1173 fulfilling the following criteria: several serum liver function tests (albumin, bilirubin, prothrombin time, ammonia and transaminase, etc.) and the 3 tumor markers (AFP, AFP-L3 and DCP) were measured at the time of diagnosis. Diagnosis of HCC based on histological or reliable clinical criteria fulfilling the following conditions: a compatible clinical background (association with liver cirrhosis or viral hepatitis) with typical imaging findings and a rising trend of the three tumor markers. Typical imaging findings include a high-density mass in the arterial phase dynamic CT with a low-density mass in the portal phase dynamic CT or MRI. A liver biopsy was performed in cases that did not show typical imaging findings or an increase in any tumor markers. **Exclusion Criteria:** -	Pugh stage score and the TNM stages by the Liver Cancer Study Group of Japan (LCSGJ) bm-JIS Score (c-JIS score and the values of the three tumor markers AFP, AFP-L3 and DCP.) **Comparison:** BALAD Score	patients; median age 68 years; predominantly males (70.9%). Most frequent cause of HCC was an HCV infection (74.5%). 70.8% of the patients were classified as Child-Pugh stage A. Accordingly, radical treatments were performed in the majority of patients (28.9%). **Results:** These three staging systems effectively predicted the patient survival. When accounting for the best prognostic sub-group of each staging systems (i.e. score of 0), there were significant differences between the bm-JIS score and the BALAD score and, likewise, between the c-JIS score and the BALAD score. The likelihood ratio Chi ^{2} test showed the highest value (370.564) and the Akaike information criterion value (3981.440) was lowest in the bm-JIS score. **Author's Conclusion:** "In conclusion, the bm-JIS scoring system showed better stratification ability than the BALAD score and the c-JIS score. Therefore, the residual liver function, the grade of cancer and these three tumor markers should be taken into account in a clinical staging system in order to more accurately predict the prognosis of patients with HCC."

Methodical Notes

Funding Sources: not stated

COI: "The authors declare that they have no financial conflict of interest."

Randomization: not randomized.

Blinding: not blinded.

Dropout Rate/ITT-Analysis: Not described.

Notes: Evidence level 3: Cohort study or control arm of randomized trial.

Leung, T. W. et al. Construction of the Chinese University Prognostic Index for hepatocellular carcinoma and comparison with the TNM staging system, the Okuda staging system, and the Cancer of the Liver Italian Program staging system: a study based on 926 patients. Cancer. 94. 1760-9. 2002

Population	Intervention	Outcomes/Results
Evidence level: 3 **Study type:** Prospective prognostic study. **Number of Patient:** 926 **Recruitung Phase:** 1996-2002 **Inclusion Criteria:** All consecutive adult patients (age ≥ 18 years) who were diagnosed with HCC and registered in the Joint Hepatoma Clinic at the Prince of Wales Hospital from 1996 to 1998 were included in this study. 926 patients with complete survival data and a confirmed diagnosis. Patients were diagnosed with HCC on the basis of either histologic examination of tumor tissue or serum AFP ≥ 500 ng/mL with radiologic evidence of space-occupying lesion(s) in the liver. Survival was measured from the date of diagnosis to the date of death or last contact for surviving patients. The study population was censored on September 30, 1999. The study sample was split randomly once into two sets: a training set (75% of the population) and a confirmatory set (25% of the population). The training set was used to construct the new CUPI, and the confirmatory set was used to validate the index. **Exclusion Criteria:** 11% of these patients (109 of 1035 patients) were excluded due to incomplete survival data, but they had no systemic differences compared with the study cohort.	**Intervention: Aim:** Construct a new prognostic index for patients with HCC, the Chinese University Prognostic Index (CUPI), and to compare it with existing staging systems in terms of their ability to classify patients into different risk groups. **Prognostic factor: CUPI:** The CUPI score for an individual patient was the sum of the weights of the relevant prognostic factors. "The CUPI was constructed by adding the following factors into the TNM staging system: total bilirubin, ascites, alkaline phosphatase, alpha fetoprotein, and asymptomatic disease on presentation" The probability of a patient surviving for 3 months was estimated by using the CUPI in a logistic regression model. The high-risk group was defined as patients with a probability > 70% of dying within 3 months. Patients with a probability < 30% of dying within 3 months were classified as the low-risk group, and the intermediate-risk group had a probability between 30% and 70% of dying within 3 months. **Comparison:** Othe staging systems: TNM, Okuda	**Primary:** Survival. **Secondary:** - **Results: Population:** There were 769 male patients and 157 female patients in the study cohort with a mean age of 58.5 years (range, 22–88 years). Positive hepatitis B and C serology was found in 79% and 3.3% of male and female patients, respectively. The average proportion of missing data was 1.9% for the 19 study variables, and the missing data were random. All patients in the sample population were ethnic Chinese. **Results: Prognostic factores** TNM staging was a highly significant predictor (P = 0.0001) for survival. According to the likelihood test on the two nested models (Model 1 and Model 2), the addition of asymptomatic disease on presentation, AFP, total bilirubin (TB), alkaline phosphatase (ALP), and as(cites to TNM staging significantly improved the estimation (P= 0.00001). **Prognostic Index** The difference in survival among different risk groups classified by the CUPI (P = 0.00001), the TNM staging system (P = 0.00001), the Okuda staging system (P = 0.00001), and the CLIP score (P = 0.00001) were highly significant. However, patients identified with Okuda Stage I and II disease were not significantly different with regard to survival (P = 0.27). Unlike the two other staging systems, the CUPI was highly significant during during the whole period of follow-up. With the goodness- of-fit test, it was found that the CUPI (P = 0.001) was more predictive of survival compared with the CLIP prognostic score (P = 0.001). **Author's Conclusion:** "In the study population of patients with mainly hepatitis B-associated HCC, the CUPI was more discriminant than the TNM staging system, the Okuda staging systems, or the CLIP prognostic score in classifying patients into different risk groups and

		was better at predicting survival. The CUPI needs to be validated by different cohorts of patients before it can be recommended for general use."

Methodical Notes

Funding Sources: Not stated

COI: Not stated

Randomization: -

Blinding: No blinding was performed.

Dropout Rate/ITT-Analysis: No description.

Notes: Evidence level 3: Cohort study or control arm of randomized trial.
No description of blinding or loss to follow-up. Short follow-up (33 weeks).

Marrero, J. A. et al. Prognosis of hepatocellular carcinoma: comparison of 7 staging systems in an American cohort. Hepatology. 41. 707-16. 2005

Population	Intervention	Outcomes/Results
Evidence level: 3 **Study type:** Prognostic, prospective study. **Number of Patient:** Consecutive patients with HCC. Diagnosis of HCC was based on histology in 192 patients and on nonhistological criteria in 52 patients. Tumor staging was performed in 209 patients who had chest CT. **Recruitung Phase:** January 1, 2000, and December 31, 2003. Follow-up was censored on May 31, 2004. **Inclusion Criteria:** HCC diagnosis based on histology or on nonhistological criteria. **Exclusion Criteria:** -	**Intervention:** UNOS-modified tumor node metastasis (TNM), Barcelona Clinic Liver Cancer (BCLC), Cancer of Liver Italian Program (CLIP), Japanese Integrated System (JIS), Groupe d'Etude de Traitement du Carcinoma Hepatocellulaire (GRETCH), Chinese University Prognostic Index (CUPI), Okuda staging system. **Comparison:** see intervention	**Primary:** Survival. **Secondary:** - **Results: Survival:** The overall median survival of the entire cohort was 16.4 months (95% CI 12.9-19.8 mo) and the 1- and 3-year probability of survival was 58% and 29%,respectively. **Baseline predictors of survival:** After controlling for differences in baseline factors and MELD (to also control for hepatic function), a significantly better survival persisted among the patients who received treatment (those treated had a median survival of 13.2 mo vs. 2.8 mo in those untreated; P < .0001). Patients who underwent liver transplantation had the best survival. Cox regression analysis identified performance status (P < .0001), MELD score (P = .001), maximum tumor diameter (P = .001), and portal vein thrombosis (P=.001) as independent baseline predictors of survival for the entire cohort of HCC patients. Performance status of 0 and 1 were protective with hazard ratios of 0.07 (95% CI 0.02-0.16) and 0.46 (95% CI 0.31-0.69), respectively. **Staging system and survival:** TNM (stages II and III), JIS (stages 1, 2, and 3), CLIP (stages 1, 2, and 3), and GRETCH (stages B and C) systems had poor stratification of survival at the intermediate stages, while the BCLC, Okuda, and CUPI systems had a better stratification of survival across all stages. The BCLC system had: - the highest homogeneity (LR x2 76.8), indicating small

		differences in survival among patients in the same stages. - the highest discriminatory score (liner trend x2 28.7) compared with other systems. - the best monotonicity of gradient based on the LR x2 and linear trend x2. - the lowest Akaike information criterion, indicating that the model containing the BCLC system was the most informative when explaining the survival of HCC patients The BCLC was the only staging system that had a significant impact on theCox survival model when it was removed from the model containing all other staging systems (Log likelihood903.1; LR x2 42.7;P <.0001> **Author's Conclusion:** In conclusion, our study shows that measures of hepatic function (MELD score), performance status, tumor characteristics (size and presence of portal vein thrombosis), and the effect of treatment are predictors of survival in cirrhotic patients with HCC.We show that among the seven prognostic staging systems available for HCC, the BCLC system provided the best independent prediction of survival. The superior performance of BCLC may be related to the fact that it includes the same characteristics that had been identified as independent predictive variables in our cohort. Our results should be confirmed in a larger multicenter cohort to study the effect of multiple etiologies, ethnicity, and the effect of various treatments on overall survival. A consensus in prognostic staging for HCC is urgently needed to assure progress in the development of biomarkers for early detection and novel therapies.

Methodical Notes

Funding Sources: Supported by National Institutes of Health Grant CA864000 (Great Lakes New England Clinical Epidemiology Center of the Early Detection Research Network) (J. A. M.) and Grant DK064909 (J. A. M.).

COI: Nothing to report.

Randomization: -

Blinding: -

Dropout Rate/ITT-Analysis: -

Notes: Cohort study or control arm of randomized trial

Pinato, D. J. et al. The ALBI grade provides objective hepatic reserve estimation across each BCLC stage of hepatocellular carcinoma. J Hepatol. 66. 338-346. 2017

Population	Intervention	Outcomes/Results
Evidence level: 2 **Study type:** Retrospective diagnostic study, mutlicentric (USA, Asia, Europe) **Number of Patient:** 2426	**Intervention:** ALBI grade: based solely on albumin and bilirubin, as alternative to MELD. The ALBI grade was calculated using the following equation: linear predictor = (log10 bilirubin	**Primary:** Overall survival (OS). The primary clinical endpoint of the study was overall survival (OS), calculated from the date of initiation of treatment (surgery, first chemoembolization or initiation of sorafenib) to the date of death and/or last follow-up. Due to the significant heterogeneity in the study

Recruitung Phase: **Inclusion Criteria: Aim:** Validation of grading HCC by ALBI grade. **Inclusion:**Consecutively recruited patients diagnosed with HCC either on imaging or by histologic criteria. The patient population considered for this study was accrued aspart of routine clinical care and was not selected amongst clinical trial participants. **Exclusion Criteria:** Patients who underwent liver transplantation as primary therapy for HCC were excluded.	lmol/L x 0.66) + (albumin g/L x -0.085). The continuous linear predictor was further categorised into three different grades for prognostic stratification purposes: grade 1 (less than -2.60), grade 2 (between -2.60 and -1.39) and grade 3 (above -1.39). **Comparison:** -	population, survival analysis was stratified by treatment modality to include patients treated with curative resection and palliative patients amenable to locoregional therapies and systemic treatment with sorafenib. **Secondary:** **Results: Population:** NO overall demographics for age, sex. Instead each HCC intervention is regarded individually. F.e locoregional therapy cohort in the USA, in Europe, Asia. Age median 63-72. Male participants 71-80%. **Results:** Median OS was 54 months for the surgical cohort, whilst in the LRT cohorts survival ranged between 10 and 36 months, being worse in the LRT-USA cohort. Patient in the sorafenib cohort had a median OS of 9 months. **ALBI as predictor for OS:** "Analysis of survival by primary treatment modality confirmed the ALBI grade as a significant predictor of patient OS after surgical resection (p <0.001), transarterial chemoembolization (p <0.001) and sorafenib (p <0.001). Stratification by Barcelona Clinic Liver Cancer stage confirmed the independent prognostic value of the ALBI across the diverse stages of the disease, geographical regions of origin and time of recruitment to the study (p <0.001)." **Author's Conclusion:** "In summary, this study has validated the ALBI grade as an objective, inexpensive, readily available stratifying biomarker of poor liver reserve in HCC. Consideration should be given to its prospective validation in future clinical studies to facilitate its use in routine clinical practice."

Methodical Notes

Funding Sources: "DJP is supported by the National Institute for Health Research (NIHR) and has received grant funding from Action Against Cancer and the Imperial NIHR Biomedical Research Centre (BRC). This work was funded in part by the Academy of Medical
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COI: "The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript."

Randomization: -

Blinding: -

Dropout Rate/ITT-Analysis: -

Notes: Evidence level 2: Inception cohort study

Toso, C. et al. Total tumor volume and alpha-fetoprotein for selection of transplant candidates with hepatocellular carcinoma: A prospective validation. Hepatology. 62. 158-65. 2015

Population	Intervention	Outcomes/Results
Evidence level: 2 **Study type:** Prospective prognostic study, multicentric **Number of Patient:** 233 **Recruitung Phase:** 2007-2013 **Inclusion Criteria:** Webbased multicentric database, which prospectively includes data on patients with HCC listed for LT. TTV/AFP criteria were used for candidate selection. The composite criteria allowed access to listing for transplantation to patients with TTV ≤115 cm3 and AFP ≤400 ng/mL, in the absence of EHD and HCC MVI on radiology. All patients beyond the TTV/AFP cutoffs were eligible for listing if they could be downstaged to within criteria according to modified Response Evaluation Criteria in Solid Tumors and stabilized within the criteria for a minimum of 3 months. **Exclusion Criteria:** Patients with AFP >400 ng/ mL were excluded,	**Intervention:** TTV/AFP criteria for grading. Total tumor volumen, alpha fetoprotein. **Comparison:** Milan criteria. "Patients with AFP >400 ng/ mL were excluded, and, as such, the Milan group was modified to include only patients with AFP <400 ng/mL; these patients were compared to patients beyond Milan, but within TTV/AFP.	**Primary:** date and cause of waitlist dropout, post-transplant recurrence, and death. **Secondary:** - **Results: Population:** 233 patients with HCC were listed for LT; 43 females and 190 males, with a mean age of 57.1 6 6.4 years. Cirrhosis was most often related to HCV, HBV, and alcohol. The mean calculated MELD score was 9.9 6 4.9. At the time of listing, 195 patients were within Milan criteria and 38 beyond Milan, but within TTV/AFP. Most patients had a limited number of small HCCs; the median AFP was 11 ± 25 ng/mL. **Follow-up:** The average follow-up from listing was 33.9± 24.9 months. Risk of dropout was higher for patientsbeyond Milan, but within TTV/AFP (16 of 38; 42.1%), than for those within Milan (49 of 195 [25.1%]; P 5 0.033). **Survival:** Intent-to-treat survival from listing was lower in patients beyond Milan (53.8% vs. 71.6% at 4 years; P < 0.001). After a median waiting time of 8 months, 166 patients were transplanted, 134 within Milan criteria, and 32 beyond Milan but within TTV/AFP. **Reuccurence:** Transplanted patients demonstrated acceptable and similar recurrence rates (4.5% vs. 9.4%; P 5 0.138) and post-transplant survivals (78.7% vs. 74.6% at 4 years; P 5 0.932). **Author's Conclusion:** Based on the present prospective study, HCC LT candidate selection could be expanded to the TTV (≤115 cm3)/AFP (≤400 ng/mL) criteria in centers with at least 8-month waiting time. An increased risk of dropout on the waiting list can be expected, but with equivalent and satisfactory post-transplant survival.

Methodical Notes

Funding Sources: "The study was supported by the University of Alberta Liver Transplant Program Academic Fund and the Arte`res Foundation."

COI: "Potential conflict of interest: Prof. Dufour advises Bristol-Myers Squibb, Novartis, AbbVie, and Gilead. He received grants from Bayer."

Randomization: -

Blinding: -

Dropout Rate/ITT-Analysis: Dropout rates and cause were part of the outcomes. ITT analysis was performed.

Notes: Evidence level 2: Inception cohort study

Vitale, A. et al. Validation of the BCLC prognostic system in surgical hepatocellular cancer patients. Transplant Proc. 41. 1260-3. 2009

Population	Intervention	Outcomes/Results
Evidence level: 3 **Study type:** Prognostic study. **Number of Patient:** 715 HCC patients were prospectively enrolled. **Recruitung Phase:** 2000 –2007. Follow-up data were collected until December 31, 2007. **Inclusion Criteria:** HCC diagnosis according to EASL criteria or histology and Child A or B score in patients undergoing surgery. **Exclusion Criteria:** -	**Intervention:** BCLC **Comparison:** Okuda, CLIP (both part of the prospective observational study), and retrospective applied analysis for UNOS and JIS.	**Primary:** Survival in a surgical population. **Secondary:** - **Results: Prognostic Ability of Staging Systems in Surgical Patients:** BCLC classification is the only staging system showing a significant discriminative ability in terms of survival prediction , namely calculated 3-year survivals of 81%, 56%, and 44% for BCLC stages A, B, and C, respectively (P = .03). **Prognostic Role of Surgery in Different BCLC Stages:** Operative treatment was a significant predictor of survival among all evaluated BCLC stages. In fact, the 3-year survival rates of surgical versus nonsurgical patients in various stages were: 81% versus 52% in BCLC A stage (P =.02); 56% versus 13% in BCLC B stage (P = .03); and 44% versus 0% in BCLC C stage (P= .02). **Author's Conclusion:** In conclusion, this study confirmed the potential usefulness of the BCLC staging system to predict survival of HCC patients and to design randomized trials for specific therapeutic subgroups of patients undergoing surgery. However, the present analysis confirmed the prognostic benefit of surgery in each BCLC stage.

Methodical Notes

Funding Sources: n.s.

COI: n.s.

Randomization: -

Blinding: -

Dropout Rate/ITT-Analysis: -

Notes: Prognostic cohort study or control arm of randomized trial.

Yau, T. et al. Development of Hong Kong Liver Cancer staging system with treatment stratification for patients with hepatocellular carcinoma. Gastroenterology. 146. 1691-700.e3. 2014

Population	Intervention	Outcomes/Results
Evidence level: 3 **Study type:** Retrospective prognostic study **Number of Patient:** 3856 **Recruitung Phase:** 1995-2008 **Inclusion Criteria:** HCC patients at Queen Mary Hospital in Hong Kong. HCC diagnosis was confirmed either by histology or cytology, increased a-fetoprotein level (≥400 ng/mL), or bytypical radiologic appearance. Staging mostly by contrast computed tomography scan. **Exclusion Criteria:** 9 pediatric patients and 63 patients who died or were censored within 7 days after the first consultation and received no treatment were excluded.	**Intervention:** Prognostic Classification Scheme Hong Kong Liver Cancer (HKLC) **Comparison:** Barcelona Clinic Liver Cancer (BCLC)	**Primary:** Survival **Secondary:** **Results: Population:** 3856 eligible adult HCC; Median age at presentation was 58years (range, 18–97 y). Men (81.90%); predominantly hepatitis B carriers(80%); 73% had underlying Child–Pugh class A liver function, 21% had class B liver function, and only 6% had class C liver function. About 59% of patients had a tumor size >5 cm or had diffuse-type tumor, and 48% of patients had a solitary tumor. Extrahepatic vascular involvement or metastasis was present in 20.85% of patients. Median follow-up time was 11.68 months (range, 0.03–182.21 mo). Among the 3856 patients, 1968 (51.04%) and 1888 patients (48.96%) were assigned randomly to the training set and the test set. **Results:** HKLC system had significantly better ability than the BCLC system to distinguish between patients with specific overall survival times (area under the receiver operating characteristic curve values, approximately 0.84 vs 0.80; concordance index, 0.74 vs 0.70). HKLC identified subsets of BCLC intermediate- and advanced-stage patients for more aggressive treatments than what were recommended by the BCLC system, which improved survival outcomes. Of BCLC-B patients classified as HKLC-II in our system, the survival benefit of radical therapies, compared with transarterial chemoembolization, was substantial (5-year survival probability, 52.1% vs 18.7%; P < .0001). In BCLC-C patients classified as HKLC-II, the survival benefit of radical therapies compared with systemic therapy was even more pronounced (5-year survival probability, 48.6% vs 0.0%; P < .0001). **Author's Conclusion:** "In conclusion, this study has established a new prognostic classification scheme, the HKLC staging classification, which may provide better prognostic classification than BCLC staging and may be effective in identifying patients suitable for more aggressive treatments, hence yielding a better survival outcome."

Methodical Notes

Funding Sources: not stated

COI: The authors disclose no conflicts.

Randomization: "Among the 3856 patients, 1968 (51.04%) and 1888 patients (48.96%) were assigned randomly to the training set and the test set."

Blinding: no blinding

Dropout Rate/ITT-Analysis: not stated

Notes: Cohort study or control arm of a randomized trial.

Schlüsselfrage:

HCC 12
Wann ist eine Operation bei einem Patienten mit HCC indiziert, wie wird diese durchgeführt, wie soll die Nachsorge erfolgen?

Inhalt: *13 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Bruix, J. 2015	2	RCT, multi-institutional (America, Asia, Europe)
Chen, M. S. 2006	2	RCT, single center (China)
Eguchi, S. 2008	3	nationwide follow-up survey study (Japan)
Feng, K. 2012	2	RCT, single center (China)
Huang, J. 2010	2	RCT, single center (China)
Lee, J. H. 2015	2	RCT, multi-center (Korea)
Mazzaferro, V. 2006	2	RCT, multi-center (Italy)
Ng, K. K. C. 2017	2	RCT, single-center (China)
Roayaie, S. 2015	3	multiregional, longitudinal cohort study (Asia-Pacific, Europe, North America)
Takayama, T. 2000	2	RCT, single-center (Japan)
Torzilli, G. 2013	3	multicentric, retrospective observational study (Asia, America, Europe)
Wong, J. S. 2013	3	prospective cohort study, single center (China)
Yin, L. 2014	2	RCT, single-center (China)

OXFORD (2011) Appraisal Sheet: RCT: *9 Bewertung(en)*

Bruix, J. et al. Adjuvant sorafenib for hepatocellular carcinoma after resection or ablation (STORM): a phase 3, randomised, double-blind, placebo-controlled trial. Lancet Oncol. 16. 1344-54. 2015

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** RCT, multi-institutional (America, Asia, Europe)	**Intervention:** - 400 mg twice a day of oral sorafenib for a maximum treatment	**Primary:** recurrence-free survival (RFS), defined as the time from randomisation to the first documented disease recurrence by independent

Number of Patient: Of 1602 patients screened, 1114 met eligibility criteria and were randomly assigned: 556 to the sorafenib group and 558 to the placebo group **Recruitung Phase:** between Aug 15, 2008, and Nov 17, 2010 **Inclusion Criteria:** - men and women aged 18 years or older with a confirmed first diagnosis of HCC suitable for curative treatment. - Patients were required to have an eligibility scan (CT or MRI of chest, abdomen, and pelvis) confirming complete radiological response by masked central independent review between 3 and 7 weeks after curative treatment. - Maximum tumour load before curative therapy comprising one lesion of any size for resection, or a single lesion 5 cm or smaller or two or three lesions each 3 cm or smaller in size for ablation. Other eligibility criteria included a Child-Pugh score of 5–7 (Child-Pugh score 7 allowed only in the absence of ascites), Eastern Cooperative Oncology Group performance status of 0, and alpha fetoprotein concentration lower than 400 ng/mL. - Patients were also required to have adequate bone marrow, liver, and renal function as assessed by laboratory tests done with samples taken within 14 days before randomisation, including haemoglobin, bilirubin, platelet count, neutrophil count, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, and serum creatinine. **Exclusion Criteria:** Exclusion criteria included: - recurrent HCC - macrovascular invasion - a history of cardiovascular disease (myocardial infarction >6 months before study entry was allowed) - infection with HIV or other clinically serious infections - seizure disorder requiring drugs - previous anticancer treatment for HCC, including sorafenib.	period of 4 years (204 weeks ± 1) or until disease recurrence. - treatment interruptions and up to two levels of dose reductions (first to 400 mg once a day and then to 400 mg every other day) were allowed if drug-related adverse events were recorded. **Comparison:** - 400 mg twice a day of oral placebo for a maximum treatment period of 4 years (204 weeks ± 1) or until disease recurrence. - treatment interruptions and up to two levels of dose reductions (first to 400 mg once a day and then to 400 mg every other day) were allowed if drug-related adverse events were recorded.	radiological assessment or death by any cause. **Secondary:** - time to recurrence, defined as the time from randomisation to the first documented disease recurrence by independent radiological assessment - overall survival, defined as the time from randomisation to death by any cause. **Results:** Median RFS according to the independent radiological assessment - Sorafenib: 33.3 months (95% CI 27.6–44.0 vs placebo: 33.7 months (27.6–39.0) - No significant treatment effect of sorafenib on RFS was recorded (HR 0.940; 95% CI 0.780–1.134; one-sided p=0.26). - Subgroup analysis of RFS by factors region, risk of recurrence, Child-Pugh status, primary treatment, age, sex, and cause of underlying liver disease, showed no significant treatment effect of sorafenib. Median Time to recurrence according to the independent radiological assessment - sorafenib: 38.5 months (95% CI 30.4–not estimable) vs. placebo: 35.8 months (30.3–41.4) - No significant treatment effect of sorafenib on time to recurrence was recorded (HR 0.891; 95% CI 0.735–1.081; one-sided p=0.12) - Subgroup analysis of time to recurrence by factors Child-Pugh status, previous curative treatment, or risk of recurrence showed no significant treatment effect of sorafenib. Median overall survival - The median follow-up for overall survival was 23.0 months (IQR 12.7–36.0) in the sorafenib group and 22.0 months (IQR 14.4–35.5) in the placebo group. - No significant treatment effect of sorafenib on overall survival was shown (HR 0.995; 95% CI 0.761–1.300; one-sided p=0.48). Median overall survival was not reached in either treatment group. **Author's Conclusion:** In conclusion, this phase 3 randomised study of

		sorafenib as adjuvant treatment after potentially curative therapy for HCC showed no significant treatment effect with sorafenib, with regards to RFS, time to recurrence, or overall survival. The adjuvant setting remains an area of high unmet need in HCC management and further research into strategies to prevent HCC recurrence is needed.

Methodical Notes

Funding Sources: Funding: Bayer HealthCare Pharmaceuticals and Onyx Pharmaceuticals.
- The funder was responsible for the study design and data collection and analysed and interpreted data, in collaboration with all authors. The funder also had input into the writing of the manuscript. JB and JML had full access to all of the study data, and all authors had access upon request. The corresponding author had access to the study data and had the final responsibility to submit the manuscript for publication.

COI: - G-YC reports grants from Bayer outside the submitted work.
- GM reports employment and stock ownership from Bayer HealthCare during the conduct of the study.
- HCL reports personal fees from Bayer outside the submitted work.
- JB reports personal fees from Daichi, AbbVie, Arquile, Bayer, Biocompatibles, Bristol-Myers Squibb, Novartis, Gilead, Terumo, Syrtex, and Roche outside the submitted work.
- JML reports personal fees from Bayer HealthCare, Bristol-Myers Squibb, Lilly, GSK, Nanostring, Biosphere Medical, Boehringer Ingelheim, Blueprint Medicines, and Celsion outside the submitted work.
- LB reports personal fees from Bayer, Bristol-Myers Squibb, MSD, Bracco, and Syrtex outside the submitted work.
- FS reports employment by Bayer HealthCare during the conduct of this study.
- M-ALB reports employment by Bayer HealthCare during the conduct of this study.
- WYT reports grants from Samil Pharm and personal fees from Gilead Sciences Korea outside the submitted work.
- MM reports personal fees from Bayer HealthCare outside the submitted work.
- VM reports personal fees from BTG and Bayer HealthCare outside the submitted work.
- TS, JC, K-HH, MK, SR, TT, RTP, JY, and KSL declare no competing interests

Randomization: Randomisation was done in a parallel, stratified fashion using permuted blocks (block size of four) via a computer-generated system. Sequences were generated by an internal randomisation group and the list loaded into an interactive voice-response system (IVRS).

Blinding: The study was double-blinded. Sorafenib and placebo tablets were identical in appearance to ensure treatment was masked.
Outcomes were assessed by independent radiological assessment.

Dropout Rate/ITT-Analysis: - Loss to follow-up 1 % (sorafenib) or less (placebo).
- Efficacy endpoints were analysed in the intention-to-treat population, defined as all randomly assigned patients.
- 553 patients in the sorafenib group and 554 in the placebo group received treatment as initially assigned. Six patients assigned to placebo received one or more dose of sorafenib, and hence the safety analysis population consisted of 559 patients in the sorafenib group and 548 in the placebo group.

Notes:
Evidence level 2: RCT

Chen, M. S. et al. A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma. Ann Surg. 243. 321-8. 2006

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** RCT, single center (China) **Number of Patient:** 180 patients randomized **Recruitung Phase:** November 1999 - June 2004 **Inclusion Criteria:** Inclusion criteria for this study were as follows: 1. age 18 to 75 years 2. a solitary HCC smaller than 5 cm in diameter 3. no extrahepatic metastasis 4. no radiologic evidence of invasion into the major portal/hepatic vein branches 5. good liver function with Pugh-Child Class A, with no history of encephalopathy, ascites refractory to diuretics or variceal bleeding 6. indocyanine green retention at 15 minutes (ICG-R15) <30% 7. a platelet count of >40,000/mm3 8. no previous treatment of HCC 9. patient should be suitable to be treated by either surgical resection or PLAT **Exclusion Criteria:** none stated	**Intervention:** percutaneous local ablative therapy (PLAT): Radio frequence ablation (RFA) **Comparison:** Surgical resection	**Primary:** overall survival rate **Secondary:** **Results:** The 1-, 2-, 3-, and 4-year overall survival rates - PLAT group: 94.4%, 79.8%, 68.6%, 65.9% - surgical resection group: 93.3%, 82.3%, 73.4%, 64.0% - no significant difference between the 2 groups **Author's Conclusion:** This prospective randomized trial showed PLAT to give the same overall and disease-free survivals as surgical resection for patients with solitary and small HCC. PLAT has the advantage over liver resection in giving a better short-term postoperative results because PLAT is a less invasive procedure.

Methodical Notes

Funding Sources: Supported by the grant of Sciences and Technology Committee of Guangdo Province, China, 2002

COI: not addressed

Randomization: Randomization was done by using random numbers generated from a computer in a central registry for this study.

Blinding: no blinding reported, but outcome (survival) objective

Dropout Rate/ITT-Analysis: from 90 patients randomized to PLAT, 19 withdrew consent and were treated with surgical resection.
Intent-to-treat-analysis were performed and additionally one analysis after post-randomization exclusion (without the 19 patients) - results did not differ significantly.

Notes:
Evidence level 2: RCT

Feng, K. et al. A randomized controlled trial of radiofrequency ablation and surgical resection in the treatment of small hepatocellular carcinoma. J Hepatol. 57. 794-802. 2012

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** RCT, single center (China) **Number of Patient:** 168 patients met the inclusion criteria and were randomized to the two treatment groups **Recruitung Phase:** January 2005 to March 2008 **Inclusion Criteria:** (1) Diagnosis of HCC confirmed at our hospital. (2) Intrahepatic number of tumors not greater than 2 and a maximum tumordiameter of <4 cm. (3) Child–Pugh class A or B liver disease. (4) No intrahepatic and extrahepatic metastases. (5) No invasion of the portal vein, the hepatic vein trunk or secondarybranches. (6) Indocyanine green retention rates of <30% at 15 min (ICG-15). (7) No evidence of coagulopathy, with a platelet count >50*10^9/L and aprolonged prothrombin time of <5 s. (8) No other anti-tumor therapy received before treatment. (9) All included patients had to be suitable candidates for both RES and RFA. **Exclusion Criteria:** (1) Patients met the inclusion	**Intervention:** Radiofrequency ablation **Comparison:** Surgical resection	**Primary:** 36-month overall survival rate **Secondary:** - recurrence-free survival rate - overall recurrence rate - complications **Results:** 1-, 2-, and 3-year overall survival rates - RES-group: 96.0%, 87.6%, 74.8% - RFA-group: 93.1%, 83.1%, 67.2% recurrence-free survival rates - RES-group: 90.6%, 76.7%,61.1% - RFA-group: 86.2%, 66.6%, 49.6% There were no significant differences between the two groups in overall survival and recurrence-free survival rates. 1-, 2-, and 3-year overall recurrence rates - RES-group: 9.4%, 23.3%, and 37.7% - RFA-group: 13.8%, 32.3%,and 49.6% There were no significant differences between the two groups (log-rank test,chi-quadrat= 2.425,p= 0.119) overall complication rate - RES-group: 21.4% - RFA-group: 9.5% Chi-Quadrat= 6.269,p= 0.017 **Author's Conclusion:** In conclusion, for HCC patients with tumor diameters smaller than 4 cm and no more than two tumors, percutaneous RFA was equivalent to surgical resection for overall survival, but it was associated with increased local recurrence because of the residual tumors. For the treatment of small HCCs located at specific sites of the liver, open or laparoscopic surgery may be the better choice. Compared to surgical resection, RFA is less invasive.

criteria but declined to participate. (2) Patients with severe portal hypertension, a history of esophageal variceal hemorrhage, severe hypersplenism syndrome, or refractory ascites. (3) Patients whose permanent pathology after treatment suggested meta-static liver cancer or primary liver cancer of another tissue type. (4) Patients who were willing to receive a liver transplantation.		

Methodical Notes

Funding Sources: This study was supported by the Key Projects Fund of the Military Medical and Health Research Fund of China (2004–2007) (Project Number 02Z005) and National Basic Research Program ("973" Program No. 2005CB522605).

COI: The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

Randomization: Randomization was performed with stratification according to the tumor diameter (62 cm vs. >2 cm but <4 cm). The sealed numbers were generated by a computerized random number generator.

Blinding: patients and physicians were not blinded

Dropout Rate/ITT-Analysis: Seven patients (4.2%) were lost to follow-up (four in the RES group and three in the RFA group). All patients with protocol violations, intrahepatic metastases, misdiagnosis on postoperative pathology and residual tumors were kept in their respective groups for intention-to-treat analysis of survival and recurrence.

Notes:
Evidence level 2: RCT

Huang, J. et al. A randomized trial comparing radiofrequency ablation and surgical resection for HCC conforming to the Milan criteria. Ann Surg. 252. 903-12. 2010

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** RCT, single center (China) **Number of Patient:** 230 patents randomized: 115 assigned in the RFA group, 115 patients in the RES group. **Recruitung Phase:** March 2003 to January 2005 **Inclusion Criteria:** 1. Diagnosis of HCC confirmed in our hospital	**Intervention:** Radiofrequency Ablation **Comparison:** Surgical Resection	**Primary:** overall survival **Secondary:** recurrence-free survival overall recurrence early-stage recurrence **Results:** 1-, 2-, 3-, 4-, and 5-year overall survival rates - RFA-group: 86.96%, 76.52%, 69.57%,66.09%, 54.78% - RES-group: 98.26%, 96.52%, 92.17%, 82.60%, 75.65% 1-, 2-, 3-, 4-, and 5-year recurrence-free survival rates

2. Met the Milan criteria: single HCC≤5 cm or up to 3 nodules, each <3cm 3. No extrahepatic metastasis or obvious vascular invasion 4. Liver function of Child-Pugh Class A or B 5. No previous or simultaneous malignancies 6. Indocyanine green retention at 15 minutes (ICG-R15)<20% 7. Absence of evident bleeding tendency: a platelet count>50×10^9/L or correctable by transfusion, a prothrombin time prolon-gation of<5 seconds 8. HBV-infected patient with a HBV-DNA-PCR quantitation of<10^5copies/mL 9. No previous treatment of HCC 10. Suitable to be treated by either RES or RFA **Exclusion Criteria:** 1. Patients with severe portal hypertension: with history of esophageal variceal hemorrhage, with large esophageal varices,or refractory ascites 2. Patient who is willing to receive liver transplantation		- RFA-group: 81.74%, 59.13%, 46.08%, 33.91%, 28.69% - RES-group: 85.22%, 73.92%, 60.87%, 54.78%, 51.30%. Overall survival (P=0.001) and recurrence-free survival (P=0.017) were significantly higher in the RES group than in the RFA group. Overall recurrence - RFA-group: 73 - RES-group: 48 Overall recurrence rate was significantly higher in the RFA-group than in the RES-group by intention-to-treat analysis (P=0.001) as well as by actual intervention analysis (69 vs 52,P=0.002) Early-stage recurrence (<2 years) - significantly higher in the RFA group than in the RES group (44 vs 26, P=0.010 ITT-analysis; 42 vs 28, P=0.045 actual intervention analysis) Subgroup analyses - overall survival in (1) solitary HCC≤3cm,(2) solitary HCC 3cm-5cm: Significant differences of RES's superiority in survival were shown in both subgroups ((1) P=0.030;(2) P=0.046) **Author's Conclusion:** Surgical resection may provide better survival and lower recurrence rates than RFA for patients with HCC to the Milan criteria.

Methodical Notes

Funding Sources: This study has not received any support from industry or private corporations.

COI: This study has not received any support from industry or private corporations.

Randomization: An independent statistician from the registry center assigned the patients to 2 groups (the RFA group and the RES group) beforehand by a blocking/stratification randomization method with a computer.

Blinding: Because of the nature of the interventions, the double-blind technique was not used

Dropout Rate/ITT-Analysis: - 25 patients were lost to follow-up (18 in the RES group and 7 in the RFA group).
- All 115 assigned in the RFA group and 115 patients in the RES group were included in the intention-to-treat analysis for survival and recurrence.
- Of note, 7 patients in the RFA group withdrew their consent after interventions were exposed. They chose and were treated with RES.

Notes:
Evidence level 2: RCT

Lee, J. H. et al. Adjuvant immunotherapy with autologous cytokine-induced killer cells for hepatocellular carcinoma. Gastroenterology. 148. 1383-91.e6. 2015

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** RCT, multi-center (Korea) **Number of Patient:** 230 randomized patients: 115 in intervention group, 115 in control group **Recruitung Phase:** between July 3, 2008 and November 29, 2012 **Inclusion Criteria:** - adults between 20 and 80 - HCC of pretreatment clinical stage I or II - who had undergone curative treatment (surgical resection, radiofrequency ablation [RFA], or percutaneousethanol injection [PEI]) - Child–Pugh class A, - Eastern Cooperative Oncology Group performance status score of 0 or 1 **Exclusion Criteria:** patients with - immune deficiency or autoimmune diseases - previous or current other malignancies - severe allergic disorder Pregnant or breast-feeding women and women planning to get pregnant	**Intervention:** - 200 mL of the CIK cell agent intravenously over 60 minutes without any premedication followes by observation for at least 30 minutes. - treatment schedule: 4 treatments at a frequency of once per week, followed by 4 treatments every 2 weeks, then 4 treatments every 4 weeks and finally 4 treatments every 8 weeks (=16 treatments in total) **Comparison:** no therapy	**Primary:** Recurrence Free Survival(RFS), measured from the date of randomization to the first recurrence or to death from any cause **Secondary:** 1. Overall survival, measured from the date of randomization until death from any cause 2. Cancer-specific survival, measured from the date of randomization until death resulting from HCC **Results:** primary outcome median RFS in immunotherapy group 44.0 months vs. 30.0 months in control group. (P= 0.010 by 1-sided log-rank test). secondary outcome In the immunotherapy group, patients died of recurrent HCC (2 patients) or new primary gastric cancer (1 patient). In the control group, patients died of recurrent HCC (9 patients) or unknown causes (3 patients). Both the median overall and cancer-specific survivals in both groups were not reached. OS was longer in the immunotherapy group than in the control group (HR, 0.21;95% CI, 0.06–0.75;P=0.008). In addition, cancer-specific survival was longer in the immunotherapy group (HR, 0.19;95% CI, 0.04–0.87;P=0.02) **Author's Conclusion:** In conclusion, this study showed that adjuvant CIK cell immunotherapy prolongs RFS and OS in patients who have undergone curative treatment for HCC. The immunotherapy was associated with a higher frequency of AEs, which were mainly mild to moderate.

Methodical Notes

Funding Sources: Supported by Green Cross Cell Corp (Seoul, Korea). This study was designed by the sponsor in conjunction with the principal academic investigators. Data were managed in parallel by the sponsor and the principal investigators.

COI: - Joon Hyeok Lee has received grantsfrom Green Cross Cell Corp
- Joon Hyeok Lee, Jung-Hwan Yoon, Young-Suk Lim, Jong Eun Yeon, Yoon Jun Kim, Kang Mo Kim, Geum-Youn Gwak and Su Jong Yu recieved grants and/or lecture fees from or worked on advisory boards of several other pharma companies
- The remaining authors disclose no conflicts

Randomization: Random assignment was performed through a central telephone system using computer-generated, permuted blocks with a block size of 4 or 6 and stratified according to study center.

Blinding: - open-labeled trial
- for tumor assessments, scans were reviewed by 2 independent radiologists who were unaware of the

group assignment

Dropout Rate/ITT-Analysis: - efficacy outcomes were assessed according to the intention-to-treat principle.
- Among 230 randomized patients, 226 (114 in the immunotherapy group and 112 in the control group) were included in the efficacy analysis: 4 patients were excluded from the efficacy analysis because they violated the inclusion and exclusion criteria (1 in the immunotherapy group and 3 in the control group)
- 1 patient in the immunotherapy group was lost to follow-up evaluation and 10 patients in the immunotherapy group discontinued intervention.
- 15 patients in the control group were lost to follow-up
- All 230 randomized patients were included in the safety population

Notes:
Evidence level 2: RCT

Mazzaferro, V. et al. Prevention of hepatocellular carcinoma recurrence with alpha-interferon after liver resection in HCV cirrhosis. Hepatology. 44. 1543-54. 2006

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** RCT, multi-center (Italy) **Number of Patient:** 190 consecutive HCV RNA–positive/hepatitis B surface antigen–negative Caucasian patients with HCC undergoing liver resection in four surgical centers; 161 met the predetermined selection criteria and **150** were eventually randomized within 6 weeks of surgery. **Recruitung Phase:** From June 1998 to November 2002 **Inclusion Criteria:** - HCV-RNA positive / HBsAg-negative patients with HCC undergoing potentially curative resection - Curative surgery (i.e. no residual tumor intraoperative US and tumor-free margins at pathology) - No recurrence 1 month after surgery (CT, NMR, US) - Pre-resection treatments allowed (TACE, RFA, PEI) - HCV-RNA positive (lower limit of detection: 100 copies/ml) regardless of blood titers or genotype **Exclusion Criteria:** - HBsAg-positivity	**Intervention:** - IFN-alpha (within 6 weeks of surgery) was given subcutaneously 3 million units 3 times every week for 48 weeks - Patients received outpatient evaluations at 1, 2, 4, 6, 8,and 12 weeks, then every 3 to 4 weeks for up to 6 months,then every 2 months thereafter, unless symptoms of toxicity, adverse events, or other complications occurred **Comparison:** no treatment	**Primary:** Recurrence Free Survival **Secondary:** - Disease Specific Survival - Overall Patient Survival **Results:** <u>recurrence free survival</u> - IFN: 24.3% (5 years) - control: 5.8% (5 years) (P=0.499) <u>disease specific survival</u> IFN: 63.6% (5 years) - control: 52.4% (5 years) (P=0.471) <u>overall surival</u> - no significant difference (data not shown) <u>viral status stratification</u> - late recurrence (2-5 years): in HCV-pure patients risk of HCC recurrence stabilized at 36.4% in the treated arm after 3 years, while it approached 100% in controls (P=0.032) - no differences were observed in the mixed HCV+HBV subpopulation <u>per-protocol-analysis</u> Out of 76 IFN patients, only 28 were adherent to protocol (15 were HCV-pure and 13 were HCV+HBV): these were included in a per-protocol-analysis: - The hazard ratio estimate of 0.30 (95% CI: 0.094-0.989;P=.048) identified a 70% reduction of HCC recurrence rate in the subgroup of HCV-pure patients **Author's Conclusion:** In conclusion, the results of this RCT suggest that interferon is not recommended as a single chemopreventive agent after resection in patients with HCV-related

- Evidence of any active neoplastic site - Previous IFN or chemotherapy or treatment of other tumors - Severe surgical complication and/or causes of cirrhosis not related to HCV - Patient comorbidity (Hb <12 g/dl, HIV infection, autoimmune disease, psychiatric disorder, seizure, severe cardiovascular disease, poorly controlled diabetes, BMI >35) - Active alcohol intake (>80 g/day)		HCC. However, IFN could be indicated in the subgroup of patients with HCV-pure infection in whom late recurrences can be significantly reduced.

Methodical Notes

Funding Sources: Supported by the Italian Association for Cancer Research.
The Italian National Health Service supported the cost of treatment in the interferon group as a part of a clinical strategy preventing complications of chronic hepatitis C.

COI: No sponsorship or funding sources for treating patients with interferon-alpha were solicited.
Dr. Bonino advises for Roche.

Randomization: Sequence generation, stratum assignment, and randomization were computer-driven and centralized at the National Cancer Institute of Milan (also accounting for two thirds of the operations) in a protected database that did not disclose individual or center-specific information.
Patient allocation was performed via telephone from the coordinating office after confirmation of eligibility criteria.
Participants were stratified according to HBV status before randomization.

Blinding: The RCT was not double-blind; participants knew the group assignment during follow-up. No specification regarding blinding of outcome measurements

Dropout Rate/ITT-Analysis: The entire series of 150 patients was analyzed after 45 months of median follow-up. Only 1 patient randomized to IFN-alpha treatment was lost to follow-up and censored at 1 month after randomization.

Notes:
Evidence level 2: RCT

Ng, K. K. C. et al. Randomized clinical trial of hepatic resection versus radiofrequency ablation for early-stage hepatocellular carcinoma. Br J Surg. 104. 1775-1784. 2017

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** RCT, single-center (China) **Number of Patient:** 218 patients were randomized into the hepatic resection group (109 patients) and RFA group (109) **Recruitung Phase:** July 2002 to June 2007	**Intervention:** Radiofrequency ablation **Comparison:** Hepatic resection	**Primary:** Overall tumour recurrence (local recurrence or intrahepatic or extrahepatic recurrence) **Secondary:** overall and disease-free survival rates **Results:** tumour recurrence 77 patients (71.3%) in the resection group and 89 (81.7%) in the RFA group developed tumour recurrence. P=0.092 The 1-, 3-, 5- and 10-year overall survival rates

Inclusion Criteria: - HCC with a maximum diameter no larger than 5 cm - 3 or fewer tumour nodules - absence of extrahepatic metastases - absence of radiological evidence of tumour invasion of major portal or hepatic vein branches - Child–Pugh grade A or B liver function, with no history of hepatic encephalopathy, refractory ascites or variceal bleeding; - general condition fit for either hepatic resection or RFA **Exclusion Criteria:** - tumour location unfavourable for RFA (close to hilar structures) - previous treatment for HCC (transarterial chemoembolization (TACE), percutaneous ethanol injection or chemotherapy) - presence of extrahepatic metastases or evidence of tumour invasion into major portal or hepatic vein branches		- resection group: 94.5%, 80.6%, 66.5% and 47.6% - RFA-group: 95.4%, 82.3%, 66.4% and 41.8% Median overall survival - resection group: 118.8 months - RFA-group: 93.5 months There was no significant difference in overall survival rate between the two groups (P=0.531) The 1-, 3-, 5- and 10-year disease-free survival rates - resection group: 74.1%, 50.9%, 41.5% and 31.9% - RFA group: 70.6%, 46.6%, 33.6% and 18.6% Median disease-free survival - resection group: was 39.5 months - RFA group: 23.7 months. There was no significant difference between the two groups (P=0·072) short-term outcomes The RFA group had a shorter treatment duration, less blood loss and shorter hospital stay than the resection group. **Author's Conclusion:** This RCT has shown that RFA is not superior to hepatic resection for treatment of early-stage HCC, in terms of tumour recurrence, or 10-year overall and disease-free survival.

Methodical Notes

Funding Sources: This work was supported financially by a research grant from the Hong Kong Research Grant Council.

COI: The authors declare no conflict of interest.

Randomization: Randomization (1:1 ratio) was performed using sealed consecutively numbered envelopes. The envelopes were kept by a research assistant not involved in the treatment of the patient.

Blinding: Double-blinding was not used because of the nature of the interventions.

Dropout Rate/ITT-Analysis: All analyses were performed on an intention-to-treat basis.
Hospital deaths were included in the overall survival analysis, but were excluded from the disease-free survival analysis.

Notes:
Evidence level 2: RCT

No statistical analyses shown for baseline characteristics.

Takayama, T. et al. Adoptive immunotherapy to lower postsurgical recurrence rates of hepatocellular carcinoma: a randomised trial. Lancet. 356. 802-7. 2000

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** RCT,	**Intervention:** Patients received autologous lymphocytes intravenously at weeks 2, 3, 4,	**Primary:** 1. time to first recurrence 2. recurrence-free survival

single-center (Japan) **Number of Patient:** 216 patients underwent hepatectomy of which 155 were deemed eligible and randomised to either of the 2 study groups **Recruitung Phase:** From May, 1992, to September, 1995 **Inclusion Criteria:** - histologically confirmed HCC - UICC tumour-node-metastasis clinical grouping of stage I, II, IIIA, or IVA - hepatic function of Child-Pugh class A or B - had undergone curative hepatic resection - hadnadequate bone-marrow and renal reserve (white cell count >3*10^9/L, platelets >5*10^10/L, and creatinine <88.4 µmol/L) - aged between 18 and 80 years **Exclusion Criteria:** - clinically confirmed extrahepatic metastasis (stage IIIB or IVB) - previous or simultaneous other malignant disorders - previous cancer treatment - postoperative dysfunction of any organ	12 and 24 after surgery (the last two or three infusions as outpatients). This schedule was designed to transfer sufficient cells (>3*10^10) to produce a tumour response, as confirmed in phase 2 studies. **Comparison:** no therapy	**Secondary:** 3. disease-specific survival 4. overall survival **Results:** 1. HCC recurred in 45 (59%) immunotherapy patients compared with 57 (77%) controls. The time to first recurrence in the immunotherapy group was significantly longer than that in the control group (p=0.008). The median time to first recurrence was 1.6 years (range 0.2–6.7) for the control group and 2.8 years (0.2–6.6) for the immunotherapy group. 2. Recurrence-free survival was also significantly higher in the immunotherapy group than in the control group (28 [37%] vs 16 [22%] patients; p=0.01). 3. Disease-specific survival was significantly higher in the immunotherapy group than in the control group (p=0·04). 4. The difference in overall survival was not significant (p=0·09); the estimated rates for years 3 and 5 were 88% (95% CI 81–95) compared with 74% (64–85) and 68% (53–83) compared with 62% (47–77) **Author's Conclusion:** Adoptive immunotherapy can be recommended as a new adjuvant in patients with HCC. Treatment refinements, such as defining the best schedule, finding the optimum use of known immunomodulators and developing more potent effectors, could improve clinical benefits.

Methodical Notes

Funding Sources: This work was supported in part by a grant-in-aid for Cancer Research and a grant-in-aid for the Comprehensive 10-year Strategy of Cancer Control from the Ministry of Health and Welfare, Japan.

COI: not addressed

Randomization: Randomisation was done by permuted block without stratification

Blinding: - clinicians and patients were blinded to the study groups
- The first detected recurrence was documented by two independent radiologists unaware of the study group

Dropout Rate/ITT-Analysis: No patients were lost to follow-up

Notes:
Evidence level 2: RCT

Yin, L. et al. Partial hepatectomy vs. transcatheter arterial chemoembolization for resectable multiple hepatocellular carcinoma beyond Milan Criteria: a RCT. J Hepatol. 61. 82-8. 2014

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** RCT, single-center (China) **Number of Patient:** 180 patients met the inclusion criteria and were randomized to the two groups. **Recruitung Phase:** November 2008 to September 2010 **Inclusion Criteria:** (1) good surgical risk patients >18 years and ≤70 years of age; (2) at least two rounds of radiological imaging showing characteristic features of HCC, or one radiological imaging associated with alpha fetoprotein (AFP) >400µlg/L, or cytological/histological evidence of HCC (3) resectable HCC with tumors outside of Milan Criteria (4) adequate liver remnant size after liver resection (5) no radiological evidence of vascular invasion or extrahepatic metastasis (6) tumors resectable with a single or multiple liver resections (7) liver function status of Child-Pugh A-B, with serum bilirubin ≤1.5 times the upper limit of normal, alanine aminotransferase and aspartate aminotransferase ≤2 times the upper limit of normal (8) no major organ dysfunction (9) hemoglobin ≥90 g/L, white bloodcell ≥3000 cells/mm^3,	**Intervention:** Partial hepatectomy (PH) included single or multiple liver resections aiming to remove all macroscopic tumors. **Comparison:** transcatheter arterial chemoembolization (TACE)	**Primary:** overall survival (OS) **Secondary:** prognostic risk factors associated with OS **Results:** 1-, 2-, and 3-year OS rates - PH-group: 76.1%,63.5%,51.5%; median survival 41 months (range 1–50 months) - TACE-group: 51.8%, 34.8%, 18.1%; median survival 14 months (range 5–47 months) The PH group had significantly better OS than the TACE group (log-rank test,chi^2= 24.246,p<0.001) prognostic risk factors - type of treatment, serum AFP level, total tumor size, gender and number of tumor (univariate analysis) - type of treatment (hazard ratio, 0.434; 95% CI, 0.293 to 0.644, p<0.001), number of tumor (hazard ratio, 1.758; 95% CI, 1.213 to 2.548, p= 0.003) and gender (hazard ratio, 0.451; 95% CI,0.236 to 0.862, p=0.016) (multivariate analysis) **Author's Conclusion:** In conclusion, the outcome of PH as an initial treatment for patients with tumor outside of Milan Criteria was superior to conventional TACE. The number of tumor and gender were also found to be independent risk factors associated with OS for these patients. To achieve good results of PH, patients should be carefully selected to minimize postoperative mortality and major morbidity.

platelets ≥80.000 cells/mm^3; (10) informed consent had been obtained. **Exclusion Criteria:** (1) cardiac, pulmonary, cerebral and renal dysfunction (2) a history of other malignancy (3) extrahepatic metastasis, portal vein or other major vascular involvement (4) liver functional status of Child-Pugh C (5) any other contraindication like: active gastrointestinal bleeding, refractory ascites, coagulopathy,severe portal hypertension (6) no prior TACE or liver resection.		

Methodical Notes

Funding Sources: This study was supported by State Key Infection Disease Project of China (Project Number: 2012ZX10002010, 2012ZX10002016), Science Fund for Creative Research Groups of China (Project Number 81201940), Youth Fund of Health Bureau of Shanghai (Project Number 201144172) and Natural Science Fund of Shanghai (Project Number 13ZR1450800).

COI: The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

Randomization: included patients (1:1 ratio) were randomly assigned to either the PH group or the TACE group using random numbers generated from a computer by a research nurse who was not involved in this study.

Blinding: The double-blind technique was not used

Dropout Rate/ITT-Analysis: Of 180 patients who were randomized to the PH group and the TACE group, 2 patients in the PH group and 5 patients in the TACE group were excluded from this study after randomization because of violation of study protocol or because of allergy to iohexol. The remaining 173 patients, including 88 patients in the PH group and 85 patients in the TACE group were included for the intention-to-treat analysis.
5 patients in the PH group and 2 in the TACE group were lost to follow-up.

Notes:
Evidence level 2: RCT

OXFORD (2011) Appraisal Sheet: Prognostic Studies: *1 Bewertung(en)*

Torzilli, G. et al. A snapshot of the effective indications and results of surgery for hepatocellular carcinoma in tertiary referral centers: is it adherent to the EASL/AASLD recommendations?: an observational study of the HCC East-West study group. Ann Surg. 257. 929-37. 2013

Population	Intervention	Outcomes/Results

Evidence level: 3 **Study type:** multicentric, retrospective observational study (Asia, America, Europe) **Number of Patient:** 2046 patients were studied: - 746 (36%) from the 3 Asian centers - 307 (15%) from the 3 American centers - 993 (49%) from the 4 European centers. BCLC stage: - 1012(50%) BCLC 0-A - 737 (36%) BCLC B - 297 (14%) BCLC C **Recruitung Phase:** none **Inclusion Criteria:** patients resected for HCC: The centers of the network were asked to enter their data, consecutively and without restrictions, for BCLC stages. **Exclusion Criteria:** none	**Intervention:** hepatic resection **Comparison:** none	**Primary:** overall survival of patients resected for HCC in any BCLC stage **Secondary:** - disease-free survival of patients resected for HCC among the BCLC stages - postoperative outcome (morbidity and mortality) - prognostic factors for overall survival **Results:** <u>1, 3, and 5 years overall survival</u> - BCLC 0-A: 95%, 80%, and 61% - BCLC B: 88%, 71% and 57% - BCLC C: 76%, 49%,and 38% significant differences P=0.000 <u>1, 3, and 5 years disease-free survival</u> - BCLC 0-A: 77%, 41%, and 21% - BCLC B: 63%, 38%, and 27% - BCLC C: 46%, 28%, and 18% significant differences P=0.000 <u>30- and 90-day mortality rate</u> - BCLC 0-A: 1.6% and 2% - BCLC B: 3.1% and 3% - BCLC C: 2.5% and 3% 3 day mortality P=0.121; 90-day mortality (P=0.163) <u>minor morbidity (grade I-II)</u> - 21%, 17%, and 29% for BCLC 0-A, B, and C patients,respectively (P=0.001) <u>major morbidity (grade III-IV)</u> - no significant differences in major morbidity among the 3 BCLC stages (P=0.606) <u>prognostic factors</u> - number of tumors more than 3, tumor size more than 5 cm, presence of macrovascular invasion, presence of cirrhosis, presence of esophageal varices, major resection, BCLC classification, and preoperative bilirubin values statistically correlated to overall survival (univariate analysis) - tumor size more than 5 cm, macrovascular invasion, cirrhosis, esophageal varices, and preoperative total serum bilirubin statistically and independently significant for overall survival (multivariate analysis) **Author's Conclusion:** This large multicentric survey shows that surgery is in current practice widely applied among patients with multinodular, large, and macrovascular invasive HCC, providing acceptable short- and long-term results and justifying an update of the EASL/AASLD therapeutic guidelines in this sense.	

Methodical Notes

Funding Sources: Specific funding was not used to perform this study.

COI: All authors deny any conflicts of interests.

Randomization: none

Blinding: none

Dropout Rate/ITT-Analysis: none

Notes: Evidence level 3: retrospective non-randomized follow-up study

NEWCASTLE - OTTAWA Checklist: Cohort: *3 Bewertung(en)*

Eguchi, S. et al. Comparison of the outcomes between an anatomical subsegmentectomy and a non-anatomical minor hepatectomy for single hepatocellular carcinomas based on a Japanese nationwide survey. Surgery. 143. 469-75. 2008

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 3 **Study type:** nationwide follow-up survey study (Japan)	**Funding sources:** no statement **Conflict of Interests:** no statement **Randomization:** none **Blinding:** none **Dropout rates:** This study is an "As treated" analysis and not an "Intention to treat" analysis.	**Total no. patients:** 5781 patients with a single HCC who had undergone either an AS (n =2267) or an MH (n =3514) were enrolled. **Recruiting Phase:** between 1994 and 2001 **Inclusion criteria:** patients with a single HCC who had undergone AS or MH **Exclusion criteria:** none	**Interventions:** anatomical subsegmentectomy (AS) **Comparison:** non-anatomical minor hepatectomy (MH)
Notes:	Evidence level 3: non-randomized followup-study **Author's conclusion:** In conclusion, an AS resulted in a better DFS for selected patients with a single HCC. Therefore, an AS is recommended, especially when the size of the HCC ranges from 2 to 5 cm in diameter. However,an MH is also considered to be an alternative treatment option for single HCC, if an AS cannot be performed safely.		
Outcome Measures/results	**Primary** patient survival **Secondary** disease-free survival	**Results:** 5- and 10-year patient survival - AS: 65.5% and 34.1% - MH: 62.4% and 28.5% hazard ratio 1.120,P= 0.0531 5- and 10-year disease-free survival - AS: 39.8% and 9.4% - MH: 34.4% and 10% hazard ratio 1.121,P= .0089 subgroup analysis - DFS for HCC between 2cm-5cm: AS: 37.4% (5-year) and 7.8% (10-year); MH: 30.1% (5-year) and 4.6% (10-year); P=0.0005 - no significant difference betweeen AS and MH for HCC≤ 2cm and HCC≥ 5cm - no significant difference betweeen AS and MH when data were stratified according to liver damage status	

Roayaie, S. et al. The role of hepatic resection in the treatment of hepatocellular cancer. Hepatology. 62. 440-51. 2015

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 3 **Study type:**	**Funding sources:** The BRIDGE database and data collection were funded by	**Total no. patients:** 8656 patients included	**Interventions:** A) ideal candidates resected

multiregional, longitudinal cohort study (Asia-Pacific, Europe, North America)	Bristol-Meyers Squibb. Centers were provided with funds for entry of data. The analysis of the data reported here and the preparation of the manuscript were not funded by any source or company. **Conflict of Interests:** no statement **Randomization:** none **Blinding:** none **Dropout rates:** none	**Recruiting Phase:** January 1, 2005, and June 30, 2011 **Inclusion criteria:** newly diagnosed HCC recieving treatment (transplantation, resection, ablation, embolization, other) **Exclusion criteria:** no statement	**Comparison:** B) ideal candidates not resected C) non-ideal candidates resected D) non-ideal candidates not resected
Notes:	Evidence level 3: cohort study **Author's conclusion:** Our study suggests that the current AASLD/EASL criteria might be expanded to include patients with either moderate portal hypertension or slightly elevated total bilirubin>1 mg/dL, but not both, without any appreciable increase in mortality. Finally, for patients who do not meet AASLD/EASL criteria for surgery, resection may still be associated with longer survival, when compared to embolization and “other” treatments and shorter survival in comparison to ablation and transplantation, when controlling for other relevant factors.		
Outcome Measures/results	**Primary** survival **Secondary**	**Results:** 3- and 5-year survival rates - group A: 74% and 65%; median survival not reached - group B: 55% and 55%; median survival not reached - group C: 47% and 35%; median survival 32.4 months - Multivariate analysis of groups A&B revealed a nearly 2-fold increase in risk of mortality treatments other than resection - Expansion of AASLD/EASL criteria to include more-severe liver dysfunction, advanced tumor characteristics or compromised performance status was associated with a significant detrimental effect on survival - portal hypertension was not associated with a decrease in survival - total bilirubin over 1 mg/dL did not have an appreciable impact on survival; - patients who didn't met criteria as ideal candidates (group C+D) for resection, surgery was associated with lower mortality, when compared to embolization and “other” treatments when controlling for variables that significantly impact survival of HCC patients; surgery fared worse than ablation and transplantation.	

Wong, J. S. et al. Liver stiffness measurement by transient elastography as a predictor on posthepatectomy outcomes. Ann Surg. 257. 922-8. 2013			
Evidence level	**Methodical Notes**	**Patient characteristics**	**Interventions**

Evidence level: 3 **Study type:** prospective cohort study, single center (China)	**Funding sources:** no statement **Conflict of Interests:** G.L.H.W. has served as a speaker for Echosens. V.W.S.W. has served as a speaker for Roche and Bristol-Myers Squibb. H.L.Y.C. has served as a consultant and advisory board member for Bristol-Myers Squibb, F. Hoffmann La Roche, Novartis Pharmaceutical, Gilead, Merck, and Abbott Diagnostic. The remaining authors declare no conflicts of interest. **Randomization:** none **Blinding:** none **Dropout rates:** none	**Total no. patients:** 105 consecutive patients who underwent hepatectomies were included for analysis **Recruiting Phase:** February 2010 to July 2011 **Inclusion criteria:** consecutive patients who underwent hepatectomy for various indications and had a detailed preoperative assessment including LSM and indocyanine green (ICG) clearance test. **Exclusion criteria:** Major hepatectomy could not be offered to patients with ICG R15 of more than 14%	**Interventions:** liver stiffness measurement before hepatectomy **Comparison:** indocyanine green (ICG) clearance test before hepatectomy
Notes:	Evidence level 3: cohort study **Author's conclusion:** n conclusions, high preoperative LSM could predict posthepatectomy complication and operative blood loss. Liver stiffness measurement had a high diagnostic accuracy for advanced liver fibrosis and cirrhosis. It was better than ICG R15, radiological, or intra-operative assessment of cirrhosis in the prediction of postoperative outcomes. It may also serve as a noninvasive and convenient tool for risk stratification or risk disclosure to patients before hepatectomy.		
Outcome Measures/results	**Primary** major postoperative complication **Secondary** overall complication, operative blood loss, transfusion rate, and histological fibrosis score	**Results:** **major postoperative complication** - AUROC curve LSM: 0.79(95% confidence interval, 0.65–0.93;P<0.001) - AUROC curve ICG R15: 0.51 (95% confidence interval, 0.38–0.72;P=0.90). - The calculated cut off value for LSM was 12.0kPa, with sensitivity of 85.7%, specificity of 71.8%, positive predictive value of 33.3%, and negative predictive value of 95.7% **correlation of LSM with postoperative complications** Major Complication Rate,n(%) LSM value >12.0kPa= 12 (33.3) vs. LSM value ≤12.0kPa= 3 (4.3); P<0.001 Overall Complication Rate,n(%) LSM value >12.0kPa= 14 (38.4) vs. LSM value ≤12.0kPa= 8 (11.6); P=0.001 Blood Loss Per Transection Area, mL/cm LSM value >12.0kPa= 10.0 (2.1–40.8) vs. LSM value ≤12.0kPa= 6.3 (1.1–69.3); P=0.03 Transfusion rate n(%) LSM value >12.0kPa= 8 (22.2) vs. LSM value ≤12.0kPa= 3 (4.4); P=0.008	

		correlation of LSM with histological fibrosis staging - AUROC curve for LSM in relation to advanced liver fibrosis: 0.89 (95% confidence interval, 0.80–0.95;P<0.001) - diagnostic accuracy for the prediction of advanced liver fibrosis and cirrhosis was 83.8%

Schlüsselfrage:

HCC 13 Transplantation - 1
Haben Patienten mit HCC outside Milano und mit einer neoadjuvanten Therapie zum Downstaging ein schlechteres Outcome als Patienten inside Milano?

Inhalt: *3 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Braat, M. N. 2016	2	Systematic review. 11 Studies
Pardo, F. 2017	4	Retrospective (cohort) study, non-interventional, international mulcticentric.
Parikh, N. D. 2015	1	Systematic Review and Meta-Analysis (of cohort studies)

OXFORD (2011) Appraisal Sheet: Systematic Reviews: *2 Bewertung(en)*

Braat, M. N. et al. The role of (90)Y-radioembolization in downstaging primary and secondary hepatic malignancies: a systematic review. Clin Transl Imaging. 4. 283-295. 2016

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 2 **Study type:** Systematic review. 11 Studies **Databases:** PubMed **Search period:** ?-11/2015 **Inclusion Criteria:** Not specified **Exclusion Criteria:** Animal studies, reviews, metaananalyses, conference abstracts, consensus statements and protocol publications, and languages other than English or German.	**Population:** primary and secondary hepatic malignancies **Intervention:** ^{90}Y-radioembolization (RE) **Comparison:**	**Primary:** Downstaging success, response rate **Secondary:** **Results: Primary: Downstaging success rate with RE:** 8-100% in 9 HCC studies (n=8-102). 8-80% in 4 ICC studies (n=10-46), and 9-85% in 5 studies (n=8-44) on metastatic hepatic malignancies. See article for full results table. **Author's Conclusion:** "Based on the available evidence RE seems a promising addition to the currently applied downstaging and bridging strategies. The combination of the anti-tumoral effect and simultaneous hypertrophy induction of the non-embolized segments may have clear advantages over preoperative PVE or in situ splitting techniques in terms of	Kulyk 2006 Heckman 2008 Lewandowski 2009 Ibrahim 2012 Inaaraireaguui 2012 Tohme 2013 Donahue 2013 Vouche 2014 Ettore 2014 Kulik 2014 Abdelfattah 2015 Ibrahim 2008 Mouli 2013 Rayar 2015 Edeline 2015 Whitney 2011 Vouche 2013 Moir 2015 Justinger 2015 HEnry 2015

		tumor control and morbidity."	

Methodical Notes

Funding Sources: not described.

COI: MGEH Lam is a consultant for Sirtex, BTG and Bayer Healthcare. All other authors have no conflict of interest.

Study Quality: not investigated

Heterogeneity: Not a meta-analysis

Publication Bias: Not investigated

Notes:
Only one database was searched, which is not considered a comprehensive search. Unclear/lacking definition of research question, search specifics and inclusion criteria. No evaluation of study quality. Downgrade to evidence level 2.

Parikh, N. D. et al. Downstaging hepatocellular carcinoma: A systematic review and pooled analysis. Liver Transpl. 21. 1142-52. 2015

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 **Study type:** Systematic Review and Meta-Analysis (of cohort studies) **Databases:** MEDLINE and Embase **Search period:** 01.1996 - 03.2015 **Inclusion Criteria:** Cohort studies (retrospective or prospective); evaluating downstaging in patients with cirrhosis and HCC; studies in which downstaging was performed using surgical resection, RFA, TACE, TARE, SBRT, or a combination of therapies; and studies that reported rates of success for downstaging patients to within Milan criteria using imaging criteria and/or posttransplant outcomes (including recurrence rates and/or survival) among those who were downstaged to within Milan criteria. **Exclusion Criteria:** We excluded articles that evaluated investigational procedures;	**Population:** Patients with cirrhosis and HCC: Child-Pugh class A disease (54%), Child-Pugh class B (36%)Child-Pugh class C (8%). 15 obeservational Studies. 13 studies with 950 patients described the success of downstaging patients to within Milan criteria and 15 studies with 320 patients which described posttransplant recurrence rates among patients who were downstaged. **Intervention:** downstaging was performed using surgical resection, RFA, TACE, TARE, SBRT, or a combination **Comparison:** Other methods	**Primary:** Success rate of downstaging to within Milan criteria and HCC (decrease of tumor burden to within Milan) Recurrence rates after LT. **Secondary:** Post-LT Survival **Results: Primary: Downstaging success:** 13 Studies n=950: Aggregate success rate of 0.48% (95% CI, 0.39%-0.58%). High heterogeneity (I^2 5 84.8%). Studies that included patients with tumor thrombus had the lowest success rates; when these studies were excluded, the pooled success rate was 0.54% (95% CI, 0.45%-0.63%). Studies with prospectively designed protocols for downstaging also yielded a significantly higher success rate compared to retrospective studies (0.68% versus 0.44% P < 0.001;). There was no significant difference in the success rate of TACE and TARE for downstaging (0.48% versus 0.37%; P 5 0.51; however, the highest	Green 2013 Pracht 2013 Tohme 2013 Bova 2013 Inarrairaegui 2012 Barakat 010 Jang 2010 De Luna 2009 Lewandowski 2009 Chapman 2008 Otto 2006 Yao 2015 Ravaioli 2008

evaluated systemic chemotherapeutic agents; used explant data for evaluation of downstaging success; had incomplete data for primary outcomes of interest; included less than 5 patients; and/or used surgical resection as the only method for downstaging patients.		downstaging success rates were reported in cohorts undergoing multimodal therapy for downstaging. **Primary: Post-LT Recurrence:** 12 Studies n=320 patients. In total 58 (0.16; 95% CI, 0.11-0.23) patients had HCC recurrence after LT; There was no significant difference in recurrence rates between TACE and TARE (P = 0.33). **Secondary:** Post-LT survival could not be aggregated because of heterogeneity **Author's Conclusion:** "We have shown that downstaging patients outside of Milan can be achieved in approximately half of all patients; however, post-LT recurrence is higher than what has been reported in patients who present within Milan. It is important to note that in well-designed studies with downstaging protocols, equivalent posttransplant results between downstaged patients and those who present within Milan criteria can be achieved."	

Methodical Notes

Funding Sources: "This work was conducted with support from the Agency for Health Research and Quality Center for Patient-Centered Outcomes Research (R24 HS022418)."

COI: Nothing to report.

Study Quality: Study quality was rated by 1 investigator using the modified Newcastle-Ottawa scale NOS. Quality ranged from 5-9 points.

Heterogeneity: "There was heterogeneity in downstaging success rate among included studies (I^2 = 84.8%)".
"One of the most notable findings of our systematic review is the substantial heterogeneity and limitations of data evaluating downstaging."

Publication Bias: "Publication bias was assessed by visual inspection of a funnel plot. "Our funnel plots showed no evidence of bias; however, this may reflect the large number of small studies included in this meta-analysis."

Notes:
Evidence level 1:Systematic review
High heterogeneity in the main analysis (Downstaging success).

NEWCASTLE - OTTAWA Checklist: Cohort: *1 Bewertung(en)*

Pardo, F. et al. The Post-SIR-Spheres Surgery Study (P4S): Retrospective Analysis of Safety Following Hepatic Resection or Transplantation in Patients Previously Treated with Selective Internal Radiation Therapy with Yttrium-90 Resin Microspheres. Ann Surg Oncol. 24. 2465-2473. 2017

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 4 **Study type:** Retrospective (cohort) study, non-interventional, international mulcticentric.	**Funding sources:** This study was sponsored by Sirtex, with set funding provided for each study entrant, assuming 80% of the required data were collected. The authors received no payment for their involvement as authors of this manuscript. **Conflict of Interests:** Independently of P4S, the authors declare the following additional conflicts. Fernando Pardo has received lecture and consulting fees from Sirtex Medical; Bruno Sangro has received lecture and consulting fees from Sirtex Medical; Derek Manas has received support for travel to meetings, as well as honoraria for lecturing and attendance at advisory boards from Sirtex Medical; Pierce K. Chow has received honoraria and research grants from Sirtex Medical; Fernando Rotellar has received travel support and lecture and consulting fees from Sirtex Medical; IB has received lecture fees from Sirtex Medical. Paul J. Gow, Geert Maleux,Gianluca Masi, Lourens Bester, David L. Morris, Wan Y. Lau, Konstantinos Kouladouros, Georgios Katsanos, and Giorgio Ercolani have no conflict of interest to declare. **Randomization:** - **Blinding:** - **Dropout rates:** -	**Total no. patients:** 100 patients in 16 centers **Recruiting Phase:** 1998-2014 **Inclusion criteria:** "Data were collected from centers in Asia-Pacific, Europe, and the US on all consecutive patients who had received SIRT (± other treatments) for primary or secondary liver tumors before resection or transplantation, when data were available for at least 90 days postsurgery or until death." **Exclusion criteria:** Patients who only received ablation or were enrolled in ongoing or unreported prospective clinical studies were excluded.	**Interventions:** Selective internal radiation therapy (SIRT) with yttrium - 90 (Y-90)-labelled resin microspheres. **Comparison:** -
Notes:	Evidence level 4: retrospective cohort study **Author's conclusion:** "In 100 patients undergoing liver surgery after receiving		

	SIRT, mortality and complication rates appeared acceptable given the risk profile of the recruited patients."	
Outcome Measures/results	**Primary** perioperative and 90-day postoperative morbidity (complications with a Clavien–Dindo classification score of ≥3) and mortality. **Secondary** Postoperative hospital stay	**Results: Population:** In 100 patients with primary or secondary liver tumors from 16 centeers. 71 underwent hepatic resection after SIRT and 29 received liver transplant post-SIRT. The extent of resection was minor in 20 (28.2%) patients, major but not extended in 32 (45.0%) patients, and extended in 19 (26.8%) patients. Two-stage resections were performed in 10 patients undergoing major resection. **Primary outcome:** Complications: In the liver resection group, most grade 3+ complications of any type (12/20; 63.2%) occurred in patients undergoing extended resection of five or more segments. Eight of 10 liver failure complications occurred in patients undergoing extended resection; both remaining liver failure cases were grade 1 and occurred in patients undergoing major but not extended resection). All seven grade 3+ liver failures were in patients undergoing extended resection. The only liver failure complication among those receiving a liver transplant was grade 2. Any grade 3+ complications occurred in 24.0% of resected patients with FLR exposed to SIRT, compared with 30.4% in those whose FLR did not receive SIRT (p = 0.783). Any grade and grade 3+ liver failure complications were reported in 16.0 and 12.0% of patients with FLR exposed to SIRT, respectively, compared with 13.0 and 8.7%, respectively, in those whose FLR did not receive SIRT (p = 0.733 and p = 0.691). Death: Four deaths occurred within 90 days of surgery, all in the cohort that underwent extended resection of five or more segments. The treating physician did not consider SIRT to be the cause of death in any of these four cases. One 66-year-old patient with cholangiocarcinoma died within 30 days of surgery; the patient had a BMI of 35, an American Society of Anesthesiologists score of 3 (severe systemic disease), and cardiopathy, diabetes and hypertension pre-SIRT. This patient had received one line of chemotherapy pre-SIRT and further chemotherapy between SIRT and surgery, and had FLR partially exposed to prior SIRT.

Schlüsselfrage:

HCC 13 Transplantation - 2
Profitieren Patienten mit HCC inside Milano von Bridging-Therapien?

Inhalt: *5 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Agopian, V. G. 2017	2	Multicentric cohort/registry, 20 US centers, HCC Transplant Consortium (UMHTC)
Huang, X. 2017	1	Systematic review and Meta-Analysis. 12 studies Preoperative locoregional therapy on recurrence and survival in HCC.
Kulik, L. 2018	1	Systematic review and meta-analysis. Effectiveness of LRT in the management of HCC patients on the LT waitlist.
Salem, R. 2016	2	RCT, open-label, singlecenter, investigator initiated phase 2 Prospective Chemoembolization vs Radioembolization for the Treatment of Hepatocellular Carcinoma.
Sneiders, D. 2018	1	Systematic review and meta-analysis. 14 retrospective studies. HCC undergoing preliver transplantation TACE.

OXFORD (2011) Appraisal Sheet: Systematic Reviews: *3 Bewertung(en)*

Huang, X. et al. Impact of preoperative locoregional therapy on recurrence and patient survival following liver transplantation for hepatocellular carcinoma: a meta-analysis. Scand J Gastroenterol. 52. 143-149. 2017

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 **Study type:** Systematic review and Meta-Analysis. 12 studies Preoperative locoregional therapy on recurrence and survival in HCC. **Databases:** PubMed, EMBASE, Google Scholar, the Cochrane	**Population:** HCC patients. 12 studies, n=35-200, predominantly US studies. **Intervention:** Preoperative locoregional therapy including TACE, RFA, PEI and	**Primary:** five-year survival and five-year recurrence-free survival **Secondary:** - **Results:** Locoregional therapy and 5-year survival rate :10 studies (n = 1,235). Only one study showed statistical significance; pooled results preoperative locoregional therapy was not associated with	Stockland, A.H., et al., Preoperative chemoembolization in patients with hepato-cellular carcinoma undergoing liver transplantation: influence of emergent versus elective procedures on patient survival and tumor recurrence rate. Cardiovasc Intervent Radiol, 2007. 30(5): p.

Library, the China National Knowledge Infrastructure whole-article database (CNKI), and the VIP Chinese Journals Database **Search period:** Inception-04/2014 **Inclusion Criteria:** Study patients who had undergone preoperative locoregional therapy prior to liver transplantation, an intervention with locoregional therapy and a control group, the reporting of survival results, and a sufficiently long follow-up period (e.g., five years). Studies could be designed as randomized control trials (RCTs) or non-RCTs. **Exclusion Criteria:** Reviews and case reports were excluded.	combination of these treatments. **Comparison:** No treatment	a decreased risk of five-year survival (HR = 1.06; 95% CI = 0.82–1.38). In random-effects model HR of 1.04 (95% CI = 0.74–1.45). Locoregional therapy and 5-year recurrence-free survival rate 6 studies found that preoperative locoregional therapy had no association with five-year recurrence-free survival rates, same was true for pooled results (pooled HR = 1.02, 95% CI = 0.70-1.50. **Author's Conclusion:** Meta-analysis suggests that preoperative locoregional therapy has no association with survival following liver transplantation for HCC. However, the majority of included studies were performed via retrospective analysis and/or examined small numbers of patients at single centers. Therefore, we believe that a multi-center prospective study with a longer follow-up period and more clearly defined parameters would be the best way to study this issue in the future.	888-93. Bharat, A., et al., Pre-Liver Transplantation Locoregional Adjuvant Therapy for Hepatocellular Carcinoma as a Strategy to Improve Longterm Survival. Journal of the American College of Surgeons, 2006. 203(4): p. 411–420 Seehofer, D, et al., impact of neoadjuvant TACE on tumor recurrence and patient survival after liver transplantation for HCC: 2613. Transplantation, 2010. 90. DuBay DA, et al. Radiofrequency ablation of hepatocellular carcinoma as a bridge to liver transplantation. HPB (Oxford), 2011. 13(1): p. 24-32. Yao, F.Y., et al., The impact of pre-operative loco-regional therapy on outcome after liver transplantation for hepatocellular carcinoma. Am J Transplant, 2005. 5(4 Pt 1): p. 795-804. Kim, JM, et al., Effectiveness of Locoregional Therapy Before Living Donor Liver Transplantation in Patients With Hepatocellular Carcinoma Who Meet the Milan Criteria. Transplantation Proceedings, 2012. 44(2): p. 403–408. Lao, O.B., J. Weissman, and J.D. Perkins, Pre-transplant therapy for hepato-cellular carcinoma is associated with a lower recurrence after liver trans- plantation. Clin Transplant, 2009. 23(6): p. 874-81. Porrett, P.M., et al., Lack of benefit of pre-transplant locoregional hepatic therapy for hepatocellular

			cancer in the current MELD era. Liver Transpl, 2006. 12(4): p. 665-73. Kim, P.T., et al., Tumor biology and pre-transplant locoregional treatments determine outcomes in patients with T3 hepatocellular carcinoma undergoing liver transplantation. Clin Transplant, 2013. 27(2): p. 311-8. S.L., et al., Transarterial chemoembolization for HCC in patients with extensive liver transplantation waiting times. Angiology, 2012. 63(3): p.206-12. Decaens, T., et al., Impact of pretransplantation transarterial chemo embolization on survival and recurrence after liver transplantation for hepato- cellular carcinoma. Liver Transpl, 2005. 11(7): p. 767-75 Heckman, J.T., et al., Bridging locoregional therapy for hepatocellular carcinoma prior to liver transplantation. Ann Surg Oncol, 2008. 15(11): p. 3169-77.

Methodical Notes

Funding Sources: "we thank all those persons, organizations and funds that have provided us with any help."

COI: The authors have declared that no competing interest exists.

Study Quality: "We used the Newcastle-Ottawa Scale (NOS) to assess the quality of the studies included in our analysis....The studies included in the MA were deemed to have moderate to high overall quality, with all of the included studies ranking ≥5 stars on the modified NOS which meant a relative high quality."

Heterogeneity: "If the heterogeneity was not obvious, HRs were pooled using a fixed effects model. Otherwise, we used a random effects model to pool the HRs. We also conducted a sensitivity analysis to examine the stability of the pooled results. There was no significant heterogeneity among the studies."

Publication Bias: "Publication bias was detected using the funnel plot of the meta-analysis results. ..The plots are relatively symmetric, suggesting that there is no significant publication bias in the reports of five-year survival rates."

Notes:

Kulik, L. et al. Therapies for patients with hepatocellular carcinoma awaiting liver transplantation: A systematic review and meta-analysis. Hepatology. 67. 381-400. 2018

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 **Study type:** Systematic review and meta-analysis. Effectiveness of LRT in the management of HCC patients on the LT waitlist. **Databases:** Ovid Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, and Scopus **Search period:** inception to April 25, 2016. **Inclusion Criteria:** studies that enrolled adults with cirrhosis awaiting LT and treated with bridging or down-staging therapies before transplant. Therapies included TACE,transarterial radioembolization (TARE), ablation, and radiotherapy. We included both comparative and noncomparative studies with no language restrictions. **Exclusion Criteria:** studies with patients enrolled before 1996, case reports, cohorts with fewer than 5 patients, reviews, letters, errata, commentaries, and studies published only as abstracts.	**Population:** Three research questions 1.) Adults with cirrhosis awaiting LT andT1 HCC 2.)Adults with cirrhosis awaiting LT and T2 HCC 3.)Adults with cirrhosis awaiting LT and beyond Milan (T3) HCC 63 studies were included (comparative and non-comparative). **Intervention:** three research questions. 1.) Observation versus any therapy (TACE,TARE, ablation, or radiotherapy) 2.)Transplant alone versus transplant with any bridging therapy (TACE, TARE, ablation, or radiotherapy) 3.) Transplant without down-staging versus transplant following down-staging to within Milan (T2) **Comparison:** -	**Primary:** Waitlist dropout due to progression beyond transplant criteria, post-LT survival, recurrence. **Secondary:** - **Results:** 1.): For adults with T1 HCC and waiting for LT, there were only 2 nonrandomized comparative studies, both with a high risk of bias. In one series, the rate of dropout from all causes at 6 months in T1 HCC patients who underwent LRT was 5.3%, while in the other series of T1 HCC patients who did not receive LRT, the dropout rate at median follow-up of 2.4 years and the progression rate to T2 HCC were 30% and 88%, respectively. 2: For adults with T2 HCC awaiting LT, transplant with any bridging therapy showed a nonsignificant reduction in the risk of waitlist dropout due to progression (relative risk [RR], 0.32; 95%CI, 0.06-1.85; I2 5 0%) and of waitlist dropout from all causes (RR, 0.38; 95% CI, 0.060-2.370; I2 5 85.7%) compared to no therapy based on three comparative studies. The quality of evidence is very low due to high risk of bias, imprecision, and inconsistency. There were five comparative studies which reported on posttransplant survival rates and 10 comparative studiesvwhich reported on posttransplant recurrence, and there was no significant difference seen in either of these endpoints. 3.)For adults initially with stage T3 HCC who received LRT, there were three studies reporting on transplant with any downstaging therapy versus no downstaging, and this showed a significant increase in 1-year (two studies, RR, 1.11; 95% CI,1.01-1.23) and 5-year (1 study, RR, 1.17; 95% CI, 1.03-1.32) post-LT survival rates for patients who received LRT. The quality of evidence is very low due to serious risk of bias and imprecision **Author's Conclusion:** "In patients with HCC listed for LT, the use of LRT is associated with a non-significant trend toward improved waitlist and	see article, 63 references.

		posttransplant outcomes, though there is a high risk of selection bias in the available evidence."	

Methodical Notes

Funding Sources: not stated.

COI: "Potential conflict of interest: Dr. Kulik advises Bayer."

Study Quality: Modified Newcastle-Ottawa Scale was used to assess the risk of bias in observational studies. Quality of evidence was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methods.
Quality of evidence was rated very low for all outcomes.

Heterogeneity: "There was significant heterogeneity among the three studies that looked at down-staging for T3 HCC compared to transplant for T3 HCC without downstaging in terms of the comparative group"

Publication Bias: Not investigated

Notes:
Publication bias not investigated.

Sneiders, D. et al. Systematic Review and Meta-Analysis of Posttransplant Hepatic Artery and Biliary Complications in Patients Treated With Transarterial Chemoembolization Before Liver Transplantation. Transplantation. 102. 88-96. 2018

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 **Study type:** Systematic review and meta-analysis. 14 retrospective studies. HCC undergoing preliver transplantation TACE. **Databases:** Embase, MEDLINE OvidSP, Web of Science, Google Scholar, and Cochrane **Search period:** Inception - March 2016. **Inclusion Criteria:** Studiey investigating posttransplant complications of the hepatic artery or biliary tract, in patients treated with TACE before deceased or living-donor liver transplantation,	**Population:** 14 retrospective observational studies on HCC patients. n=1122 TACE patients. **Intervention:** TACE before liver transplantation **Comparison:** Liver transplantation without prior TACE	**Primary:** postoperative hepatic artery **Secondary:** biliary complications **Results:** Hepatic Artery Complications: Posttransplant hepatic artery complications occurred more frequently in TACE recipients (76/837) compared with non-TACE recipients (145/2294). WWe observed a significant association between preliver transplantation TACE and posttransplantation occurrence of hepatic artery complications, including thrombosis, stenosis, and (pseudo)-aneurysms (OR, 1.57; 95% CI, 1.09-2.26; P = 0.016; I2 = 0%) No evidence of an	Casadaban L, et al. Presurgical transarterial chemoembolization does not increase biliary stricture incidence in orthotopic liver transplant patients. Transplant Proc. 2014;46:1413–1419. Goel A, et al. Hepatic artery and biliary complications in liver transplant recipients undergoing pretransplant transarterial chemoembolization. Liver Transpl. 2014;20:1221–1228. Kanakadandi V, et al. Chemoembolization therapy of hepatocellular carcinoma prior to liver transplant is associated with the development of post-transplant biliary anastomotic strictures. Hepatology. 2012;56:475A–476A. Li H, et al. Preoperative transarterial chemoembolization does not increase hepatic artery complications after liver transplantation: a single center 12-year experience. Clin Res Hepatol Gastroenterol.2015;39:451–457. Lin TS, et al. Intimal dissection of the hepatic artery following transarterial embolization for

compared with liver transplantation recipients who had not undergone TACE. We included articles describing transarterial embolization or chemoinfusion alone, embolization with drug eluting beads or chemoembolization. **Exclusion Criteria:** Articles describing radioembolization. Case reports, letters, and editorials, pediatric and nonhuman studies.		association between pretransplant TACE and posttransplant occurrence of hepatic artery thrombosis, alone, was found (OR, 1.31; 95% CI, 0.74-2.35; I2 = 0%) Biliary Tract Complications No strong evidence of a significant association was observed between preliver transplantation TACE and occurrence of biliary tract complications posttransplantation (OR, 1.30; 95% CI, 0.96-1.76; P = 0.087; I2 = 0%) **Author's Conclusion:** "Patients treated with TACE before liver transplantation may be at increased risk for development of hepatic artery complications after liver transplantation."	hepatocellular carcinoma: an intraoperative problem in adult living donor liver transplantation. Liver Transpl.2009;15:1553–1556. Majno PE, et al. Influence of preoperative transarterial lipiodol chemo-embolization on resection and transplantation for hepatocellular carcinoma in patients with cirrhosis. Ann Surg. 1997;226:688–701. Mekeel KL, et al. The risk of hepatic arterial complications associated with trans-arterial chemoembolization prior to liver transplantation for hepato-cellular carcinoma. Transplantation. 2010;90(Suppl 1):781. Panaro F, et al. Hepatic artery complications following liver transplantation. Does preoperative chemoembolization impact the postoperative course? Clin Transplant. 2014;28:598–605. Pravisani R, et al. Transarterial chemoembolization does not harm the hepatic artery at transplantation. Transplant Int. 2015;28:212. Ramanathan M, et al. Downstaging or bridging therapy of hepatocellular cancer does not increase incidence of biliary complications after liver trans-plantation. Hepatology. 2015;62:833A. Richard HM 3rd, et al. Hepatic arterial complications in liver transplant recipients treated with pretransplantation chemoembolization for hepatocellular carcinoma. Radiology. 2000;214:775–779. Saborido BP, et al. Is transarterial chemoembolization necessary before liver transplantation for hepatocellular carcinoma?Am J Surg. 2005;190:383–387. Shiani A, et al. Incidence of biliary stricture after transarterial chemoembolization for hepatocellular carcinoma in orthotopic liver transplant patients. Am J Gastroenterol. 2015;110:S907–S908. Shiani A, et al. Vascular complications after transarterial chemoembolization in orthotopic liver transplant patients.Am J Gastroenterol. 2015;110:S906.

Methodical Notes
Funding Sources: not stated. **COI:** "The authors declare no conflicts of interest." **Study Quality:** Quality assessment of studies was done by the validated checklist of Downs and Black. Therefore, the quality of all included studies according to GRADE is low to very low. **Heterogeneity:** "Potential heterogeneity between studies was assessed with I2 tests... There was no significant heterogeneity between studies in both analyses." **Publication Bias:** Not investigated. **Notes:** Publication bias not investigated.

OXFORD (2011) Appraisal Sheet: RCT: *1 Bewertung(en)*

Salem, R. et al. Y90 Radioembolization Significantly Prolongs Time to Progression Compared With Chemoembolization in Patients With Hepatocellular Carcinoma. Gastroenterology. 151. 1155-1163.e2. 2016

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** RCT, open-label, singlecenter, investigator initiated phase 2 Prospective Chemoembolization vs Radioembolization for the Treatment of Hepatocellular Carcinoma. **Number of Patient:** 45 randomized (21 cTACE, 24 Y90) **Recruitung Phase:** 2009-2015 **Inclusion Criteria:** Image/biopsy-proven HCC by guidelines, unablatable/unresectable disease, no vascular invasion, Child–Pugh A/B, bilirubin level of 2.0 mg/dL or less, and aspartate aminotransferase/alanine aminotransferase 5 times the upper limit of normal or less. **Exclusion Criteria:** Infiltrative/bulk disease (≥70% tumor burden), 50% or more tumor burden with albumin level less than 3 g/dL, cardiac comorbidities, major surgery within the past 4 weeks, or active infection.	**Intervention:** cTACE. Chemoembolization was performed with 75 mg/ m2 (maximum, 150 mg) dosing. The drug/lipiodol combination was followed by embolic microspheres. **Comparison:** Y90. Angiography and technetium-99m scintigraphy were used to estimate lung shunting, identify extrahepatic perfusion, and perform coil embolization if necessary. Glass microspheres were used at a 120-Gy dose, with treatment on an outpatient basis.	**Primary:** Time to progression (TTP) **Secondary:** safety, rate of response (based on tumor size and necrosis criteria), and Kaplan–Meier survival time. **Results: Population:** n=45 (cTACE 21, Y90 =24). For all 45 patients, the median length of followup evaluation was 17.2 months (range, 1.4–62.1 mo). **Primary: Time to progression** The median TTP was significantly longer in the Y90 group: 6.8 months for cTACE vs not reached for Y90 (>26 mo; P ¼ .0012; HR, 0.122; 95% CI, 0.027–0.557; P = .007). Competing risk analysis: Y90 again showed a significantly reduced hazard of progression compared with cTACE (subdistribution HR, 0.13; 95% CI, 0.03–0.57; P = .006), with transplant/death as competing events. By IPCW analysis, risk reduction of progression in the Y90 group was more pronounced (HR,

		0.071; 95% CI, 0.008–0.645; P = .019). **Secondary outcomes** Imaging outcomes: Primary index lesions (n = 43) were defined in 184 reviewed studies (mean, 4.3 scans/patient), with follow-up imaging available in 42 of 43 patients (98%). WHO response was 12 of 19 (63%) for cTACE vs 12 of 23 (52%) for Y90 (P = .542), with comparable median times with PR by group (7.3 mo; 95% CI, 3.9–12.6 after cTACE vs 7.6 mo. Overall survival: KM curves (censored to liver transplantation) showing the median of 17.7 months (95% CI, 8.3–not calculable) and 18.6 months (95% CI, 7.4–32.5) OS for cTACE and Y90, respectively (P = .99) **Author's Conclusion:** "In a randomized phase 2 study of patients with HCC of BCLC stages A or B, we found Y90 radioembolization to provide significantly longer TTP than cTACE. Y90 radioembolization provides better tumor control and could reduce drop-out from transplant waitlists."

Methodical Notes

Funding Sources: "This study was supported in part by National Institutes of Health grant CA126809. Also supported by a Medical Scientist Training Program student (T32GM008152 to A.C.G.) with support for research provided by an Allied Scientist grant from the Society of Interventional Radiology Foundation.

COI: "These authors disclose the following: Robert J. Lewandowski, Laura Kulik, and Riad Salem serve as advisors to BTG International. The remaining authors disclose no conflicts.

Randomization: Prospective randomization 1:1 to conventional chemoembolization (cTACE; control arm) or radioembolization (Y90; test arm). Method not described.

Blinding: No blinding of patients, open label.
CT, MRT Scans (for outcome assesment) were reviewed in a blinded manner by 2 board-certified radiologists.

Dropout Rate/ITT-Analysis: Intention to treat analysis was performed.

Notes:
Time to initial treatment different between groups. A lot of censored datasets due to transplants.

NEWCASTLE - OTTAWA Checklist: Cohort: *1 Bewertung(en)*

Agopian, V. G. et al. Impact of Pretransplant Bridging Locoregional Therapy for Patients With Hepatocellular Carcinoma Within Milan Criteria Undergoing Liver Transplantation: Analysis of 3601 Patients From the US Multicenter HCC Transplant Consortium. Ann Surg. 266. 525-535. 2017

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 2 **Study type:** Multicentric cohort/registry, 20 US centers, HCC Transplant Consortium (UMHTC)	**Funding sources:** not described. **Conflict of Interests:** The authors report no conflicts of interest. **Randomization:** - **Blinding:** - **Dropout rates:** -	**Total no. patients:** 3601 with a known pre-LT diagnosis of HCC meeting MC **Recruiting Phase:** 2002 to 2013 **Inclusion criteria:** Consecutive, adult (≥18 years) HCC patients undergoing LT regardless of tumor size, requirement for MELD exception points, follow-up time, or non- HCC-related death. HCC diagnosis was based on pretransplant radiographic imaging, biopsy, or incidental discovery on explant pathology. **Exclusion criteria:** Patients with cholangiocarcinoma, mixed hepatocellular/ cholangiocarcinoma, fibrolamellar HCC, or hepatoblastoma were excluded.	**Interventions:** pre liver transplant locoregional therapy (pre LT LRT) **Comparison:** LT without LRT
Notes:	**Author's conclusion:** "Bridging LRT in HCC patients within MC does not improve post-LT survival or HCC recurrence in the majority of patients who fail to achieve cPR. The need for increasing LRT treatments and lack of alphafetoprotein response to LRT independently predict post-LT recurrence, serving as a surrogate for underlying tumor biology which can be utilized for prioritization of HCC LT candidates"		
Outcome Measures/results	**Primary** Recurrence-free survival and post-LT recurrence **Secondary**	**Results: Population:** Of 3601 patients in the UMHTC with a known pre-LT diagnosis of HCC meeting MC, 2854 (79.3%) received pre-LT LRT, 747 (20.7%) did not. At a median follow-up time of 46.7 months [IQR 24.2–76.2], 375 patients developed post-LT HCC recurrence (10.4%); median time to recurrence of 17.2 months (IQR 8.5–34.1). At time of last follow-up, 2433 (67.6%) were alive without recurrence, 95 (2.6%) had recurred but were alive, 279 (7.7%) had died of HCC recurrence, and 794 (22.1%) had non-HCC-related mortality. thermal ablation, 464 (12.9%) received ablation without TACE, 298 (8.3) received both TACE and ablation, and 170 recipients received Of 3601 HCC LT recipients, In the LT LRT group 1922 (53.4%) received TACE and not thermal ablation, 464 (12.9%) received ablation without TACE, 298 (8.3) received both TACE and ablation, and 170 recipients received other LRT without TACE or ablation (4.7%).	

		Comparison LT and Pre-LT LRT **Survival and recurrence:**747 LT recipients not receiving LRT, 2854 receiving LRT had similar 1, 3, and 5-year recurrence-free survival (89%, 77%, 68% vs85%, 75%, 68%; P = 0.490) and 5-year post-LT recurrence (11.2% vs 10.1%; P = 0.474). **Post-LT recurrence:** Increasing LRT number [3 LRTs: hazard ratio (HR) 2.1, P < 0.001; 4þ LRTs: HR 2.5, P < 0.001), and unfavorable waitlist alphafetorotein trend significantly predicted post-LT recurrence, whereas LRT modality did not. Treated **Stratification by by LRT modality:** no significant differences in the 1, 3, and 5- year RFS. **Complete Pathological response** Treated patients achieving cPR had superior 5-year RFS (72%) and lower post-LT recurrence (HR 0.52, P < 0.001) compared with both untreated patients (69%; P ¼ 0.010; HR 1.0) and treated patients not achieving cPR (67%; P = 0.010; HR 1.31, P = 0.039).

Schlüsselfrage:

HCC 15
Profitieren Patienten mit einem auf die Leber beschränkten Tumor von einer Radiofrequenzablation?

Inhalt: *1 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Di Costanzo, G. G. 2015	2	Randomized clinical trial.

OXFORD (2011) Appraisal Sheet: RCT: *1 Bewertung(en)*

Di Costanzo, G. G. et al. Radiofrequency ablation versus laser ablation for the treatment of small hepatocellular carcinoma in cirrhosis: a randomized trial. J Gastroenterol Hepatol. 30. 559-65. 2015

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** Randomized clinical trial. **Number of Patient:** 432 naïve HCCs in patients with cirrhosis were consecutively observed. Among these, 140 patients met the entry criteria, Eighteen of these 140 (13%) patients were considered resectable but refused surgery. RFA (70 patients with 77 nodules) or LA (70 patients with 80 nodules) **Recruitung Phase:** January 2009 to September 2012 **Inclusion Criteria:** (i) unresectable HCC (due to nodule location, multifocality, presence of portal hypertension, age > 75 years, or comorbidity) or refusal of	**Intervention:** RFA Four weeks after ablation, the treatment response was assessed by dynamic contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI). In case of residual enhancing tumor tissue an additional session of ablation was given. The design of the study was scheduled up to three ablation procedures during a 6-month period. **Comparison:** LA	**Primary:** Complete tumor ablation (CTA): defined as absence of any contrast enhancement within or at the periphery of the HCC nodule. **Secondary:** Time to local progression (TTLP) and overall survival (OS); TTLP was defined as the time from CTA to reappearance of arterial enhancement on CT or MRI either within a treated tumor or near its borders. The OS was defined as the interval between the first treatment and either death or last follow-up visit before November 30, 2013. **Results: Treatment response_CFA:** RFA group: patients: 97.1% (95% CI, 90.2–99.2) nodules: 97.4% (91.0–99.3) LA group, patients: 95.7% (95% CI, 88.1–98.5) nodules: 96.3% (89.6–98.7) Therefore, the rate of CTA was comparable between the two techniques with a difference per patient of 1.4% (95% CI from −6.0% to + 9.0%) and per nodule of 1.1% (from −5.7% to + 8.1%) (P = .5). **HCC recurrence and survival:**

surgery; (ii) solitary HCC ≤ 5.0 cm, or ≤ 3 lesions each ≤ 3.0 cm in diameter; (iii) Child–Pugh class A or B; (iv) a platelet count > 40 000/μL and INR < 2.0; and (v) no previous HCC treatment. **Exclusion Criteria:** (i) history of encephalopathy or refractory ascites; (ii) vascular invasion or extrahepatic metastasis; and (iii) unfeasible percutaneous thermal ablation (inconspicuous nodules and tumors located within 5 mm of liver hilum or the main bile duct branches).		Local tumor progression occurred in 25.7% of RFA patients and in 22.9% of LA patients. The mean TTLP was comparable between RFA (42.0 months; 95% CI, 36.83–47.3) and LA groups (46.7 months; 95% CI, 41.5–51.9) (P = .591). The mean local progression-free survival was 35.7 (95% CI, 30.6–40.9) months and 35.5 (30.1–40.8) months in RFA and LA groups, respectively. During the study period, 18 patients in the RFA group and 24 patients in the LA group had died. The mean OS was 42 months in both groups, the 1- and 3-year survival probability was 94% and 89% in RFA group, and 94% and 80% in LA group. **Complications:** There were no treatment-related deaths. moderate pain (SIR class A) was recorded in 36% and 33% of RFA and LA patients, respectively. Self-limiting fever lasting < 15 days (SIR class A) occurred in 32% and 35% of RFA and LA patients, respectively. One case per group of subcutaneous tumor seeding was observed (SIR class C). **Author's Conclusion:** In conclusion, this is the first study that validates the use of LA for the treatment of HCC. LA resulted not inferior to RFA in achieving the CTA and therefore it should be considered as an evaluable alternative for thermal ablation of small HCC in cirrhotic patients.

Methodical Notes

Funding Sources: n.s.

COI: The authors indicated no potential conflicts of interest.

Randomization: computer-generated random numbers, patients were assigned to either RFA or LA on the day of hospitalization.

Blinding: -

Dropout Rate/ITT-Analysis: In two patients of LA group treatment was not repeated: in one due to the distant cancer progression and in the other for liver failure. Three patients in LA group and one patient in RFA group underwent liver transplantation; evaluation of explanted livers showed complete necrosis of treated nodules.

Notes:

Oxford CEBM Level 2- randomized clinical trial

Schlüsselfrage:

HCC 16
Profitieren Patienten mit einem auf die Leber beschränkten Tumor von einer TACE?

Inhalt: *6 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Golfieri, R. 2014	2	RCT, multi-center (Italy)
Lammer, J. 2010	2	RCT (Phase II), multi-center (Europe)
Lo, C. M. 2002	2	RCT, single-center (China)
Malagari, K. 2012	4	prospective nonrandomized, 1-arm interventional trial
Ogasawara, S. 2017	2	RCT, single center (Japan)
Takayasu, K. 2010	3	cohort study, multi-center (Japan)

OXFORD (2011) Appraisal Sheet: RCT: *4 Bewertung(en)*

Golfieri, R. et al. Randomised controlled trial of doxorubicin-eluting beads vs conventional chemoembolisation for hepatocellular carcinoma. Br J Cancer. 111. 255-64. 2014

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** RCT, multi-center (Italy) **Number of Patient:** 177 randomized patients - 88 in cTACE-group - 89 in DEB-TACE-group **Recruitung Phase:** March 2008 and December 2010; **Inclusion Criteria:** ≥18 years of age - HCC unsuitable for curative treatment or had failed/recurred after resection/ablation	**Intervention:** Transcatheter arterial chemoembolisation with calibrated dox-orubicin-carrying microspheres, DC-Beads **Comparison:** conventional TACE	**Primary:** 2-year survival **Secondary:** - radiological tumour response (CR: complete response, OR: objective response, DC: disease control) - time-to-tumour progression (TTP: interval between randomisation and radiological tumour progression) - impact on ECOG PS and liver function - number of treatments - duration of in-hospital stay - need for other types of treatment of residual/recurrent tumours **Results:** <u>1- and 2-year survival rates</u> - cTACE: 83.5% and 55.4% - DEB-TACE: 6.2% and 56.8% (P=0.949) <u>median number of treatments</u> - 2 in both the cTACE (range: 1–4) and the DEB-TACE arms (range: 1–5) <u>radiological tumour response</u> - No significant differences were found in the rates of local (CR, OR, and DC) and overall tumour responses

- diagnosed by biopsy or according to the AASLD criteria - Child-Pugh A or B (score 7) - Eastern Cooperative Oncology Group (ECOG) PS ≤1 - no previous treatment on target lesions (prior treatments on non-target lesions were accepted). **Exclusion Criteria:** - poor liver function (Child-Pugh class B or MELD score ≥10) - severe comorbidities - patient refusal for resection - critical location or non-visibility at ultrasonography of nodules and not permissive clotting/platelet count for ablation. - infiltrative HCC - portal vein thrombosis - ascites - F3 oesophageal varices - advanced liver disease (bilirubin levels ≥2.5 mg dl^{-1}, albumin ≤30 g l^{-1}, platelets ≤50x10^9 per litre, INR ≥1.5) - other tumours in the previous 5 years - contraindications to arteriography or TACE.		during the follow-up period (P≥0.05 in all cases), except for a more frequent overall CR at 1 month after cTACE than after DEB-TACE (59.8% vs 43.8%; P=0.036) TTP - cTACE: 9 months (95% CI: 6.3–11.7) - DEB-TACE: 9 months (95% CI: 6.8–11.2) (P=0.766) median in-hospital stay - cTACE: 4 days (range: 1–26) - DEB-TACE: 3 days (range: 1–34)(P=0.323) adverse events - post-procedural pain two-fold more frequent and more severe in the cTACE arm (71.6% vs. 24.7%; P=0.001) need for other types of treatment of residual/recurrent tumours - In all, 36 (20%) patients received subsequent treatments that were equally distributed in the two arms (P=0.404) **Author's Conclusion:** In conclusion, the present study failed to demonstrate a superiority of DEB-TACE over cTACE in terms of efficacy, safety and more importantly, 2-year survival. The only benefit of DEB-TACE was a lower incidence and intensity of post-procedural abdominal pain. However, since this did not affect the length of in-hospital stay and patient acceptance of additional TACEs, this marginal advantage is offset, in our opinion, by the higher cost of the new technique. Hence, the routine use of DEB-TACE in clinical practice is debatable, unless further studies can identify patient subgroups in which its use is more beneficial for outcome.

Methodical Notes

Funding Sources: no statement

COI: The authors declare no conflict of interest

Randomization: Upon enrolment, alphanumeric identification codes were assigned to the patients who were then randomised to one of the two treatments. The randomisation was stratified according to Child-Pugh class and BCLC stage and it was centralised at the Investigational Drug Service of the Pharmacy of the Bologna center, allocating the first and lowest randomisation code available, and generating the randomisation list.

Blinding: none

Dropout Rate/ITT-Analysis: drop-out
cTACE-group: 2
DEB-TACE-group: 1
Survival and safety analyses included all randomised patients who underwent at least one TACE (intention-to-treat analysis)

Notes:
Literatur from submitted hand search.
Evidence level 2: RCT

Lammer, J. et al. Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: results of the PRECISION V study. Cardiovasc Intervent Radiol. 33. 41-52. 2010

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** RCT (Phase II), multi-center (Europe) **Number of Patient:** 212 patients were randomized to TACE with DC Bead (n=102) or cTACE (n=110) **Recruitung Phase:** 25 November 2005 and 27 June 2007 **Inclusion Criteria:** - Patients aged ≥18 years - with HCC unsuitable for resection or percutaneous ablation, (BCLC A/B, without portal invasion or extrahepatic spread) - no previous chemotherapy, radiotherapy or transarterial embolization (with or without chemotherapy), - confirmed diagnosis of HCC according to EASL, - an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, - preserved liver function (Child-Pugh Class A or B) **Exclusion Criteria:** - another primary tumor - advanced liver disease (bilirubin levels ≥3 mg/dl, AST or ALT ≥ 5x upper limit of normal or ≥250 U/l) - advanced tumoral disease (vascular invasion or extrahepatic spread, or diffuse	**Intervention:** doxorubicin via TACE with DC Bead **Comparison:** doxorubicin via cTACE	**Primary:** primary efficacy endpoint - 6-month tumor response rate, according to the amended EASL response criteria primary safety endpoint - incidence of treatment-related serious adverse events (SAEs) occurring within 30 days of a treatment procedure **Secondary:** Secondary safety outcomes - incidence and severity of adverse events (AEs) and SAEs, - liver function parameters, - laboratory abnormalities - cardiac function (ejection fraction) **Results:** efficacy (6-months tumour response) - complete response 25 (26.9%) DC Bead vs. 24 (22.2%) cTACE - partial response 23 (24.7%)DC Bead vs. 23 (21.3%) cTACE - stable disease 11 (11.8%) DC Bead vs. 9 (8.3%) cTACE - progressive disease 30(32.3%) DC Bead vs. 44 (40.7%) cTACE - Overall response rate 51.6% DC Bead vs. 43.5% cTACE; the hypothesis of superiority was not met (one-sided P=0.11) - in patients with more advanced disease (Child Pugh B, ECOG1, bilobar or recurrent disease), Overall response and disease control rates were statistically higher (P=0.038 and P=0.026, respectively) in the DC Bead compared with the cTACE group safety (incidence of SAEs within first 30 days) - 19 (20.4%) DC Bead patients experiencing 28 events vs. 21 (19.4%) cTACE patients experiencing 24 events. (P=0.86) secondary safety outcomes - overall frequency of treatment-emergent AEs (TE-AEs) per 100 treatments lower in the DC Bead compared with the cTACE group - majority of TEAEs mild or moderate in intensity,

HCC, defined as ≥50% liver involvement) - contraindications for doxorubicin administration		with a lower frequency of severe events (20.4% vs. 30.6%) reported in DC Bead vs. cTACE patients - Serious liver toxicity postchemoembolization lower in the DC Bead group - Observed postprocedural increases in liver enzymes AST and ALT significantly less in the DC Bead group than in the cTACE group - Cardiac function maintained in DC Bead group vs. deterioration in left ventricular ejection fraction in cTACE group **Author's Conclusion:** In conclusion, TACE with DC Bead and doxorubicin is safe and effective in the treatment of intermediate-stage HCC and offers benefit to patients with more advanced disease.

Methodical Notes

Funding Sources: The study was sponsored by Biocompatibles UK Ltd.

COI: no statement

Randomization: Randomization was centralized, with stratification factors of Child-Pugh class (A/B), ECOG performance status (0/1), prior curative (resection or percutaneous ablation) treatment (yes/no), and bilobar disease (yes/no), representing more advanced disease. Randomized treatment allocation was predetermined by an independent statistician and used a randomized permuted block design to ensure that, at the conclusion of the study treatment, group sizes were similar both overall and for each level of stratification factor. The randomization was integrated into the web-based Case Report Form after screening.

Blinding: single-blind; MRI scans were assessed independently by two assessors blinded to treatment allocation (followed by adjudication in case of disagreement)

Dropout Rate/ITT-Analysis: Modified Intention-to-Treat (MITT) population, defined as all randomized patients who received at least one chemoembolization
- Due to dropouts prior to first treatment, the MITT population included 93 (DC Bead) and 108 patients 8 (cTACE).

Notes:
Literatur from submitted hand search.
Evidence level 2: RCT

Lo, C. M. et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology. 35. 1164-71. 2002

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** RCT, single-center (China) **Number of Patient:** 80 patients were allocated randomly to the chemoembolization group (40 patients) or the control group (40 patients)	**Intervention:** - transarterial Lipiodol chemoembolization after a standard protocol with an emulsion containing cisplatin (1 mg/mL) with Lipiodol in a volume ratio of 1 to 1 - various amounts of the emulsion, up to a maximum of 60 mL (containing 30 mg of cisplatin) were injected	**Primary:** survival calculated from the date of randomization **Secondary:** tumor response, patient tolerance and liver function **Results:** 1-year, 2-year, and 3-year survival rates - chemoembolization: 57%, 31%, and 26% - control: 32%, 11%, and 3% - patients who received

Recruitung Phase: March 1996 to October 1997 **Inclusion Criteria:** diagnoses of unresectable hepatocellular carcinoma that were based on histology, cytology or persistently elevated serum alpha-fetoprotein levels (≥400 ng/mL) with typical imaging findings **Exclusion Criteria:** patients who had - poor hepatic function (presence of hepatic encephalopathy, ascites not controlled by diuretics, history of variceal bleeding within last three months, a serum total bilirubin level over 50µmol/L, a serum albumin level below 28 g/L, or a pro-thrombin time of more than 4 seconds over the control) - serum creatinine level of over 180µmol/L - history of previous treatment for the tumor or acute tumor rupture - presence of extrahepatic metastasis or vascular contra indications to chemoembolization (hepatic artery thrombosis, main portal vein thrombosis or arteriovenous shunting) - poor performance status (Eastern Cooperative Oncology Group performance status rating grade 4)	slowly under fluoroscopic monitoring according to the size of the tumor and the arterial bloodflow. **Comparison:** only treatment for symptoms and complications	chemoembolization had a relative risk of death of 0.49 (95%CI, 0.29-0.81;P=.006) as compared with those of the control group tumor response - chemoenbolization: no complete response, 11 major responses, 6 minor responses, 7 stabilizations and 4 progressions - control: no complete response, 1 major response, 2 minorresponses, 6 stabilizations and 9 progressions - rate of objective tumor response in measurable patients significantly higher in the chemoembolization group than in the control group (39% vs. 6%;P=.014) patient tolerance - most common clinical adverse effect self-limiting syndrome consisting of fever, abdominal pain and vomiting liver function - lower serum bilirubin level in the chemoembolization group at 3 months (P=.038), **Author's Conclusion:** In conclusion, transarterial Lipiodol chemoembolization using the present regimen prolongs the survival of a selected group of Asian patients with unresectable hepa-tocellular carcinoma and is an effective palliative treatment option. Whether non-Asian patients with this disease condition will benefit from a similar regimen or other regimens of chemoembolization remains to be determined by further randomized controlled trials.

Methodical Notes

Funding Sources: no statement

COI: no statement

Randomization: randomization was performed without stratification by drawing consecutively numbered sealed envelopes.

Blinding: none

Dropout Rate/ITT-Analysis: Comparison between groups was made on an intention-to-treat basis. One patient assigned to the control group was excluded secondarily because of unrecognized pulmonary and bone metastases on computed tomography scan taken before randomization.
Two patients, 1 in each group, were lost and could not be contacted after a follow-up of 4 months and 9 months. These were treated as censored observations.

Notes:
Literatur from submitted hand search.

Evidence level 2: RCT

Ogasawara, S. et al. A randomized placebo-controlled trial of prophylactic dexamethasone for transcatheter arterial chemoembolization. Hepatology. . . 2017

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** RCT, single center (Japan) **Number of Patient:** 120 patients (dexamethasone n=60; control n=60) **Recruitung Phase:** October 2010 and June 2013 **Inclusion Criteria:** - age ≥20years - presence of histologically confirmed or clinically diagnosed HCC (fulfilling the criteria for lesions with typical imaging) - absence of benefit from a treatment of established efficacy such as resection and local ablation - presence of Child-Pugh class A or B disease - an Eastern Cooperative Oncology Group performance status of 0, 1, or 2 - hemoglobin ≥8.5 g/dL; - whiteblood cell count ≥2,000/mm3 - neutrophil count ≥1,000/mm3 - total bilirubin level ≤3.0 mg/dL - aspartate aminotransferase and alanine aminotransferase levels ≤10 times the upper limit of normal - prothrombin time ≤2.3 (international normalized ratio) - serumalbumin ≥2.5g/dL	**Intervention:** dexamethasone regimen (day 1, intravenous dexamethasone [20 mg] and granisetron [3 mg] before TACE; days 2 and 3, intravenous dexamethasone [8mg]) **Comparison:** control regimen (day 1, intravenous placebo[saline] and granisetron [3 mg]; days 2 and 3, intravenous placebo)	**Primary:** overall rate of complete response (CR), defined as no fever,anorexia, or nausea/vomiting and no rescue therapy within 120 hours after TACE. **Secondary:** cumulative incidences of fever, anorexia and nausea/vomiting - evaluation of the nutritional state determined by the levels of prealbumin and retinol-binding protein - the response rate of TACE - the rate of hepatitis B virus (HBV) reactivation - and safety **Results:** rate of complete response within 120 hours - dexamethasone: 47.5%, 95% confidence interval 34.3%-60.9% control: 10.2%, 95% CI 3.8%-20.8%; P<0.001 cumulative incidence rates of fever, anorexia, and nausea/vomiting within 120 hours - higher in control group than those in the dexamethasone group (P<0.001, P<0.001, and P=0.095, respectively) nutritional state In both treatment groups, mean levels of prealbumin and retinol-binding protein decreased from baseline to days 3 and 7 and recovered by week 12. - Mean changes in prealbumin and retinol-binding protein levels between baseline and days 3 and 7 were significantly greater with the control regimen than with the dexamethasone regimen (day 3, P=0.016 and P<0.001, respectively; day 7, P=0.012 and P=0.025, respectively) radiological tumor response at 4 and 12 weeks - no significant differences between the dexamethasone and control groups according to both the RECIST version 1.1 and mRECIST HBV reactivation - no patient exhibited HBV reactivation during the observation period **Author's Conclusion:** In conclusion, the dexamethasone-containing prophylactic regimen was superior to the control regimen for the prevention of fever, anorexia, and nausea/vomiting in HCC patients receiving TACE. This study demonstrated the utility and tolerability of dexamethasone for the prevention of postembolization syndrome with respect to TACE, based on a well-designed randomized, placebo-controlled trial. Our results provide a standard for

- serum creatinine level ≤1.5 times the upper limit of normal. **Exclusion Criteria:** - history of other malignancies diagnosed in the past 3 years - uncontrolled or significant cardiovascular disease - active bacterial infection - human immunodeficiency virus infection/adult immunodeficiency syndrome - grade 1 or higher fever, anorexia, and/or nausea/vomiting - uncontrollable DM with HbA1c ≥8.0 g/dL - autoimmune hepatitis - presence of HBV DNA at or above the sensitivity of detection in patients who did not receive nucleos(t)ide analogue treatment - extrahepatic metastasis and/or microvascular invasion - use of nonsteroidal anti-inflammatory drugs or steroids periodically		further development of prophylactic regimens to prevent TACE-induced postembolization syndrome.

Methodical Notes

Funding Sources: no statement

COI: Dr. Yokosuka received grants from Dainippon Sumitomo

Randomization: The allocation was generated by a computer program located in the Clinical Research Center. The allocation coordinators at the Clinical Research Center enrolled patients and assigned them to the trial groups. Allocation factors were TACE history (absent/present), tumor burden (≤50%/>50%), and Child-Pugh classification (A/B).

Blinding: The study drugs were prepared by nonblinded clinical pharmacists in Chiba University Hospital and distributed to the investigators at the start of trial. The allocation coordinators and the nonblinded clinical pharmacists had no involvement in the rest of the trial. All study investigators and patients were masked to treatment group allocation.

Dropout Rate/ITT-Analysis: 2 different analysis sets:
- 1 patient in dexamethason group did not recieve TACE and was excluded. Therefore, a total of 119 patients were included in intention-to-treat analysis set.
- 3 patients in the dexamethasone regimen and 4 patients in the placebo regimen were excluded for division of protocol due to using cisplatin during TACE, one patient discontinued participation in the study because of intra-abdominal bleeding related to a liver tumor biopsy that was performed before TACE. Therefore, the per-protocol set comprised 56 patients in each of the dexamethasone and placebo regimens.

Notes:
Literatur from submitted hand search.
Evidence label 2: RCT

OXFORD (2011) Appraisal Sheet: Prognostic Studies: *1 Bewertung(en)*

Malagari, K. et al. Chemoembolization with doxorubicin-eluting beads for unresectable hepatocellular carcinoma: five-year survival analysis. Cardiovasc Intervent Radiol. 35. 1119-28. 2012

Population	Intervention	Outcomes/Results
Evidence level: 4 **Study type:** prospective nonrandomized, 1-arm interventional trial **Number of Patient:** initial cohort= 185 patients with 173 finally analysed **Recruitung Phase:** November 2004 until the end of 2007 **Inclusion Criteria:** - intermediate-stage HCC - bilirubin ≤3 mg/dl, aspartate aminotransferase (AST) and alanine amino transferase (ALT) ≤270 IU/l. - chemo-naive **Exclusion Criteria:** - arteriovenous shunts - thrombus within main portal vein - extrahepatic metastases - listed for transplantation	**Intervention:** chemoembolization with DC Beads loaded with doxorubicin (DEB-DOX) every 2 or 3 months - 3 procedures were the routine number of scheduled sessions unless complete response was achieved with two treatments. - During the scheduled DEB-DOX sessions, patients were not receiving any additional treatment with the exception of antiviral medication. - During follow-up, additional therapy (DEB-DOX, ablation, systemic therapy) was applied if suitable. **Comparison:** none	**Primary:** 5-year survival rate **Secondary:** **Results:** Mean overall survival= 43.8 months (range 1.2–64.8) - 48.7 months for Child class A - 36.7 months for Child class B 1, 3, and 5 year survival rates= 93.6%, 62%, and 22.5% - higher rates achieved in Child class A compared with class B (p=0.029) Multivariate analysis Number of lesions, lesion hypervascularity, additional local ablation, sorafenib administration and initially achieved CR and OR are significant and independent determinants of 5-year survival. **Author's Conclusion:** Conclusively, this study (1) shows overall survival rates of 93.6, 62, and 22.5% at 1, 3, and 5 years after sequential sessions of DEB-DOX in HCC patients not amenable to curative treatments and (2) indicates that initially achieved CR and OR are significant and independent determinants of 5-year survival. However, this was a single-arm study, and more solid data are necessary from a randomized study with c-TACE with survival among the primary end points.

Methodical Notes

Funding Sources: no statement

COI: none

Randomization: none

Blinding: none

Dropout Rate/ITT-Analysis: From the initial cohort, 12 patients were lost to follow-up and were excluded (initial cohort= 185 patients with 173 finally analysed)

Notes: Literatur from submitted hand search.
Evidence level 4: Prospective study without blinding and reference standard

NEWCASTLE - OTTAWA Checklist: Cohort: *1 Bewertung(en)*

Takayasu, K. et al. Overall survival after transarterial lipiodol infusion chemotherapy with or without embolization for unresectable hepatocellular carcinoma: propensity score analysis. AJR Am J Roentgenol. 194. 830-7. 2010

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 3 **Study type:** cohort study, multi-center (Japan)	**Funding sources:** no statement **Conflict of Interests:** no statement **Randomization:** none **Blinding:** none **Dropout rates:** none	**Total no. patients:** 11030 patients with unresectable hepatocellular carcinoma: - 8507 in TACE-group - 2523 in transarterial infusion therapy group **Recruiting Phase:** January 1994–December 2001 **Inclusion criteria:** patients with unresectable HCC who underwent TACE or iodized oil transarterial infusion therapy without embolization as initial treatment **Exclusion criteria:** - extrahepatic metastasis to lymph nodes and other organs - any previous treatment before the one studied	**Interventions:** iodized oil transarterial chemoembolization (TACE) **Comparison:** transarterial infusion therapy with an emulsion of iodized oil and an anticancer agent
Notes:	**Literatur from submitted hand search.** Evidence level 3: nonrandomized cohort study **Author's conclusion:** Although a randomized controlled trial remains the reference standard, our analysis of an entire sample and of matched patients with a propensity score showed that in the care of patients with unresectable HCC, the survival rate associated with TACE was significantly higher than that associated with iodized oil infusion chemotherapy without embolization. These results may enhance or change decision-making about the strategy for transcatheter arterial therapy for HCC.		
Outcome Measures/results	**Primary** all-cause mortality **Secondary**	**Results:** crude survival - TACE-group: 1-, 2-, 3-, 4-, 5-, and 7-year overall survival rates: 82%, 62%, 46%, 34%, 25% and 15%; median survival time 2.74 years - no embolization group: 1-, 2-, 3-, 4-, 5-, and 7-year overall survival rates: 66%, 45%, 31%, 23%, 15% and 7%; median survival time 1.69 years	

		- TACE was associated with a significantly higher survival rate than infusion therapy without embolization (hazard ratio, 0.60; 95% CI, 0.56–0.64; p = 0.0001). propensity score analysis - groups were matched for the factors age, sex, degree of liver damage, hepatitis B and C virus status, max. tumor size, no. of tumors, degree of portal vein invasion, degree of hepatic vein invasion, alpha-Fetoprotein level, TNM stage - TACE-group: 1-, 2-, 3-, 4-, 5-, and 7-year overall survival rates: 81%, 62%, 46%, 34%, 25% and 15%; median survival time 2.74 years - no embolization group: 1-, 2-, 3-, 4-, 5-, and 7-year overall survival rates: 71%, 49%, 33%, 23%, 16%, and 7%; median survival time 1.98 years - TACE was associated with a significantly higher survival rate than infusion therapy without embolization (HR, 0.70; 95% CI, 0.63–0.76; p = 0.0001).

Schlüsselfrage:

HCC 16 TACE Ablation
Soll vor Ablation (Radiofrequenz- oder Thermoablation) eines HCC-Herdes bis 5cm eine (Chemo-)Embolisation durchgeführt werden?

Inhalt: *2 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Jianyong, L. 2017	3	non-randomized controlled trial
Majumdar, A. 2017	1	Cochrane Review of randomized clinical trials.

OXFORD (2011) Appraisal Sheet: Systematic Reviews: *1 Bewertung(en)*

Majumdar, A. et al. Management of people with early? or very early?stage hepatocellular carcinoma. Cochrane Database of Systematic Reviews. . . 2017

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 **Study type:** Cochrane Review of randomized clinical trials. **Databases:** Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, MEDLINE (OvidSP), Embase (OvidSP), and Science Citation Index Expanded (Web of Knowledge). World Health Organization International Clinical Trials Registry Platform search portal (apps.who.int/trialsearch/), which searches various trial registers, including ISRCTN (www.isrctn.com/) and ClinicalTrials.gov (clinicaltrials.gov/). **Search period:** From inception to 30 September 2016.	**Population:** Patients with early or very early hepatocellular carcinoma irrespective of the presence of cirrhosis, size of tumour(s), and number of tumours (provided that they met the criteria of early or very early hepatocellular carcinoma (i.e. BCLC stages 0 and A)), presence or absence of portal hypertension, aetiology of hepatocellular carcinoma, and the future remnant liver volume. **Intervention:** Some of the interventions that we considered	**Primary:** 1. Mortality at maximal follow-up (time to death): i) all-cause mortality; ii) cancer-related mortality. 2. Mortality: i) short-term mortality (up to one year); ii) medium-term mortality (one to five years). 3. Adverse events (within three months of cessation of treatment). 4. Quality of life as defined in the included trials using a validated scale such as EQ-5D or 36-Item Short Form Health Survey (SF-36). **Secondary:** 1. Disease recurrence (maximum follow-up): i) proportion of participants with hepatocellular carcinoma recurrence (includes recurrence in the liver and metastatic disease); ii) proportion of participants	TACE plus radiofrequency ablation vs. Radiofrequency ablation: Aikata 2016 Hepatology. El Kady 2013, Hepatology, others: see publication.

Inclusion Criteria: Randomised clinical trials irrespective of language, publication status, or date of publication. **Exclusion Criteria:** Studies of other design because of the risk of bias in such studies. We excluded randomised clinical trials in which participants were previously liver transplanted. In addition, we planned to exclude trials in which liver resection or liver transplantation was combined with ablation, TAE, or TACE.	were: • liver resection; • liver transplantation; • radiofrequency ablation; • microwave ablation; • other ablations (laser ablation, cryoablation, high-intensity focused ultrasound, irreversible electroporation); • alcohol injection; • acetic acid injection; • TAE; • TACE. **Comparison:** either alone or in combination tested versus each other or versus sham or no intervention.	with local recurrence (recurrence in the liver). 2. Length of hospital stay for the treatment and treatment related complications. **Results: Surgery versus radiofrequency ablation:** not part of this evidence table. **Non-surgical interventions:** **by Outcome:** Quality of life: None of the trials reported health related quality of life. Adverse events: There was no evidence of a difference in any of the comparisons that reported serious adverse events (number of participants or number of events). **Transarterial embolisation plus radiofrequency ablation versus radiofrequency ablation** Mortality at maximal follow-up (one trial, 44 participants): HR 1.12 (0.48 to 2.58) Cancer-related mortality at maximal follow-up: None of the trials reported this outcome Serious adverse events (number of participants)(2 trials, 84 participants): OR 2.11 (0.18 to 25.35) (Follow-up: 6 months in 1 trial and not stated in another trial). Further interventions (some evidence of difference): - Mortality at maximal follow-up was higher in the percutaneous acetic acid injection group (HR 1.77, 95% CI 1.12 to 2.79; 125 participants; 1 trial) and the percutaneous alcohol injection group (HR 1.49, 95% CI 1.18 to 1.88; 882 participants; 5 trials; I2 = 57%) than in the radiofrequency ablation group. • Cancer-related mortality at maximal follow-up was higher in the percutaneous alcohol injection group than in the radiofrequency ablation group (OR 2.18, 95% CI 1.22 to 3.89; 458 participants; 3 trials; I2 =	

		0%). • Mortality (> 1 year) was higher in the percutaneous alcohol injection group than in the radiofrequency ablation group (OR 1.69, 95% CI 1.15 to 2.49; 598 participants; 4 trials; I2 = 0%). • Number of any adverse events was lower in the TACE plus percutaneous alcohol injection group than the percutaneous alcohol injection group (RR 0.53, 95% CI 0.42 to 0.67; 52 participants; 1 trial). - The proportion of people with hepatocellular carcinoma recurrence (local or distal) was higher in the percutaneous alcohol injection group than in the radiofrequency ablation group (OR 1.58, 95% CI 1.02 to 2.45; 371 participants; 2 trials; I2 = 0%). • Length of hospital stay was longer in the percutaneous alcohol injection group than in the radiofrequency ablation group (MD 15.30 days, 95% CI 13.23 to 17.37; 232 participants; 1 trial). **Author's Conclusion:** The evidence was of low or very low quality. There was no evidence of a difference in all-cause mortality at maximal follow-up between surgery and radiofrequency ablation in people eligible for surgery. All-cause mortality at maximal follow-up was higher with percutaneous acetic acid injection and percutaneous alcohol injection than with radiofrequency ablation in people not eligible for surgery. There was no evidence of a difference in all-cause mortality at maximal follow-up for the other comparisons. High-quality RCTs designed to assess clinically important differences in all-cause mortality and health-related quality of life, and having an adequate follow-up period (approximately five years) are needed.	

Methodical Notes
Funding Sources: Participants not eligible for surgery: Five trials did not receive any special funding or received funding from parties without vested interest in the results. The source of funding was not reported in the remaining trials. The Danish State is the largest single funder of the Cochrane Hepato-Biliary Group through its investment in The Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen University Hospital, Denmark. **COI:** see puclication **Study Quality:** None of the trials was at low risk of bias for all domains; hence, we considered all trials to be at high risk of bias. Studies regarding **Transarterial embolisation plus radiofrequency ablation versus radiofrequency ablation**: 1Downgraded one level because of within-study risk of bias: there was unclear or high risk of bias in the trial(s). 2Downgraded one level because of imprecision: the sample size was small. 3Downgraded one level because of imprecision: the confidence intervals overlapped clinically significant effect and clinically insignificant effect. **Heterogeneity:** assessed. Subgroup analysis if necessary. **Publication Bias:** We did not assess reporting bias by creating a funnel plot because of the few trials included for each comparison. **Notes:** CEBM Oxford Level of evidence 1 (SR) Only two studies relevant for PICO question.

OXFORD (2011) Appraisal Sheet: RCT: *1 Bewertung(en)*

Jianyong, L. et al. Preoperative adjuvant transarterial chemoembolization cannot improve the long term outcome of radical therapies for hepatocellular carcinoma. Sci Rep. 7. 41624. 2017		
Population	**Intervention - Comparison**	**Outcomes/Results**
Evidence level: 3 **Study type:** non-randomized controlled trial **Number of Patient:** 1560 consecutive patients. **Recruitung Phase:** January 2002 and May 2008, **Inclusion Criteria:** Primary hepatocellular carcinoma, Targets with no previous treatment, Liver cirrhosis classified as Child class A or B, BCLC-HCC stage 0 or A, Accepting RFA, resection or LT.	**Intervention:** - TACE plus RFA group (81 cases), - TACE plus resection group (268 case), - TACE plus LT group (78 cases) and the solitary radical therapy included the RFA group (163 cases), resection group (633 cases), and LT group (337 cases).	**Primary:** The overall survival rate (OSR) and tumor-free survival rate (TFSR). **Secondary:** Procedure-related complications. **Results: RFA vs. TACE+RFA** Overall survival: overall 1-, 3-, and 5-year actual survival rates were comparable (P= 0.958). Tumor free survival: no significant differences (p= 0.696). General: The 1-, 3- and 5-year overall survival rates and tumor-free survival rates were comparable between the solitary radical

Exclusion Criteria: Presence of macro-vascular invasion, Present of extrahepatic target, Severe impairment of another organ, Metastatic hepatic malignancies, Child class C, Gastrointestinal hemorrhage in the past month, Gallbladder carcinoma or extrahepatic primary biliary carcinoma, Intrahepatic cholangiocarcinoma, Metastatic liver disease, Rupture of HCC, Loss to follow-up.	**Comparison:** see Intervention	therapy group and TACE combined group in the whole group and in each of the subgroups (RFA, resection and LT) (P>0.05). In the subgroup analysis, according to BCLC stage A or B, the advantages of adjuvant TACE were also not observed (P>0.05). A Neutrophil-lymphocyte ratio (NLR) more than 4, multiple tumor targets, BCLC stage B, and poor histological grade were significant contributors to the overall and tumor-free survival rates. **Author's Conclusion:** In conclusion, preoperative adjuvant TACE prolonged neither long-term overall survival nor tumor-free survival in patients who accepted RFA, resection or LT. Thus, despite its relatively safety and feasibility, we cannot recommend preoperative adjuvant TACE as a routine procedure before radical therapy in HCC patients. LT should remain the first choice for BCLC-A HCC patients.

Methodical Notes

Funding Sources: This study was supported by grants from the National major projects researches (No. 2012ZX10002-016) and Sichuan Provience Science and Technology Project of China (No. 2017SZ0139).

COI: The authors declare no competing financial interests.

Randomization: no

Blinding: no

Dropout Rate/ITT-Analysis: -

Notes:
CEBM Level of evidence 3 - non-randomized controlled cohort.

Schlüsselfrage:

HCC 17 SIRT
Profitieren Patienten mit einem auf die Leber beschränkten lokal fortgeschrittenen Tumor von einer SIRT?

Inhalt: *3 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Casadei Gardini, A. 2018	1	Systematic review and Meta-analysis of prospective randomized trials. TARE vs. TACE for unresectable HCC.
Ludwig, J. M. 2017	2	Systematic review and Meta-analysis. DEB-TACE vs. 90Y-radioembolization for HCC.
Yang, Y. 2018	1	Systematic review and meta-analysis. Evaluation of the effects and safety of cTACE and TARE (90Y) regimens for HCC.

OXFORD (2011) Appraisal Sheet: Systematic Reviews: *3 Bewertung(en)*

Casadei Gardini, A. et al. Radioembolization versus chemoembolization for unresectable hepatocellular carcinoma: a meta-analysis of randomized trials. Onco Targets Ther. 11. 7315-7321. 2018

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 **Study type:** Systematic review and Meta-analysis of prospective randomized trials. TARE vs. TACE for unresectable HCC. **Databases:** PubMed, Cochrane Library, and Embase.	**Population:** 3 RCTs included. SIRTACE, Mainz, PREMIERE. n=49for TARE, n=48 for TACE. Mean age ranged from 62-71.8 years and %males from 71-87 between trial groups. **Intervention:** TACE **Comparison:** TARE	**Primary:** 1 year survival, 1 year progression-free survival, overall survival, disease progression, disease control rate, or transplantation rate **Secondary:** - **Results:** Overall survival at 1 year: no differences in overall survival at 1 year between the two treatment groups (OR =1.31, 95%CI: 0.56–3.04, P=0.53). Progression free survival: at 1 year not statistically different between the two treatments (OR =0.23, 95% CI: 0.02–2.45, P=0.22). progression rates not significantly	Salem R, et al. Radioembolization Significantly Prolongs Time to Progression Compared With Chemoembolization in Patients With Hepatocellular Carcinoma, Gastroenterology. 2016;151(6):1155–1163. Pitton MB, et al. Randomized comparison of selective internal radiotherapy (SIRT) versus drug-eluting bead transarterial chemoembolization (DEB-TACE) for the treatment of hepatocellular carcinoma. Cardiovasc Intervent Radiol 2015;38(2):352–360. Kolligs FT, et al. Pilot

Search period: Inception -until 04.2017 **Inclusion Criteria:** Randomized controlled trials, patients with HCC were considered, TACE compared with with TARE/SIRT; published as full-text articles in a peer-reviewed journal. **Exclusion Criteria:** not described.		different between groups, with OR values of 0.61 (95% CI: 0.14–2.70, P=0.51). disease control rates were also not significantly different between groups, with OR 1.80 (95% CI: 0.51–6.30, P=0.36). Transplantation rate: Higher portion ofpatients underwent transplantation in the TARE group (30% vs 20.8%), such difference was not statistically significant (OR =0.68 95% CI: 0.23–2.01, P=0.49), **Author's Conclusion:** "Our meta-analysis reveals that TARE and TACE have similar effects in unresectable HCC patients in terms of overall survival, disease control rate, transplantation rate, and progression rate. It is very unlikely that further trials will be conducted in unrestricted HCC populations, and our results suggest that comparative trials could better focus on specific indications, including lobar portal vein invasion, downstaging, or reduction of the dropout rate from transplant waiting lists."	randomized trial of selective internal radiation therapy vs. chemoembolization in unresectable hepatocellular carcinoma. Liver Int. 2015;35(6):1715–1721.

Methodical Notes

Funding Sources: not described.

COI: "Mercedes Iñarrairaegui has received lecture fees from Bayer Healthcare. Bruno Sangro has received lecture or consult fees from SIRTEX Medical and BTG. The authors report no other conflicts of interest in this work."

Study Quality: Yes "All selected trials .. were analyzed and classified using the Jadad score when possible."

Heterogeneity: "A significant heterogeneity between the trials was detected for progression-free survival (I2 test: 76%)"

Publication Bias: not investigated

Notes:
Inclusion and exclusion criteria are vague. High heterogeneity for progression free survival outcome. Publication bias not investigated.
Two of three studies (Kolligs, Riad et al.)are also included in the Meta-Analysis by Yang et al. 2018. However this article investigates partially different outcomes (progression-free survival), therfor no exclusion is necessary.

Ludwig, J. M. et al. Meta-analysis: adjusted indirect comparison of drug-eluting bead transarterial chemoembolization versus (90)Y-radioembolization for hepatocellular carcinoma. Eur Radiol. 27. 2031-2041. 2017

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 2 **Study type:** Systematic review and Meta-analysis. DEB-TACE vs. 90Y-radioembolization for HCC. **Databases:** PubMed/MEDLINE Library, Cochrane, and Embase Database **Search period:** 01/2005-12/2014. **Inclusion Criteria:** Studies comparing DEB-TACE or 90Y-radioembolization with cTACE for HCC treatment **Exclusion Criteria:** Studies were excluded if they dealt with treatment of liver metastasis, primary liver tumours other than HCC, lack of inclusion of at least intermediate or advanced stages of BCLC patients or a comparable staging system, concurrent other treatment, or when only a subgroup (e.g. follow-up of patients after complete tumour remission only) or specifically selected patients (e.g. prior/after liver transplantation) were included in studies. In general, studies were excluded if reported information was lacking detailed information (e.g. survival data) or data was already presumably reported in another, relevant publication. Only the most recent or complete publication was included. Reviews without original data,	**Population:** HCC patients. Study population: 7 studies comparing DEB-TACE versus cTACE (660 patients with 331 in DEBTACE group) and 7 studies on 90Yradioembolization versus cTACE (1405 patients with 405 inthe 90Y-radioembolization group) were selected for meta-analysis. 3 of these were RCTs, with 2 in DEB-TACE and one in the 90Yradioembolization treatment arm. Comparison of tumour size and patients' baseline characteristics only revealed a statistically significant, but not relevant differencefor BCLC stage D between DEB-TACE and 90Yradioembolization studies (0 % vs. 0.8 %; p =0.024). **Intervention:** DEB-TACE **Comparison:** 90Y-radioembolization	**Primary:** 1-, 2-, and 3-year survival. **Secondary:** Overall response status. **Results:** <u>Survival analysis</u> pooled median overall survival estimate for DEB-TACE versus 90Y-radioembolization was 22.6 and 14.7 months. <u>1-year survival rate</u> significantly favoured DEB-TACE, with a pooled survival rate estimate of 79 % versus 54.8 % and an OR of 0.57 (95 % confidence interval (CI): 0.36–0.92; p = 0.02). Stratification revealed that this effect was mainly derived from observational study and was not significant in RCTs (see article). <u>2 and 3-year survival rate</u> Effect of the 1 year analysis was was present but not for the 2-year (61 % vs. 34 %; OR: 0.65; 95%CI: 0.294-1.437; p = 0.29) and 3 year survival 3-year survival (56.4 % vs. 20.9 %; OR:0.713; 95 % CI: 0.21-2.548; p= 0.62). Because of the significant heterogeneity in DEB-TACE versus cTACE studies, evidence for 2-year (I-squared: 71.3 %, p =0.002) and 3-year (I-squared: 79.8 %, p=0.002) survival was limited. <u>Secondary outcome: Tumour response rate:</u> different response rate were used including mRECIST, RECIST, WHO, EASL, AFP.	Golfieri R, et al. (2014) Randomised controlled trial of doxorubicin-eluting beads vs conventional chemoembolisation for hepatocellular carcinoma. Br J Cancer 111:255–264 Recchia F, et al (2012) Chemoembolization of unresectable hepatocellular carcinoma: Decreased toxicity with slow-release doxorubicineluting beads compared with lipiodol.Oncol Rep 27:1377–1383 Song MJ, et al (2012) Comparative study between doxorubicin-eluting beads and conventional transarterial chemoembolization for treatment of hepatocellular carcinoma. J Hepatol 57:1244–1250 Sacco R, et al (2011) Conventional versus doxorubicin-eluting bead trans-arterial chemoembolization for hepatocellular carcinoma. J Vasc Interv Radiol 22:1545–1552 Ferrer Puchol MD, et al (2011) Comparison of doxorubicin-eluting bead trans-arterial chemoembolization (DEBTACE) with conventional transarterial chemo-embolization(TACE) for the treatment of hepatocellular carcinoma. Radiologia 53:246–253 Wiggermann P, et al (2011) Transarterial Chemoembolization of Child-A hepatocellular carcinoma: drugeluting bead TACE (DEB TACE) vs. TACE with cisplatin/lipiodol (cTACE). Med Sci Monit 17:CR189–CR195 Dhanasekaran R, et al (2010) Comparison of conventional transarterial chemo-embolization (TACE) and chemoembolization with

abstracts only, editorials, letters, case reports, expert opinions, and single-arm studies, as well as studies in languages other than English were excluded.		mRECIST was the most frequently reported criteria, in the 3most recent studies in the DEB-TACE arm most recent studies in the DEB-TACE arm and 2 studies in the 90Y-radioembolization arm. Available mRECIST overall response: no significant difference (OR: 0.71; 95 % CI: 0.13–4.08, p = 0.07), although results favoured DEB-TACE, but high heterogeneity (I-squared: 79.1 %; p = 0.03). Safety, hospitalization, number of treatments: No meta-analysis, see paper **Author's Conclusion:** "This indirect meta-analytical comparison of 736 patients treated with 90Y-radioembolization or DEB-TACE showed a survival benefit at 1-year for DEB-TACE over 90Yradioembolization and a favourable survival trend at 2 and 3 years for DEB-TACE. However, this indirect comparison is not without limitations warranting for further direct comparative evaluation of DEB-TACE vs. 90Y-radioembolization."	doxorubicin drug eluting beads (DEB) for unresectable hepatocelluar carcinoma(HCC). J Surg Oncol 101:476–480 Kolligs FT, et al (2014) Pilot randomized trial of selective internal radiation therapy vs. chemoembolization in unresectable hepatocellular carcinoma. Liver Int. doi:10.1111/liv.12750 El Fouly A, et al (2015) In intermediate stage hepatocellular carcinoma: radioembolization with yttrium 90 or chemoembolization? Liver Int 35:627–635 Moreno-Luna LE, Yang JD, Sanchez Wet al (2013) Efficacy and safety of trans-arterial radioembolization versus chemoembolization in patients with hepato-cellular carcinoma. Cardiovasc InterventRadiol 36:714–723 Salem R, et al (2011) Radioembolization results in longer time-to-progression and reduced toxicity compared with chemoembolization in patients with hepatocellular carcinoma.Gastroenterology 140:497–507, e492 Lance C, et al (2011) Comparative analysis of the safety and efficacy of transcatheter arterial chemoembolization and yttrium-90 radioembolization in patients with unresectable hepatocellular carcinoma. J Vasc Interv Radiol 22:1697–1705 Kooby DA, et al (2010) Comparison of yttrium-90 radioembolization and trans-catheter arterial chemoembolization for the treatment of unresectable hepatocellular carcinoma. J Vasc Interv Radiol 21:224–230 Carr BI, Kondragunta V, Buch SC, Branch RA (2010) Therapeutic equivalence in survival for hepatic arterial chemoembolization and yttrium 90 microsphere

			treatments in unresectable hepatocellular carcinoma: a two-cohort study. Cancer 116:1305–1314

Methodical Notes

Funding Sources: "The authors state that this work has not received any funding."

COI: "The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article."

Study Quality: Study quality was not investigated.

Heterogeneity: High heterogeneity was found for the 2 (I-squared: 71.3 %,p =0.002) and 3 year (I-squared: 79.8 %, p=0.002) survival outcome, not for 1 year survival outcome.

Publication Bias: "There was significant publication bias in the studies used for the 3-year analysis in DEBTACE versus cTACE studies (Egger's test: p=0.02; Begg'stest: p = 0.04)."

Notes:
Study quality not investigated. High heterogeneity in the 2 and 3 year overall survival, but this is considered for the conclusion and investigated in the article.
Downgraded to evidence level 2 due to low quality

Yang, Y. et al. Yttrium-90 transarterial radioembolization versus conventional transarterial chemoembolization for patients with hepatocellular carcinoma: a systematic review and meta-analysis. Cancer Biol Med. 15. 299-310. 2018

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 **Study type:** Systematic review and meta-analysis. Evaluation of the effects and safety of cTACE and TARE (90Y) regimens for HCC. **Databases:** PubMed, Embase, EBSCO, Cochrane Library, Web of Science, and MedLine, ClinicalTrials.gov **Search period:** 01/2009-07/2017 **Inclusion Criteria:** 1) Randomized controlled trials (RCT), observational studies, and clinical studies. 2) Patients were diagnosed with HCC. 3) cTACE or TARE (90Y) as monotherapy. 4) Showed the effects and/or safety after treatment with	**Population:** HCC patients. 11 studies included in the meta-analysis (2 RCTs, 9 observational studies). Samle size 28-790. Age mean 58-66. Details on gender, tumor classification see article. **Intervention:** cTACE **Comparison:** TARE (90Y)	**Primary:** 1-year and 2-year overall survival (OS) rates, objective responses (ORs), and serious adverse events (AEs). **Secondary:** - **Results:** 1-year OS rates: No significant differences in 1-year OS rates (OR* = 0.939, 95% CI: 0.705–1.251, P = 0.66), 10 studies, fixed effects model. 2-year OS rates: (OR* = 0.575, 95% CI: 0.336–0.984, P = 0.043), 9 studies, random effects model, demonstrated that the TARE (90Y) group had a significantly higher 2-year OS rate than the cTACE group in observational studies. Objective response: 9 studies (4 with WHO	Soydal C, et al. Comparison of survival, safety, and efficacy after transarterial chemoembolization and radioembolization of Barcelona Clinic Liver Cancer stage B-C hepatocellular cancer patients. Nucl Med Commun. 2016; 37: 646-9. Salem R, et al. Y90 radioembolization significantly prolongs time to progression compared with chemoembolization in patients with hepatocellular carcinoma. Gastroenterology. 2016; 151: 1155-63.e2. Kolligs FT, et al. Pilot randomized trial of selective internal radiation therapy vs. chemoembolization in

cTACE or TARE (90Y). **Exclusion Criteria:** 1) Reviews, commentaries, case reports, meeting abstracts, experimental studies, systematic reviews, and meta-analyses. 2) No comparison between cTACE and TARE (90Y) therapies. 3) cTACE combined with TARE (90Y). 4) Drug eluting bead-TACE(DEB-TACE) as monotherapy. 5) Lacked key data from outcomes after treatment with cTACE or TARE (90Y).		criteria, 5 with mRECIST criteria). Significant differences were found in the mRECIST subgroup (OR* = 0.584, 95% CI: 0.349–0.976, P = 0.040), favoring TARE (90Y). No significant differences were noted in the WHO subgroup analysis (OR* = 1.065; 95% CI:0.500–2.268, P = 0.870). Overall pooled analysis (OR* = 0.781, 95% CI: 0.454–1.343, P = 0.371) was considered to have statistics that were less constructive than those of the other analyses and poorly reliable. Serious adverse events9 studies, serious AEs were defined as AEs of grades 3/4 (CTCAE V3.0). Subgroup and overall pooled analyses demonstrated that there was no significant difference among modalities in serious AEs using random effects model (RCT RR = 0.680; 95% CI: 0.325–1.423, P = 0.306; observational study RR = 1.925; 95% CI: 0.978–3.788, P = 0.058; overall pooled RR = 1.477, 95% CI: 0.864–2.526, P = 0.154), **Author's Conclusion:** "Although additional studies are urgently needed to establish clinical trials and RCTs, our findings generally support the application of TARE (90Y) for patients with HCC (especially intermediate or advanced stages) as a therapy that might be superior to cTACE, in 2-year OS rates and OR rates, according mRECIST criteria."	unresectable hepatocellular carcinoma. Liver Int. 2015; 35: 1715-21. El Fouly A, et al. In intermediate stage hepatocellular carcinoma: radio-embolization with yttrium 90 or chemoembolization? Liver Int. 2015; 35: 627-35. She WH, et al. Survival analysis of transarterial radioembolization with yttrium-90 for hepatocellular carcinoma patients with HBV infection. Hepatobiliary Surg Nutr. 2014; 3: 185-93. Moreno-Luna LE, et al. Efficacy and safety of transarterial radioembolization versus chemoembolization in patients with hepatocellular carcinoma. Cardiovasc Intervent Radiol.2013; 36: 714-23. Salem R, et al. Radioembolization results in longer time-to-progression and reduced toxicity compared with chemoembolization in patients with hepatocellular carcinoma. Gastroenterology. 2011;140: 497-507.e2. Lance C, et al. Comparative analysis of the safety and efficacy of transcatheter arterial chemoembolization and yttrium-90 radioembolization in patients with unresectable hepatocellular carcinoma. J Vasc Interv Radiol. 2011; 22: 1697-705. Kooby DA, et al. Comparison of yttrium-90 radioembolization and transcatheter arterial chemoembolization for the treatment of unresectable hepatocellular carcinoma. J Vasc Interv Radiol.2010; 21: 224-30.

			Carr BI, et al. Therapeutic equivalence in survival for hepatic arterial chemoembolization and yttrium 90 microsphere treatments in unresectable hepatocellular carcinoma: a two-cohort study. Cancer. 2010; 116: 1305-14. Lewandowski RJ, et al. A comparative analysis of transarterial downstaging for hepatocellular carcinoma: chemoembolization versus radioembolization. Am J Transplant. 2009; 9: 1920-8.

Methodical Notes

Funding Sources: not described.

COI: "No potential conflicts of interest are disclosed."

Study Quality: "A quality assessment of the extracted studies was performed according to the Newcastle-Ottawa Scale (NOS), which grades the quality of observational studies on a 9-point scale. The risk of bias for RCTs was assessed using the Cochrane Collaboration tool of RevMan."
"All 9 observational studies were judged as high quality. One RCT, with more than two high-risk components, was considered to have a moderate risk of bias, and another RCT was determined to have a low risk of bias."

Heterogeneity: "Great heterogeneity was observed because both observational studies and RCTs were included in the meta-analysis." "We used the Q- and I2-tests to evaluate data heterogeneity, where $P < 0.1$, for the Q-test, or $I2 > 50\%$ represented significant heterogeneity. Sensitivity analysis was conducted by limiting the quality of the studies. Only studies that were determined to be of high quality, or with moderate /low risk of bias, were extracted"

Publication Bias: "No significant publication bias was found using funnel plots. Egger's test: 1-year OS rate group, $P = 0.605$; 2-year OS rate group, $P = 0.591$; serious AEs group, $P = 0.797$."

Notes:
High heterogeneity in some analyses, but this is well discussed, investigated and interpreted in the article.

Schlüsselfrage:

HCC 20 Systemtherapie
Von welchen Systemtherapien profitieren Patienten mit fortgeschrittenem HCC?

Inhalt: *18 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Abou-Alfa, G. K. 2018	2	randomized, double-blind, phase 3 trial
Bruix, J. 2017	2	randomized, controlled, double-blind study
Bruix, Jordi 2015	2	Randomised, double-blind, placebo-controlled, phase 3 study.
Daniele, B. 2015	3	prospective, open-label, noninterventional study (sub-analysis of European population)
El-Khoueiry, A. B. 2017	3	phase 1/2, open-label, non-comparative, dose escalation and expansion trial
Ganten, T. M. 2017	3	observational cohort study, noninterventional, prospective, multicenter.
Kambhampati, S. 2019	4	retrospective case series
Leal, C. R. G. 2018	3	Non-randomized phase 2 controlled trial
Lencioni, R. 2016	2	Phase II randomized, double-blind, placebo-controlled study.
Marrero, J. A. 2016	3	Prospective, observational, registry study (GIDEON).
McNamara, M. G. 2018	2	systematic review and meta analysis
Meyer, Tim 2017	2	Randomized, double-blind, placebo-controlled study.
Park, J. W. 2019	2	Randomized, Controlled Phase III Trial
Pressiani, T. 2013	3	multicentre, phase II, open-label trial
Wang, H. 2018	1	systematic review and meta analysis
Zhu, A. X. 2018	3	non-randomised, multicentre, open-label, phase 2 trial
Zhu, A. X. 2015	2	Randomized, controlled, double-blind, phase 3 study
Zhu, Andrew X. 2019	2	randomised, double-blind, placebo-controlled, phase 3 trial

OXFORD (2011) Appraisal Sheet: Systematic Reviews: *2 Bewertung(en)*

McNamara, M. G. et al. Sorafenib as first-line therapy in patients with advanced Child-Pugh B hepatocellular carcinoma-a meta-analysis. Eur J Cancer. 105. 1-9. 2018

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 2 **Study type:** systematic review and meta analysis **Databases:** Medline [host: Ovid], Embase [host:Ovid], Cochrane database of systematic reviews) **Search period:** from 2002 to February 2015 **Inclusion Criteria:** studies investigating the use of first-line sorafenib therapy in patients with advanced HCC and Child-Pugh A or B liver function **Exclusion Criteria:** studies were excluded if they included patients with HIV or if data were split by alpha-fetoprotein (AFP) responders, development of skin toxicity or age	**Population:** patients with advanced HCC and Child-Pugh A or B liver function **Intervention:** sorafenib as first-line therapy **Comparison:** none	**Primary:** overall survival response rate adverse events **Secondary:** none **Results:** basics - 30 studies included comprising 8678 patients - Child-Pugh status was available for 8577 patients (99%), among whom 79% were classified as Child-Pugh A and 19% as Child-Pugh B overall survival - median OS for the entire cohort was 7.2 months: 8.8 months in Child-Pugh A and 4.6 months in Child-Pugh B cirrhosis. - Among the four studies (N=394) reporting a multivariable comparison of the Child-Pugh status, CP B liver function was associated with a significantly worse OS (HR 2.82, 95% CI 2.04-3.92,P<0.001) response rate - no differences in the reported response rates between those with Child-Pugh A (4.6%) or Child-Pugh B liver function (4.2%) (P=0.9) adverse events - 35% of patients with Child-Pugh A and 35% with Child-Pugh B developed a grade III or IV AE (OR 0.95,95% CI 0.73-1.23,P=0.7). - no difference in reported grade III/IV skin rash (OR 0.56,95% CI 0.21-1.49,P=0.25), diarrhoea (OR 1.12, 95%CI 0.61-2.06,P=0.72) or hypertension (OR 0.45, 95%CI 0.13-1.61,P=0.22) **Author's Conclusion:** In conclusion, there were similar response rates and rates of treatment discontinuation without progression and similar rates of treatment-related death in patients with Child-Pugh B liver function, which is unlikely to be clinically meaningful as survival was shorter than in those with a Child-Pugh A score, driven by liver dysfunction; therefore, sorafenib should be used with caution in the population of patients with a Child-Pugh score of B. In addition, use of the Child-Pugh score alone may not have adequate discriminatory ability in choosing patients for inclusion within clinical trials, and combination or alternative scores could be considered.	- 30 studies included - see article for citations

Methodical Notes

Funding Sources: - Dr. Rille Pihlak is funded by the Collins PhD fellowship and Pancreatic Cancer UK.
- Dr. Angela Lamarca was partly funded by the European Society for Medical Oncology Translational Fellowship Programme and the Pancreatic Cancer Research Fund.
- Dr Noor ul-ain-Tariq was funded by the Timpson PhD fellowship.

COI: - Dr McNamara and Dr Hubner have received travel and accommodation assistance from Bayer HealthCare Pharmaceuticals, Inc.
- All other authors have no conflicts of interest to declare.

Study Quality: not assessed

Heterogeneity: - Statistical heterogeneity was reported using Cochran Q and I^2 statistics. For analyses where there was evidence of statistical heterogeneity (Cochran Q $p<0.10$ or $I^2>50\%$), the random effect method was used. Otherwise, the fixed effect model was used.
- no hetereogeneity noticed among studies

Publication Bias: not assessed

Notes:
evidence level 2: SR and MA, downgraded due to missing study quality assessment

Wang, H. et al. Alternative treatment strategies to sorafenib in patients with advanced hepatocellular carcinoma: a meta-analysis of randomized Phase III trials. Onco Targets Ther. 11. 5195-5201. 2018

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 **Study type:** systematic review and meta analysis **Databases:** PubMed, Embase, Chinese National Knowledge Infrastructure, and Wanfang **Search period:** none **Inclusion Criteria:** - randomized Phase III trials, - OS or TTP reported, - one treatment group receiving sorafenib and the other receiving other TKIs or SIRT, - HCC patients with Child–Pugh A or B liver-function status, performance status (PS) 0–1, and Barcelona Clinic	**Population:** HCC patients with Child–Pugh A or B liver-function status, performance status (PS) 0–1, and Barcelona Clinic Liver Cancer B or C **Intervention:** sorafenib **Comparison:** other tyrosine-kinase inhibitors or Selective internal radiation therapy	**Primary:** overall survival (OS) time to progression (TTP) **Secondary:** objective response rate (ORR) disease-control rate (DCR) adverse events (AE) **Results:** <u>basics</u> - a total of four trials in the other-TKI group (sunitinib, brivanib, linifanib, lenvatinib, each) and two trials in the SIRT group were eligible **other TKIs vs. sorafenib** <u>Main analyses of OS and TTP</u> - Other TKIs showed similar benefit on OS to sorafenib for advanced HCC (HR 1.08, 95% CI 0.93–1.24; P=0.31), with heterogeneity among the trials (P=0.008, I^2=74%) - pooled HR of TTP was 0.86 (95% CI 0.66–1.12, P=0.26) with significantly high heterogeneity (I^2=92%, P<0.00001) <u>analyses of ORR and DCR</u> - Other TKIs showed greater ORR than sorafenib (RR 1.67, 95% CI 1.15–2.43; P=0.008) but no improvement compared with sorafenib for DCR (RR 1.11, 95% CI 0.98–1.26; P=0.11) <u>AE</u>	Cheng et al 2013, J Clin Oncol. Johnson et al 2013, J Clin Oncol. Cainap et al 2015, J Clin Oncol. Kudo et al 2018, Lancet Vilgrain et al 2017, Lancet Oncol. Chow et al 2018, J Clin Oncol.

Liver Cancer B or C **Exclusion Criteria:** - Reviews - retrospective studies - studies unrelated to the topics - studies without outcomes of interest		- other TKIs were associated with higher incidence of hypertension (RR 1.99, 95% CI 1.67–2.39; P<0.00001), fatigue (RR 1.79, 95% CI 1.42–2.26; P<0.00001), thrombocytopenia (RR 4.18, 95% CI 1.66–10.56; P=0.002), decreased appetite (RR 2.21, 95% CI 1.62–3.01; P<0.00001) and vomiting (RR 3.15, 95% CI 1.88–5.26; P<0.0001). - hand–foot syndrome (RR 0.39, 95% CI 0.19–0.82; P=0.01) and rash (RR 0.34, 95% CI 0.17–0.68; P=0.002) occurred less frequently in the other-TKI group than the sorafenib group **SIRT vs sorafenib** Main analyses of OS and TTP - Pooled HRs for OS and TTP were 1.14 (95% CI 0.98–1.32, P=0.09) and 0.87 (95% CI 0.74–1.02, P=0.10), showing similar efficacy in the SIRT and sorafenib groups. - no heterogeneity between the trials for OS (I^2=0, P=0.87) or TTP (I^2=0; P=0.94) analyses of ORR and DCR - The ORR was significantly greater (RR 2.60, 95% CI 1.69–4.00; P<0.0001) in the SIRT group than the sorafenib group, but no improvement in DCR (RR 0.91, 95% CI 0.81–1.02; P=0.11) was identified in the SIRT group AE - The incidence of diarrhea (RR 0.10, 95% CI 0.03–0.28; P<0.0001), fatigue (RR 0.42, 95% CI 0.26–0.69) P=0.0006) and hand–foot syndrome (RR 0.04, 95% CI 0.01–0.22; P=0.0002) was significantly lower in the SIRT group - no significant differences between SIRT and sorafenib in the occurrence of pyrexia (P=0.15), nausea (P=0.78), abdominal pain (P=0.23), ascites (P=0.62) gastric ulcer (P=0.22) or upper gastrointestinal hemorrhage (P=0.34) **Author's Conclusion:** Conclusively, other TKIs and sorafenib resulted in similar OS and TTP in advanced HCC. ORR favored other TKIs, whereas safety results favored sorafenib. For patients with locally advanced HCC, OS did not differ significantly between SIRT and sorafenib. Moreover, SIRT was associated with higher ORR and fewer AEs than sorafenib.	

Methodical Notes

Funding Sources: This work was supported by the Innovation and Entrepreneurship Program of Jiangsu Province (2017).

COI: The authors report no conflicts of interest in this work

Study Quality: - The Jadad scoring system was used to assess study quality, graded 0–5 depending on randomization, blinding, and dropout.
- 4 studies scored 3 points, while the other 2 scored 5 points

Heterogeneity: - To evaluate statistical heterogeneity across the studies, $\chi 2$ and I^2 statistics were used, with predefined significance for $\chi 2$ P-value <0.1 or I^2>50%
- see results for heterogeneity values

Publication Bias: not assessed

Notes:
evidence level 1: SR and MA

OXFORD (2011) Appraisal Sheet: RCT: *13 Bewertung(en)*

Abou-Alfa, G. K. et al. Cabozantinib in Patients with Advanced and Progressing Hepatocellular Carcinoma. N Engl J Med. 379. 54-63. 2018

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** randomized, double-blind, phase 3 trial **Number of Patient:** 707 patients (470 patients had been assigned to receive cabozantinib and 237 to receive placebo) **Recruitung Phase:** September 2013 through September 2017 (cut off date for this second interim analysis June 01, 2017) **Inclusion Criteria:** - 18 years of age or older, - received a pathological diagnosis of hepato-cellular carcinoma that was not amenable to curative treatment - Child–Pugh class A liver function - had received previous treatment	**Intervention:** 60mg tablet of cabozantinib or a matched placebo tablet to be taken orally once per day as long as they had clinical benefit or until unacceptable toxic effects. **Comparison:** matched placebo	**Primary:** - overall survival (defined as the time from randomization to death from any cause) **Secondary:** - progression-free survival (defined as the time from randomization to radiographic progression or death from any cause, whichever occurred first) - objective response rate (percentage of patients with a confirmed complete or partial response) - adverse events **Results:** <u>overall survival</u> - The median overall survival was 10.2 months (95% confidence interval [CI], 9.1 to 12.0) in the cabozantinib group and 8.0 months (95% CI, 6.8 to 9.4) in the placebo group - stratified hazard ratio for death was 0.76 (95% CI, 0.63 to 0.92; p=0.005) - results for overall survival across subgroups were more variable <u>progression-free survival</u> - median progression-free survival was 5.2 months (95% CI, 4.0 to 5.5) in the cabozantinib group and 1.9 months (95% CI, 1.9 to 1.9) in the placebo group. - stratified hazard ratio for disease progression or death was 0.44 (95% CI, 0.36 to 0.52; P<0.001 - Subgroup analyses of PFS consistently favored cabozantinib <u>objective response rate</u> - The objective response rate was 4% (18 partial responses among 470 patients) in the cabozantinib group and less than 1% (1 partial response among 237 patients) in the placebo group (P=0.009)

with sorafenib and had disease progression after at least one systemic treatment for hepatocellular carcinoma - Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1 - adequate hematologic measures - adequate renal function. **Exclusion Criteria:** - patients could not have had previous treatment with cabozantinib and could not have uncontrolled clinically significant illness.		- Disease control (defined as a partial response or stable disease) was achieved in 64% of the patients (300 patients) in the cabozantinib group, as compared with 33% (79 patients) in the placebo group. adverse events - rate of discontinuation due to adverse events (related to the trial regimen) was 16% (76 patients) in the cabozantinib group and 3% (7 patients) in the placebo group. - Grade 3 or 4 adverse events occurred in 68% of patients in the cabozantinib group and in 36% in the placebo group. - The most common high-grade events were palmar–plantar erythro-dysesthesia (17% with cabozantinib vs. 0% with placebo), hypertension (16% vs. 2%), increased aspartate aminotransferase level (12% vs. 7%), fatigue (10% vs. 4%) and diarrhea (10% vs. 2%) **Author's Conclusion:** In conclusion, treatment with cabozantinib, a tyrosine kinase inhibitor that targets MET, VEGF receptors, and AXL, resulted in longer overall survival and progression-free survival than placebo in patients with previously treated advanced hepatocellular carcinoma. Adverse events were consistent with the known safety profile of cabozantinib, and the rate of high-grade adverse events in the cabozantinib group was approximately twice that observed in the placebo group.

Methodical Notes

Funding Sources: Supported by Exelixis. Dr. Meyer is funded in part by the University College London Hospitals Biomedical Research Centre.
The trial was designed by the first and last authors in collaboration with the sponsor, and the authors and the sponsor were responsible for data collection and analysis. The authors vouch for the fidelity of the trial to the protocol and for the accuracy and complete-ness of the data. The first and last authors wrote the first draft of the manuscript in collaboration with the sponsor. Medical writing support was provided by the sponsor.

COI: - Dr. Abou-Alfa reports receiving consulting fees and advisory board fees from Bayer and BMS;
- Dr. Meyer, receiving grant support and consulting fees from Bayer and BTG, and consulting fees from BMS, Merck, and Eisai;
- Dr. Cheng, receiving consulting fees from BMS, Ono, MSD, and BeiGene, advisory board fees from Novartis, and consulting fees and honoraria from Bayer and Merck;
- Dr. El-Khoueiry, receiving advisory board fees and consulting fees from Bristol-Myers Squibb and Bayer, advisory board fees from Eisai, Novartis, Roche, Exelixis, Celgene and CytomX, grant support and advisory board fees from AstraZeneca, grant support from Astex, and fees for serving on a speakers' bureau from Merrimack;
- Dr. Rimassa, receiving advisory board fees from Lilly, Bayer, Sirtex Medical, and Exelixis, consulting fees and travel support from ArQule and Ipsen, and lecture fees from AstraZeneca and AbbVie;
- Dr. Park, receiving advisory board fees from BMS, Midatech, and AstraZeneca, advisory board fees and honoraria from Ono and Eisai, and honoraria from Bayer;
- Dr. Blanc, receiving advisory board fees from Bayer, BMS, Lilly Oncology, Shire, and Onxeo;
- Dr. Bolondi, receiving advisory board fees and lecture fees from Bayer, BMS, Sirtex, and Guerbet, and lecture fees from Eli Lilly, Meda-Pharm, and Bracco;
- Dr. Klümpen, serving on an advisory board for Ipsen;
- Dr. Zagonel, receiving consulting fees,advisory board fees, and fees for serving on a speakers' bureau from Bristol-Myers Squibb, consulting fees and advisory board fees from Celgene, consulting fees, advisory board fees, and travel support from Merck, fees for serving on a speakers' bureau and travel

support from Bayer and Roche, and fees for serving on a speakers' bureau from Pfizer and Janssen;
- Mr. Hessel and Dr. Schwab, being employed by and holding stock in Exelixis;
- Dr. Borgman-Hagey, being employed by and holding stock in Exelixis;
- Dr. Kelley, receiving grant support and travel support paid to her institution, provision of trial drugs, and printing and processing costs from AstraZeneca, grant support paid to her institution from Acceleron, grant support paid to her institution and provision of trial drugs from Adaptimmune, Eli Lilly, MedImmune, Celgene, Regeneron, Merck, Tekmira, Novartis, and Taiho, grant support and fees for serving on a steering committee paid to her institution, and provision of trial drugs from Agios, grant support and advisory board fees paid to her institution, and provision of trial drugs from Bayer and Bristol-Myers Squibb, grant support paid to her institution from Sanofi and Debio, and fees for serving on a steering committee paid to her institution from TARGET Pharma Solutions.
- No other potential conflict of interest relevant to this article was reported

Randomization: patients were randomly assigned, in a 2:1 ratio, to receive cabozantinib or placebo. Randomization was performed at a central location through an interactive response system with the use of permuted blocks, stratified according to etiologic factor (hepatitis B virus [HBV], with or without hepatitis C virus [HCV]; HCV without HBV; or other), geographic region (Asia or other), and evidence of extrahepatic spread of disease, macrovascular invasion, or both (yes or no).

Blinding: study specified as "double-blind", but no detailed description on the blinding process

Dropout Rate/ITT-Analysis: - 707 patients had undergone randomization: these patients made up the intention-to-treat population for efficacy analyses
- The safety population comprised 704 patients

Notes:
evidence level 2: randomized controlled trial

Bruix, J. et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 389. 56-66. 2017

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** randomized, controlled, double-blind study **Number of Patient:** 573 were enrolled and randomised (379 to regorafenib and 194 to placebo; population for efficacy analyses). 216 patients (38%) were from Asia. **Recruitung Phase:** Between May 14, 2013, and Dec 31, 2015 **Inclusion Criteria:** - adults with HCC confirmed by pathological assessment or non-invasive assessment according to the American Association for the Study of	**Intervention:** 160 mg regorafenib (four 40 mg tablets) orally or matching placebo once daily for the first 3 weeks of each 4-week cycle **Comparison:** matching placebo	**Primary:** overall survival (time from randomisation to death due to any cause), analysed by intention to treat (ITT). **Secondary:** - progression-free survival (randomisation to radiological or clinical disease progression or death; by ITT), - time to progression (randomisation to radiological or clinical disease progression; by ITT), - objective response rate (patients with complete or partial response), and disease control rate (patients with complete response, partial response, or stable disease maintained for ≥6 weeks), assessed by investigators using mRECIST and RECIST 1.1 **Results:** <u>overall survival</u> - Median overall survival was 10.6 months (95% CI 9.1–12.1) with regorafenib and 7.8 months (6.3–8.8) with placebo (HR 0.63 [95% CI 0.50–0.79]; one-sided p<0·0001) - improvement in overall survival with regorafenib was maintained in all preplanned subgroup analyses <u>secondary outcomes</u> - Median progression-free survival by mRECIST was

Liver Diseases criteria for patients with confirmed cirrhosis - had to have at least one measurable lesion by modified RECIST and RECIST v1.1 - Patients were BCLC stage B or C - could not benefit from resection, local ablation, or chemoembolisation, - must have had documented radiological progression during sorafenib treatment as defined in a study-specific radiology charter - must have tolerated sorafenib (≥400 mg daily for at least 20 of the 28 days before discontinuation) and received their last sorafenib dose within 10 weeks of randomisation. - were required to have Child-Pugh A liver function **Exclusion Criteria:** patients were excluded if they had received any other previous systemic treatment for HCC or if they discontinued sorafenib for toxicity		3.1 months (95% CI 2.8–4.2) with regorafenib and 1.5 months (1.4–1.6) with placebo - Median time to progression by mRECIST was 3.2 months (95% CI 2.9–4.2) with regorafenib and 1.5 months (1.4–1.6) with placebo. - Predefined subgroup analysis for progression-free survival and time to progression also showed a consistent benefit. The HRs for progression-free survival and time to progression assessed by RECIST 1.1 were comparable - Of patients who started treatment, 309 (83%) receiving regorafenib and 183 (95%) receiving placebo discontinued study treatment: The most common reason for discontinuation was disease progression (226 [60%] in the regorafenib group and 162 [84%] in the placebo group) - Two patients (1% [95% CI<1–2]) in the regorafenib group versus no patients in the placebo group had a complete response and 38 patients (10% [7–14]) in the regorafenib group versus eight patients (4% [2–8]) in the placebo group had a partial response - 40 (11%) of 379 patients in the regorafenib group versus eight (4%) of 194 patients in the placebo group achieved an objective response (p=0.0047) - 247 (65%) of 379 patients in the regorafenib group versus 70 (36%) of 194 patients in the placebo group achieved disease control (p<0.0001) adverse events - most common clinically relevant grade 3 or 4 treatment-emergent events were hypertension (57 patients [15%] in the regorafenib group vs nine patients [5%] in the placebo group), hand–foot skin reaction (47 patients [13%] vs one [1%]), fatigue (34 patients [9%] vs nine patients [5%]), and diarrhoea (12 patients [3%] vs no patients). - Of the 88 deaths (grade 5 adverse events) reported during the study (50 patients [13%] assigned to regorafenib and 38 [20%] assigned to placebo), seven (2%) were considered by the investigator to be related to study drug in the regorafenib group and two (1%) in the placebo group, including two patients (1%) with hepatic failure in the placebo group. **Author's Conclusion:** The results of this study represent a significant advance in addressing an unmet need in the treatment of HCC. All previous second-line trials of novel agents have failed; thus no effective systemic therapies after progression on sorafenib are currently available. These data underscore that prolonging exposure to multikinase inhibitors such as the sequence of sorafenib and regorafenib in conjunction with proper management of adverse events can lead to an extension in survival. In conclusion, this study met its primary endpoint showing that regorafenib improves overall survival in patients with HCC who had disease progression during first-line treatment with sorafenib.
Methodical Notes		

Funding Sources: The funder (Bayer) provided the study drug and worked with the principal investigator (JB) and the study steering committee to design the study. Data collection and interpretation and preparation of this report, were done by the investigators and the funder. Statistical analyses were performed by the funder. All authors reviewed this report and approved the submission for publication, had full access to the data, and vouch for the completeness and accuracy of the data and adherence of the study to the protocol. The funder funded writing assistance.

COI: - JB has received grants and personal fees from Bayer; consultancy and advisory fees from Bayer and Novartis; and consultancy fees from Gilead, AbbVie, Kowa, BTG, ArQule, Terumo, Bristol-Myers Squibb, Boehringer Ingelheim, OSI, Roche, Eisai, Sirtex, and Onxeo.
- PM has received consultancy fees from Bayer.
- OY has received grants from Gilead Sciences, MSD, Bayer, Mitsubishi Tanabe Pharma, and Bristol-Myers Squibb.
- OR has received personal fees from Transgene and Bristol-Myers Squibb.
- VB has received personal fees from Bayer, Boehringer Ingelheim, Pfizer, MSD, and Roche; and non-financial support from Boehringer Ingelheim, Pfizer, and MSD.
- RG has received advisory fees from Bayer France.
- PJR has received personal fees from Bayer, Celgene, Roche, Merck, and Sirtex; advisory fees from Bayer, Baxalta, Amgen, and Sanofi ; speaker fees from Celgene; and support for attending meetings from Bayer, Celgene, and Merck.
- J-PB has received grants from Bayer during the conduct of the study and lecturing and consultancy fees from Bayer.
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- A-LC has received consultancy fees from Novartis, Eisai, MSD, Bayer, Ono Pharmaceuticals, Bristol-Myers Squibb, and Merck Serono.
- JML has received grants from Bayer, Bristol-Myers Squibb, Blueprint Medicines, and Boehringer Ingelheim; and consultancy fees from Bayer, Bristol-Myers Squibb, Blueprint Medicines, Boehringer Ingelheim, Lilly Pharmaceuticals, Celsion, Biocompatibles, and Novartis.
- RSF has received grants, consultancy fees, and travel support from Bayer, Pfizer, Novartis, and Bristol-Myers Squibb.
- M-AL is an employee of Bayer.
- AB is an employee of Bayer.
- GMe is an employee of Bayer and owns stock in Bayer.
- GH has received a grant and advisory board and speaker fees from Bayer.
- SQ, AG, Y-HH, GB, MP, GMa, and TS declare no competing interests.

Randomization: Patients were randomly assigned (2:1) to regorafenib or placebo using a computer-generated randomisation list prepared by the funder. Randomisation was stratified by geographical region (Asia vs rest of world), macrovascular invasion (yes vs no), extrahepatic disease (yes vs no), α-fetoprotein concentration (<400 ng/mL vs ≥400 ng/mL), and Eastern Cooperative Oncology Group (ECOG) performance status (0 vs 1). The proportion of patients recruited from Asia was limited to 40%. The randomisation number for each patient was assigned based on information obtained from the interactive voice-response system.

Blinding: - Investigators, patients and the funder were masked to treatment assignment.
- Tablets with identical appearance were used for regorafenib and placebo.
- Investigators were blinded to study treatment for assessment of whether a death was considered related to study drug.

Dropout Rate/ITT-Analysis: - primary and secondary outcomes analysed by ITT
- for safety analysis, only patients who started treatment were included and comprise the safety analysis population (567 patients (99%): 374 in the regorafenib group and 193 in the placebo group)

Notes:
evidence level 2: randomized controlled trial

Bruix, Jordi et al. Adjuvant sorafenib for hepatocellular carcinoma after resection or ablation (STORM): a phase 3, randomised, double-blind, placebo-controlled trial. The Lancet Oncology. 16. 1344-1354. 2015

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** Randomised, double-blind, placebo-controlled, phase 3 study. **Number of Patient:** 1602 patients (from Americas, Asia-Pacific, and Europe across 202 sites (hospitals and research centres) in 28 countries) were screened, and 1114 met eligibility criteria and were randomly assigned. **Recruitung Phase:** Aug 15, 2008, and Nov 17, 2010. **Inclusion Criteria:** Eligible patients were men and women aged 18 years or older with a **confirmed first diagnosis of HCC suitable for curative treatment (resection or local ablation)** according to clinical guidelines. Patients were required to have an eligibility scan (CT or MRI of chest, abdomen, and pelvis). No more than 4 months must have passed between the initial staging scan and completion of curative treatment. Patients eligible for enrolment had a maximum tumour load before curative therapy comprising one lesion of any size for resection, or a single lesion 5 cm or smaller or two or three lesions each 3 cm or smaller in size for ablation. Other eligibility criteria included a Child-Pugh score of 5–7 (Child-Pugh score 7 allowed only in the absence of ascites), Eastern Cooperative Oncology Group performance status of 0, and alpha fetoprotein concentration lower than 400 ng/mL. Patients were also required to have adequate bone marrow, liver, and renal function as assessed by laboratory tests done with samples taken within 14 days before randomisation, including haemoglobin, bilirubin, platelet count, neutrophil count, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, and serum creatinine. We included only patients with an intermediate or high risk of recurrence (defined as a single tumour of 2 cm or larger with well differentiated or moderately differentiated microscopic	**Intervention:** Sorafenib: 400 mg twice a day of oral sorafenib or placebo for a maximum treatment period of 4 years (204 weeks ± 1) or until disease recurrence. **Comparison:** Placebo: see Intervention	**Primary:** Recurrence-free survival (RFS) (defined as the time from randomisation to the first documented disease recurrence by independent radiological assessment or death by any cause, whichever happened first. **Secondary:** Time to recurrence (defined as the time from randomisation to the first documented disease recurrence by independent radiological assessment), and Overall survival (defined as the time from randomisation to death by any cause). **Results: Treatment interruptions** and up to two levels of dose reductions (first to 400 mg once a day and then to 400 mg every other day) were allowed if drug-related adverse events were recorded. If further dose reductions were needed, treatment was to be discontinued. Patients were allowed to **withdraw** from study treatment if they had ascites or pleural effusion deemed to be malignant. 553 patients in the sorafenib group and 554 in the placebo group received treatment as initially assigned. Six patients assigned to placebo received one or more dose of sorafenib, and hence the safety analysis population consisted of 559 patients in the sorafenib group and 548 in the placebo group. **Recurrence free survival:** no significant treatment effect of sorafenib on RFS according to the independent radiological assessment (HR 0·940; 95% CI 0·780–1·134; one-sided p=0·26. Median RFS was 33·3 months (95% CI 27·6–44·0) in the sorafenib group and 33·7 months (27·6–39·0) in the placebo group. Subgroups showed no significant treatment effect of sorafenib. **Time to recurrence** according to independent assessment was not significantly different in the sorafenib

appearance, and the absence of microvascular invasionor satellite tumours. **Exclusion Criteria:** Patients high and low tumor risk were excluded: Low risk: with single tumours smaller than 2 cm without vascular invasion or satellites were deemed low risk and thus not included in our study. High risk: Patients undergoing surgical resection were defined as having a high risk of recurrence if they had one tumour of any size plus microvascular invasion, satellite tumours, or poorly differentiated microscopic appearance, or two or three tumours each 3 cm or smaller in size. Further exclusion criteria: recurrent HCC; macrovascular invasion; a history of cardiovascular disease (myocardial infarction >6 months before study entry was allowed); infection with HIV or other clinically serious infections; seizure disorder requiring drugs; and previous anticancer treatment for HCC, including sorafenib.		group compared with the placebo group (HR 0·891; 95% CI 0·735–1·081; one-sided p=0·12). Subgroups: We noted a suggestion of longer time to recurrence for patients given sorafenib who had HCV compared with those receiving placebo (median 27·8 months, 95% CI 19·0–not estimable) vs 16·8 months (13·6–33·1), although this difference was not significant (HR 0·785 [95% CI 0·546–1·129]) and the median time to recurrence in both treatment groups was shorter than in the other subgroups. **The median follow-up for overall survival** 23·0 months (IQR 12·7–36·0) in the sorafenib group 22·0 months (IQR 14·4–35·5) in the placebo group. (HR 0·995; 95% CI 0·761–1·300; one-sided p=0·48). Median overall survival was not reached in either treatment group. The 1-year discontinuation rate was 49% (275/556) for sorafenib and 35% (195/558) for placebo. The most common reason was disease recurrence. Conversely, adverse events were a more frequent reason for discontinuation in the sorafenib group (133 [24%]) than in the placebo group (41 [7%]), as was withdrawal of consent (93 [17%] in the sorafenib group vs 35 [6%] in the placebo group. **Adverse events:** Grade 3 adverse events in patients given sorafenib included hand-foot skin reaction, diarrhoea, and hypertension. Adverse events leading to a dose modification were recorded in 439 (79%) patients in the sorafenib group and 111 (20%) patients in the placebo group. 24 patients died during the study because of grade 5 adverse events, 15 (3%) in the sorafenib group and nine (2%) in the placebo group. **Author's Conclusion:** In conclusion, this phase 3 randomised study of sorafenib as adjuvant treatment after potentially curative therapy for HCC showed no significant treatment effect with sorafenib, with regards to RFS, time to recurrence, or overall survival. The adjuvant setting remains an area of high unmet need in HCC

		management, and further research into strategies to prevent HCC recurrence is needed.

Methodical Notes

Funding Sources: Bayer HealthCare Pharmaceuticals and Onyx Pharmaceuticals. The funder was responsible for the study design and data
collection and analysed and interpreted data, in collaboration with all authors. The funder also had input into the writing of the manuscript. JB and JML had full access to all of the study data, and all authors had access upon request. The corresponding author had access to
the study data and had the final responsibility to submit the manuscript for publication.

COI: G-YC reports grants from Bayer outside the submitted work. GM reports employment and stock ownership from Bayer HealthCare during the conduct of the study. HCL reports personal fees from Bayer outside the submitted work. JB reports personal fees from Daichi, AbbVie, Arquile, Bayer, Biocompatibles, Bristol-Myers Squibb, Novartis, Gilead, Terumo, Syrtex, and Roche outside the submitted work. JML reports personal fees from Bayer HealthCare, Bristol-Myers Squibb, Lilly, GSK, Nanostring, Biosphere Medical, Boehringer Ingelheim, Blueprint Medicines, and Celsion outside the submitted work. LB reports personal fees from Bayer, Bristol-Myers Squibb, MSD, Bracco, and Syrtex outside the submitted work. FS reports employment by Bayer HealthCare during the conduct of this study. M-ALB reports employment by Bayer HealthCare during the conduct of this study. WYT reports grants from Samil Pharm and personal fees from Gilead Sciences Korea outside the submitted work. MM reports personal fees from Bayer HealthCare outside the submitted work. VM reports personal fees from BTG and Bayer HealthCare outside the submitted work. TS, JC, K-HH, MK, SR, TT, RTP, JY, and KSL declare no competing interests.

Randomization: At randomisation, patients were stratified according to curative treatment (surgical resection vs local ablation), geographical region (Americas vs Europe vs AsiaPacifi c), Child-Pugh status (Child-Pugh A5 or A6 vs Child-Pugh B7), and risk of tumour recurrence (high vs intermediate). Randomisation was done in a parallel, stratified fashion using permuted blocks (block size of four) via a computer-generated system. Sequences were generated by an internal randomisation group and the list loaded into an interactive voice-response system (IVRS).

Blinding: The study was double-blinded. Sorafenib and placebo tablets were identical in appearance to ensure treatment was masked.
Allocation of treatment was by an IVRS, which assigned each patient a treatment based on a unique bottle or drug number.

Dropout Rate/ITT-Analysis: The planned sample size for the study was 1100 patients and was calculated based on the primary endpoint. Initially, the study required 611 events based on 90% power to detect a 30% increase in RFS. Because of a higher than expected number of patients discontinuing
treatment without recurrence of HCC, this was amended during the study to 457 events to achieve 80% power, assuming a 1:1 randomisation ratio and onesided alpha of 0·025. The assumed RFS in the placebo group was 21 months, and the expected median overall
survival was 60 months based on the scientifi c literature and taking into account the population to be enrolled in this study.

Notes:
CEBM Level of Evidence: 2 (randomized, controlled trial).

El-Khoueiry, A. B. et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. Lancet. 389. 2492-2502. 2017

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 3	**Intervention:** dose-excalation phase	**Primary:** - dose-escalation phase: adverse events

Study type: phase 1/2, open-label, non-comparative, dose escalation and expansion trial **Number of Patient:** 262 eligible patients were treated (48 patients in the dose-escalation phase and 214 in the dose-expansion phase) **Recruitung Phase:** Between Nov 26, 2012 and Aug 8, 2016 **Inclusion Criteria:** - 18 years old - with histologically confirmed advanced hepatocellular carcinoma (not amenable to curative surgery or local treatment); use of archival tissue samples was allowed - Fresh tumour biopsy was required at baseline if no other record of histological diagnosis was available. - Patients in the dose-escalation phase and patients in the HCV-infected and HBV-infected cohorts of the expansion phase included those whose disease progressed while receiving at least one previous line of systemic therapy, including sorafenib, or who were intolerant of or refused sorafenib treatment. - Patients were also required to have Child-Pugh scores of 7 or less (Child-Pugh A or B7) for the dose-escalation phase and 6 or less (Child-Pugh A) for the dose-expansion phase at screening and an Eastern Cooperative Oncology Group (ECOG) performance status of 1 or less. - Patients with HBV infection were required to be receiving effective antiviral therapy and have a viral load less than 100 IU/mL at screening; antiviral therapy was not required for patients with HCV infection.	- 48 patients were enrolled into three cohorts on the basis of hepatocellular carcinoma aetiology (23 without viral hepatitis, 10 HCV-infected and 15 HBV-infected) - they received the following doses of nivolumab: 0.1 mg/kg (patients with HBV infection only), 0.3 mg/kg, 1.0 mg/kg, 3.0 mg/kg, or 10 mg/kg (patients without viral hepatitis only) dose-expansion phase - a dose of 3 mg/kg was selected for dose-expansion every 2 weeks - 214 patients with advanced hepatocellular carcinoma were treated in four cohorts: 56 patients not infected with HCV or HBV and had not been treated with sorafenib previously or were intolerant (i), 57 had disease progression on sorafenib (ii), 50 patients were infected with HCV (iii), and 51 were infected with HBV (iv) **Comparison:** none	- dose-expansion phase: objective response rate **Secondary:** objective response rate (dose-escalation phase only), complete response rate, disease control rate, duration of response, time to response, time to progression, progression-free survival, overall survival, and response stratified by PD-L1 expression. Additionally, patient-reported quality of life measures and tumour response evaluation using mRECIST were exploratory endpoints. **Results: dose-escalation trial** - 37 (77%) of 48 patients had previously been treated with sorafenib. Extrahepatic metastases were present in 34 (71%) patients and vascular invasion was present in 19 (40%) patients; all patients were reported as Child-Pugh class A - 46 (96%) of 48 patients discontinued treatment; 42 (88%) discontinued due to disease progression. 23 of them (48%) patients were then treated with a subsequent therapy adverse events - Treatment-related adverse events (>10% of patients): rash in 11 (23%), aspartate aminotransferase (AST) increase in ten (21%), alanine aminotransferase (ALT) increase in 7 (15%), lipase increase in ten (21%), amylase increase in nine (19%) and pruritus in nine (19%) patients. - Treatment-related serious adverse events were reported in three (6%) patients (pemphigoid [n=1], adrenal insufficiency [n=1], liver disorder [n=1]). - 30 (63%) of 48 patients in the dose-escalation phase died, and no deaths were determined to be related to nivolumab therapy secondary outcomes - objective response rate was 15% (95% CI 6–28) including three complete responses and four partial responses. - disease control rate was 58% (95% CI 43–72) - median time to progression was 3.4 months (95% CI 1.6–6.9). - The median duration of response was 17 months (95% CI 6–24) - Median overall survival was 15.0 months (95% CI 9.6–20.2) **dose-expansion trial** - at data cut-off, 58 (27%) of 214 patients were continuing treatment. disease progression occurred in 132 (62%) of 214 patients. - An objective response was observed in 42 patients (20%; 95% CI 15–26) including

Exclusion Criteria: - Patients who had previously been treated with an agent targeting T-cell costimulation or checkpoint pathways (including those targeting PD-1, PD-L1 or PD-L2, CD137, or cytotoxic T-lymphocyte antigen [CTLA-4])		three complete responses and 39 partial responses. Stable disease was observed in 96 (45%) patients, and thus disease control was observed in 138 patients (64%). - median duration of response was 9.9 months (95% CI 8.3 to not estimable [NE]). - median time to progression was 4.1 months (95% CI 3.7–5.5). - The 6-month overall survival rate was 83% (95% CI 78–88) and the 9-month overall survival rate was 74% (95% CI 67–79) - The 6-month progression-free survival rate was 37% (95% CI 30–43) and the 9-month progression-free survival rate was 28% (95% CI 22–35). - Grade 3/4 treatment-related adverse events were seen in 40 (19%) patients and grade 3/4 treatment-related serious adverse events were seen in nine (4%) patients - Objective responses occurred in 13 (23%) of 56 patients without viral hepatitis who had not previously been treated with sorafenib or were intolerant and 12 (21%) of 57 sorafenib progressors without viral hepatitis; 15 responses were ongoing. - Disease control was seen in 42 (75%) of 56 patients without viral hepatitis who had not previously been treated with sorafenib or were intolerant and 35 (61%) of 57 patients in the sorafenib progressor cohort without viral hepatitis. - Objective response rates were ten (20%) of 50 patients infected with HCV and seven (14%) of 51 patients infected with HBV; 13 responses were ongoing. - Disease control was achieved in 33 (66%) patients infected with HCV and 28 (55%) patients infected with HBV. **Author's Conclusion:** Results from subsequent comparative, randomised phases of CheckMate 040 will further inform the therapeutic potential of nivolumab in patients with advanced hepatocellular carcinoma who have few existing treatment options. Nivolumab might provide favourable efficacy with a good safety profile in the context of the available targeted therapies. A phase 3 randomised study of nivolumab monotherapy compared with sorafenib in the first-line setting is ongoing.

Methodical Notes

Funding Sources: The study was designed by the authors in collaboration with the funder (Bristol-Myers Squibb). The authors and funder were responsible for data collection, and the sponsor was responsible for data analysis. The authors and funder were involved in data interpretation, development of the report, and the decision to submit. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

COI: - ABE-K has received research support from Astex, received personal fees from Merrimack, and served as an adviser for Bristol-Myers Squibb, AstraZeneca, Bayer, Genentech, and Novartis.
- BS has received speaking and consulting fees from Bristol-Myers Squibb and Bayer and consulting fees from AstraZeneca, Transgene, and Adaptimmune.
- TY has received speaking fees and research support from Bristol-Myers Squibb and has served as an adviser to Bristol-Myers Squibb.
- TSC has received research support from Bristol-Myers Squibb.
- S-PC has received speaking fees from Bristol-Myers Squibb.
- JT has received speaking and consulting fees from Bristol-Myers Squibb and Bayer.
- TM has served as a consultant for Bristol-Myers Squibb, Bayer, Ipsen, and Eisai. - Y-KK has received consulting fees from Bristol-Myers Squibb, Ono Pharmaceutical Co, Bayer, Blueprint, AstraZeneca, Pfizer, Dicerna, and Mirna.
- WY has received research support from Bristol-Myers Squibb and has served as an adviser to Bristol-Myers Squibb.
- ACh has received research support and personal fees from Bristol-Myers Squibb, Bayer, Astellas, MSD, and Boehringer Ingelheim, and has received personal fees from Janssen Oncology, Bayer, Lilly, AstraZeneca, Roche, and Mundipharma.
- JA, JN, and HBD are employees and stockholders of Bristol-Myers Squibb.
- CdC, LL, and HT are employees of Bristol-Myers Squibb.
- IM has received research support and personal fees from Bristol-Myers Squibb.
- MK, CH, T-YK, and THW declare no competing interests.

Randomization: none

Blinding: - one sub-analysis: In the dose-expansion phase, the objective response rate was analysed using mRECIST by blinded independent central review in the 145 patients who had previously been treated with sorafenib (irrespective of hepatocellular carcinoma aetiology); under these criteria the objective response rate was 27 (19%) of 145 patients, including five patients with a complete response.

Dropout Rate/ITT-Analysis: no specification

Notes:
evidence level 3: non-comparative, open-label, interventional trial

Leal, C. R. G. et al. Survival and tolerance to sorafenib in Child-Pugh B patients with hepatocellular carcinoma: a prospective study. Invest New Drugs. 36. 911-918. 2018

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 3 **Study type:** Non-randomized phase 2 controlled trial **Number of Patient:** 130 (65 per group) **Recruitung Phase:** 2011-2015 **Inclusion Criteria:** 326 HCC patients treated in outpatient clinic from January 2011 to December 2015. Of these, 130 had advanced HCC	**Intervention:** 400 mg of oral sorafenib twice daily **Comparison:** No control intervention	**Primary:** Survival and tolerance to sorafenib **Secondary:** - **Results: Population:** 130 HCC patients, 65 in the CP-A and 65 in the CP-B group. 108 (83.1%) were males, with a mean age of 62 ± 12 years. CP-B patients comprised 29 CP-B7 patients (22%), 21 CPB8 patients (16%), and 15 CP-B9 patients (12%). Most patients were classified as BCLC C (87.7%) before starting sorafenib therapy. Infection by Hepatitis C virus was the predominant cause of liver disease (55.4%). Sorafenib was the initial treatment modality in 44.6% of the patients. Most patients were classified as PS 0 (56.1%). **Results: Tolerance** Most patients (111/130, 85.4%) were tolerant to a full dose of sorafenib (800 mg/d). Nineteen patients who made use of anti-coagulants, had advanced age, or had ECOG-PS of 2 or more, started on half-dose sorafenib. Adverse events: The occurrence of AEs led to dose reductions in 42 (32.3%) patients: 28/65 (43.1%) were CP-A patients and

and were treated with sorafenib. All patients were consecutively enrolled in the study and assigned to one of two groups, according to the Child-Pugh classification: CP-A and CP-B. There were 65 patients in each group, through coincidence. **Exclusion Criteria:** -		14/65 (21.5%) were CP-B patients (p = 0.007). The commonest AEs were diarrhea (60.8%), hand-foot syndrome (32.3%), and fatigue (23.8%). Grade 3/4 AEs in the CP-A and CP-B patients included hyperbilirubinemia (18.5 and 30.8%, respectively, p = 0.770), ascites (33.8 and 60%, p = 0.003), and encephalopathy (6.2 and 33.8%, p < 0.001). Sorafenib was discontinued in 59 patients (45.4%): 35/65 (53.8%) were CP-A patients and 24/65 (36.9%) were CP-B patients (p = 0.039). The most common cause for ending sorafenib treatment was severe AE, which occurred in 38/59 patients (20 in CP-A and 18 in CP-B; 64% of all patients),followed by disease progression, seen in 19/59 (32%) patients. **Survival:** The patients with advanced HCC treated with sorafenib had an OS of 10 months. The median survival of CP-A patients was significantly higher than that of CP-B patients: 12 months vs. 6.0 months (p = 0.046). In CP-B patients, survival was 8 months for the CP-B7 patients, 5 months for the CP-B8 patients, and 6 months for the CP-B9 patients (p = 0.173). **Author's Conclusion:** ".This large real-life cohort of CP-B HCC patients treated with sorafenib found a higher OS than that described in the literature, with a satisfactory safety profile. The occurrence of AEs in this group of patients was high but manageable. CP-B patients can tolerate treatment and may benefit from sorafenib. Therefore, the use of sorafenib should be considered for CP-B HCC patients while further studies in this specific population of patients should be carried out."

Methodical Notes

Funding Sources: -

COI: All authors declare that they have no conflicts of interest.

Randomization: No randomization has taken place.

Blinding: no blinding

Dropout Rate/ITT-Analysis: Sorafenib was discontinued in 59 patients (45.4%): 35/65 (53.8%) were CP-A patients and 24/65 (36.9%) were CP-B patients (p = 0.039). The most common cause for ending sorafenib treatment was severe AE, which occurred in 38/59 patients (20 in CP-A and 18 in CP-B; 64% of all patients), followed by disease progression, seen in 19/59 (32%) patients. Two patients stopped treatment for other reasons.

Notes:
Non-randomized non-blinded trial.

Lencioni, R. et al. Sorafenib or placebo plus TACE with doxorubicin-eluting beads for intermediate stage HCC: The SPACE trial. J Hepatol. 64. 1090-1098. 2016

Population	**Intervention - Comparison**	**Outcomes/Results**
Evidence level: 2 **Study type:** Phase II randomized,	**Intervention:** Patients were randomized 1:1 to DEB-TACE (300–500	**Primary:** Time-to-tumor progression (TTP): measured from the time of randomization until radiologic disease

double-blind, placebo-controlled study. **Number of Patient:** 307 patients with intermediate stage HCC at 85 centers in 13 countries. **Recruitung Phase:** **Inclusion Criteria:** Patients with unresectable, multinodular, asymptomatic HCC (BCLC stage B), with measurable lesions on CT or MRI; no macrovascular invasion (MVI) or extrahepatic spread (EHS); Child-Pugh class A and compensated liver function; an Eastern Cooperative Oncology Group (ECOG) performance status of 0; no ascites; age P18 years, with a life expectancy P12 weeks; and adequate bone marrow function (hemoglobin >9.0 g/dl; absolute neutrophil count (ANC) >1500/mm3 ; platelet count P60 109/L), liver function (bilirubin <3 mg/dl; alanine aminotransferase (ALT) and aspartate aminotransferase (AST) <5 times the upper limit of normal (ULN); alkaline phosphatase <4 times ULN; prothrombin time-international normalized ratio (PT-INR) <2.3 or PT <6 seconds above control), and kidney function (serum creatinine <1.5 times ULN; amylase and lipase <3 times ULN). **Exclusion Criteria:** Patients were excluded if they had diffuse HCC; vascular invasion (including segmental portal obstruction); extrahepatic tumor spread; advanced liver disease, as shown by Child-Pugh class B or C liver function, gastrointestinal bleeding, encephalopathy, or ascites; or contraindications for embolization, including known hepatofugal blood flow or portosystemic shunt. Patients were also excluded if the target lesion had previously undergone local treatment, including resection, radiofrequency ablation (RFA), percutaneous ethanol injection (PEI), or TACE; if they had received local therapy within 4 weeks of a baseline scan; had prior transarterial embolization or TACE; were previously treated with a kinase inhibitor; or had received anthracyclines or radiotherapy for	lm beads; 150 mg doxorubicin) plus sorafenib (400 mg twice daily, continuously, n= 154) or matching placebo (n=153). Treatment was divided into 4-week cycles from the starting date of study drug. Sorafenib or placebo was initiated on day 1 and the first DEB-TACE session was performed 3–7 days later. Bilobar HCCs were treated in a single session. Subsequent TACE treatments were performed on day 1 (± 4 days) of cycles 3, 7, and 13 and every 6 cycles thereafter. Treatment interruptions and up to two dose reductions (to 400 mg once daily and to 400 mg every other day) were permitted for drug-related AEs; patients who required further dose reductions were withdrawn from the study. **Comparison:** see intervention.	progression, according to modified response evaluation criteria in solid tumors (mRECIST). **Secondary:** - time to MVI/EHS, defined as the time from randomization to evidence of MVI/EHS on CT/MRI scans; OS, measured from the time of randomization until death from any cause; - overall response rate (ORR); - disease control rate (DCR); - a novel endpoint of time to unTACEable progression (TTUP) (for details see text). Safety outcomes included AEs. Patients were assessed at screening and randomization, on day 1 of every 4-week cycle (with CT and/or MRI performed every 8 weeks), and at the end of the study (7–14 days after stopping the study drug). **Results:** The HR for **TTP** for sorafenib plus DEB-TACE vs. placebo plus DEB-TACE was 0.797 (95% CI, 0.588–1.080, one sided p = 0.072. HR for time to **MVI/EHS** for sorafenib plus DEB-TACE vs. placebo plus DEBTACE was 0.621 (95% CI, 0.321–1.200, p = 0.076; Fig. 2B); with the median not reached in either group. HR for **OS** in the sorafenib plus DEB-TACE vs. the placebo plus DEB-TACE group was 0.898 (95% CI, 0.606–1.330, p = 0.295; Fig. 2C), with the median OS not reached in either group after a median follow-up of 270 days (52 events) and 272 days (49 events), respectively. TTUP was shorter in the sorafenib plus DEB-TACE than in the placebo plus DEBTACE group (HR 1.586, 95% CI, 1.200–2.096, p = 0.999; Fig. 2D), with median TTUPs of 95 days (95% CI, 62–113 days) and 224 days (95% CI, 158–288 days). **Author's Conclusion:** The overall results of this exploratory trial suggest that the combination of sorafenib plus DEB-TACE was feasible, with manageable toxicities, in patients with intermediate stage HCC and good liver function. The combination did not provide meaningful clinical benefit compared with DEB-TACE alone. The

HCC.		regional differences highlight that the amount of combined treatment received may have been a critical determinant of the clinical outcomes. Likewise, discordance between investigator and central radiologic review and the criteria for additional TACE also may have impacted outcomes. Finally, whether DEB-TACE is the optimal backbone for combination with sorafenib is still unresolved. These experiences may help in the design of studies aiming to clarify the role of sorafenib plus TACE for patients with intermediate stage HCC.

Methodical Notes

Funding Sources: Bayer HealthCare, Onyx Pharmaceuticals and Biocompatibles UK, Ltd; NCT 00855218. Bayer, Onyx, and Biocompatibles UK, Ltd., sponsored the study, oversaw treatment, and performed all statistical analyses. Data
were managed in parallel by the sponsors and the principal investigators.

COI: Riccardo Lencioni has received honoraria from Bayer HealthCare and Biocompatibles UK Ltd, and research funding from Bayer HealthCare; Josep M. Llovet has received consulting fees from Bayer HealthCare Pharmaceuticals, Onyx Pharmaceuticals, Bristol-Myers-Squibb, Biocompatibles, Imclone-Lilly, and Novartis; and research funding from Bayer HealthCare Pharmaceuticals, Boehringer-Ingelheim, and Bristol-Myers-Squibb; Guohong Han,
Won Young Tak, Jiamei Yang, Alfredo Guglielmi, Seung Woon Paik, Do Young Kim, Gar-Yang Chau, Angelo Luca, and Luis Ruiz del Arbol have no relevant relationships to disclose; Maria Reig has received consulting fees and honoraria from Bayer HealthCare Pharmaceuticals and Onyx Pharmaceuticals; Marie-Aude Leberre, Woody Niu, Kate Nicholson, and Gerold Meinhardt are employees of Bayer HealthCare Pharmaceuticals; Jordi Bruix has received honoraria and research funding from Bayer HealthCare Pharmaceuticals and consulting fees from Bayer HealthCare Pharmaceuticals, Onyx Pharmaceuticals, Biocompatibles, BristolMyers Squibb, Glaxo, Kowa, Novartis, and ArQule.

Randomization: Patients were radomized 1:1 to sorafenib or placebo group and stratified by geographic region (Americas, Europe, Asia Pacific) and by serum alpha-fetoprotein (AFP) concentration (<400 ng/L and P400 ng/L.

Blinding: The primary efficacy objective was TTP by blinded central review.

Dropout Rate/ITT-Analysis: Efficacy was assessed in the intention-to-treat (ITT) population, defined as all randomized patients. The safety population consisted of all patients who received at least one dose of study drug. TTP, time to MVI/EHS, OS, and TTUP in the two groups were compared using stratified log-rank tests, with a one-sided alpha of 0.15.

130 patients of the sorafenib and 132 patients in the placebo group discontinued treatment. In the end 23/19 continued treatment.

Notes:
CEBM Level of evidence: 2 (randomized controlled trial).

Marrero, J. A. et al. Observational registry of sorafenib use in clinical practice across Child-Pugh subgroups: The GIDEON study. J Hepatol. 65. 1140-1147. 2016

Population	Intervention - Comparison	Outcomes/Results

Evidence level: 3 **Study type:** Prospective, observational, registry study (GIDEON). **Number of Patient:** A total of 3,371 patients were enrolled from 39 countries across five regions (USA, Europe, Japan, Latin America, and AsiaPacific). 2,708 patients had known Child-Pugh status at the start of sorafenib therapy; of these, 73% (n = 1968) had Child-Pugh A, 25% (n = 666) had Child-Pugh B, and 3% (n = 74) had Child-Pugh C. 15% (n = 494) of patients did not have all of the required information in order to be evaluable for Child-Pugh status (and were excluded). **Recruitung Phase:** January 2009 and the last patient follow-up occurred in April 2012. **Inclusion Criteria:** Patients diagnosed histologically, cytologically, or radiographically with HCC, with a life expectancy of more than 8 weeks. **Exclusion Criteria:** Exclusion criteria were based on the prescribing information for sorafenib.	**Intervention:** Sorafenib - Child-Pugh subgroups **Comparison:** see Intervention	**Primary: Safety - Adverse events** (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. For evaluation of **liver dysfunction**, Child-Pugh score was calculated. **Secondary:** Survival **Results: Sorafenib administrazion by Child-Pugh-Score:** Sorafenib initial dose of 800 mg recieved - 72% of Child-Pugh A patients, - 70 % of Child-Pugh B patients. The **median duration of treatment** was longer in Child-Pugh A patients (17.6 weeks) compared with Child-Pugh B patients (9.9 weeks) and Child-Pugh C patients (5.6 weeks) and the proportion of patients **discontinuing within 8 weeks** was lower for Child-Pugh A patients (26%) compared with ChildPugh B patients (42%). **Adverse events:** AEs leading to permanent discontinuation were more common in Child-Pugh B (40%) and C (43%) patients than in Child-Pugh A patients (29%), although the incidences of drug related AEs leading to discontinuation were similar (21%, 15%, and 17%, respectively). AEs leading to discontinuation occurred most commonly during the first 4 weeks of treatment. **Survival:** Intent-to-treat population, median overall survival was: Child-Pugh A patients (13.6 months) ChildPugh B patients (5.2 months) Child-Pugh C patients (2.6 months). **Author's Conclusion:** In summary, these findings from the final analysis of GIDEON confirm that sorafenib is used clinically across a broad spectrum of HCC patients, including those with liver dysfunction. In this cohort, the safety profile of sorafenib was generally consistent in Child-Pugh A and Child-Pugh B patients. Despite a similar safety profile, a higher rate of treatment discontinuation was observed in patients with Child-Pugh B status, who have a poorer general condition. The data show that Child-Pugh B patients are heterogeneous, and highlight that certain factors may be especially important in the assessment of patients with liver dysfunction, emphasizing the need for careful assessment when making treatment decisions in these patients. Together, the data indicate the use of the recommended sorafenib dose with subsequent monitoring as an appropriate treatment option in HCC patients with more advanced liver dysfunction.

Methodical Notes

Funding Sources: GIDEON was sponsored by Bayer HealthCare Pharmaceuticals Inc. and Onyx Pharmaceuticals, an Amgen subsidiary.

COI: Professor Marrero has received honoraria for advisory arrangements from Bayer HealthCare Pharmaceuticals, Inc. and Onyx Pharmaceuticals, an Amgen subsidiary. Professors Furuse and

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Randomization: no

Blinding: no

Dropout Rate/ITT-Analysis: Patients who received at least one dose of sorafenib and underwent at least one follow-up assessment were evaluable for safety, while the intent-to-treat population comprised any patient who received one or more doses of sorafenib. The safety population comprised 3,202 patients and the intent-to-treat population comprised 3,213 patients.

Notes:
CEBM Level of Evidence: 3 (nonrandomized, controlled study).

Meyer, Tim et al. Sorafenib in combination with transarterial chemoembolisation in patients with unresectable hepatocellular carcinoma (TACE 2): a randomised placebo-controlled, double-blind, phase 3 trial. The Lancet Gastroenterology & Hepatology. 2. 565-575. 2017

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** Randomized, double-blind, placebo-controlled study. **Number of Patient:** 399 patients (in 20 hospitals in the UK) were screened, 86 excluded, remaining 313 were randomized. **Recruitung Phase:** Nov 4, 2010, and Dec 7, 2015. **Inclusion Criteria:** Histological or non-invasive diagnosis according to the American Association for the Study of Liver Diseases (AASLD) criteria, aged 18 years or older, at least one unidimensional lesion measurable according to Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST v1.1), not being a candidate for surgical resection or liver transplant, Eastern Cooperative Oncology Group (ECOG) performance status of 1 or less, Child-Pugh A liver disease, haemoglobin of 9 g/L or higher, neutrophil count of at least $1{\cdot}5 \times 10^9$ cells per L, platelet count of at least 60×10^9 platelets per L, bilirubin of no more than 50 µmol/L, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) of 5 times upper limit of normal or less, alkaline	**Intervention:** Sorafenib + TACE (Oral sorafenib at a dose of 400 mg twice-daily or matching placebo was commenced within 24 h of randomisation and continued until disease progression. DEB-TACE was given 2–5 weeks post-randomisation using drug-eluting beads (DC Bead; BTG PLC, London, UK) loaded with doxorubicin 150 mg according to the manufacturer's instructions. Administration was via the hepatic artery accessed via the femoral artery, and a superselective approach was recommended. **Comparison:** Placebo + TACE	**Primary:** Progression-free survival defined as the interval between randomisation and progression according to RECIST v1.117 or death due to any cause. **Secondary:** Overall survival measured from date of randomisation to death; Time to progression, measured from date of randomisation to date of progression; Response and disease control according to RECIST v1.1 guidelines; QOL, scored according to the EORTC manuals; and number of TACE procedures given within 12 months of randomisation. **Results: Progression free-survival:** The formal interim futility analysis of progression-free analysis was done in July, 2015, and indicated an HR

phosphatase (ALP) of less than 4 times upper limit of normal, creatinine of 1·5 times upper limit of normal or less, international normalised ratio (INR) of 1·5 times upper limit of normal or less, and left ventricular ejection fraction of at least 45%. **Exclusion Criteria:** Extrahepatic metastasis, previous embolisation, systemic therapy or radiotherapy for hepatocellular carcinoma, any contraindication to hepatic embolisation, previous investigational therapy, major surgery or history of bleeding within 4 weeks of trial entry, hepatic encephalopathy, occlusion of the hepatic artery or main portal vein, myocardial infarction within 6 months or prolonged QT/QTc of more than 450 ms.		of 1·03 (95% CI 0·75–1·42, p=0·85), which led to early trial closure. Median progression-free survival was 238·0 days (95% CI 221·0–281·0) in the sorafenib group versus 235·0 days (209·0–322·0) in the placebo group (HR 0·99 [95% CI 0·77–1·27], p=0·94. Median **overall survival** was 631·0 days (95% CI 437·0–879·0) in the sorafenib group versus 598·0 days (500·0–697·0) in the placebo group (HR 0·91 [95% CI 0·67–1·24], p=0·57. There was no evidence for a difference time to progression between the sorafenib group and the placebo group, with an HR of 0·88 (95% CI 0·67–1·17, p=0·38). Sensitivity analysis: no evidence of a difference for all survival measures: HR for progression-free survival was 1·01 (95% CI 0·78–1·30; p=0·94); HR for overall survival was 0·99 (95% CI 0·73–1·35; p=0·96); HR for time to progression was 0·87 (95% CI 0·66–1·16; p=0·35). QoL: According to multilevel regression of QLQ-C30 scores over 360 days, both the mean social and role functioning scales were found to be up to 6% lower (p=0·045 and p=0·050) for patients in the sorafenib group (notable changes were: mean diarrhoea score was up to 13% higher on average in the sorafenib group (p=0·0095) and mean appetite loss score was up to 10% higher (p=0·0018)). Adverse events: At least one serious adverse event was reported in 65 (41%) of 157 patients in the sorafenib

		group and 50 (32%) of 156 patients in the placebo group. 181 serious adverse events were reported in total: 95 (52%) in the sorafenib group and 86 (48%) in the placebo group. **Author's Conclusion:** In summary, the TACE 2 trial contributes compelling evidence that the concurrent administration of sorafenib with DEB-TACE does not improve outcomes compared with DEB-TACE alone, and also provides valuable lessons to inform future trial development.

Methodical Notes

Funding Sources: The funders of the study (Bayer PLC and BTG PLC) had no role in the study design, data collection, analysis, interpretation, or writing of the report. Bayer PLC provided sorafenib and matching placebo and BTG provided DC Beads. The study was endorsed by Cancer Research UK and adopted into the NIHR trial portfolio. The study was sponsored by UCL and the chief investigator (TM) is employed by UCL. TM is part funded by the NIHR University College London Hospitals Biomedical Research Centre. MWJ is supported by NIHR Biomedical Research Unit in Gastrointestinal and Liver Diseases at Nottingham University Hospitals NHS Trust and University of Nottingham.

COI: TM held the grant from Bayer PLC and BTG PLC, and reports personal fees from Bristol–Myers Squibb (BMS), Eisai, Ipsen, and Merck and Bayer. YTM reports personal fees from Bayer and Baxalta. PR reports grant support from Sanofi and personal fees from Bayer, Sirtex, Celgene, Roche, Sanofi, and Amgen. LW received support from Bayer to attend a conference. NH reports personal fees from BTG, Boston Scientific, and Terumo. TRJE reports support for trials and fees to the Institution from Bayer, BMS, Clovis, Karus Therapeutics, Baxalta,
Celgene, Eisai, GlaxoSmithKline, Otsuka, Roche, TC Biopharm, Immunova, Basilea, e-Therapeutics, Immunocore, Vertex, Verastem, Daiichi, and Merck. PC reports personal fees from Bayer. RH reports personal fees from BTG and Bayer. DC reports grant funding from Amgen, AstraZeneca, Bayer, Celgene, Medimmune, Merck Serono, Merrimack, and Sanofi. DHP reports grant personal fees from Bayer.

Randomization: Randomisation was done by randomisation officers based at CRCTU. Patients were randomly assigned, on a 1:1 basis and in a
masked fashion, to the sorafenib group or placebo group based on a minimisation randomisation algorithm.
Randomisation was stratified by randomising centre and serum α-fetoprotein (AFP) concentration (<400 ng/mL and ≥400 ng/mL).

Blinding: Allocation concealment was achieved by the use of tablets identical in appearance and in numbered
bottles. Only the trial coordinator was unmasked to treatment allocation before patient progression during the study.

Dropout Rate/ITT-Analysis: 31 patients had fully withdrawn from the study. 108 discontinued treatment early but all except the 31 patients were accounted for.

Notes:
CEBM Level of Evidence: 2 (randomised controlled trial)

Limitations:
35% of study participants discontinued treatment early.

Park, J. W. et al. Sorafenib with or without concurrent transarterial chemoembolization in patients with advanced hepatocellular carcinoma: The phase III STAH trial. J Hepatol. 70. 684-691. 2019

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** Randomized, Controlled Phase III Trial **Number of Patient:** 339 patients from 13 hospitals in South Korea **Recruitung Phase:** Between January 2013 and December 2015 **Inclusion Criteria:** - stages III, IVa, or IVb HCC according to the modified Union for International Cancer Control (mUICC) TNM staging criteria (with vascular invasion, lymph node metastasis [any lymph node ≥1 cm] or extrahepatic tumor spread); - advanced HCC (mUICC stages III, IVa-b) indicated for systemic chemotherapy (but not curative therapy) as treatment of choice; - advanced HCC (mUICC stages III or IVa-b) that progressed despite prior local treatment; and advanced HCC progression and the requirement for 3 TACE sessions within the first 6 months (TACE refractoriness). - Eligible patients were aged ≥20 years and had ≥1 typical enhanced measurable tar-get lesion of ≤15 cm based on the Response Evaluation Crit-ria in Solid Tumors (RECIST) version 1.1, Child-Pugh scores≤7, Eastern Cooperative Oncology Group (ECOG) performancestatus score ≤2. **Exclusion Criteria:** - patients were excluded if they had no measurable tumor of a diffuse infiltrative HCC type or brain metastases, a- complete obstructive invasion of the main portal vein (Vp4), inferior venacava invasion (Vv3), first order branch of the biliary duct inva-sion (B3), or had received any previous systemic therapy - patients were excluded if they received any locoregional therapy for HCC or radiotherapy for	**Intervention:** sorafenib with cTACE (combination; Arm C), 400 mg twice daily (odse reduction was allowed by protocol) **Comparison:** - sorafenib without cTACE (sorafenib alone; Arm S), 400 mg twice daily - Patients randomized to Arm C received the first cTACE between 7 and 21 days after randomization then resumed sorafenib between 3 and 28 days after the first cTACE	**Primary:** overall survival (OS) **Secondary:** Time to progression (TTP) Tumor response rate (TRR) Progression free survival(PFS) adverse events (AE) **Results:** <u>overall survival</u> - median OS was 12.8 months (90% CI 11.5–15.0) for Arm C and 10.8 months (90% CI 8.7–12.7) for Arm S. - HR of arm c was 0.91 (90% CI 0.687–1.205;p= 0.2898) - Predefined subgroup analysis for OS failed to show a benefit for SOR+T with any stratification factors <u>Time to progression</u> - Median TTP was 5.3 months (90% CI 3.7–5.7) for Arm C and 3.5 months (90% CI 2.1–3.7) for Arm S (HR 0.674; 90% CI 0.533–0.852;p= 0.0028) <u>Progression free survival</u> - Median PFS was 5.2 months (90% CI 3.7–5.6) for Arm C and 3.6 months (90% CI 2.6–3.7) for Arm S (HR 0.733; 90%CI 0.589–0.912;p= 0.0097) <u>Tumor response rate</u> - Arm C TRR was significantly higher than Arm S TRR (60.6% vs. 47.3% ;p= 0.0053) <u>Adverse events</u> - Of patients in Arms C and S, 96.7% and 90.4%, respectively, experienced any AEs (p= 0.0227) - For Arms C and S, serious (grade ≥3) adverse events occurred in 33.3% vs. 19.8% (p= 0.006) of patients and included increased alanine aminotransferase levels (20.3% vs. 3.6%), hyperbilirubinemia (11.8% vs. 3.0%), ascites (11.8% vs. 4.2%), thrombocytopenia (7.2% vs. 1.2%), anorexia (7.2% vs. 1.2%),and hand-foot skin reaction (10.5% vs. 11.4%). **Author's Conclusion:** In conclusion, in patients with advanced HCC, compared tosorafenib alone, SOR+T therapy did not improve OS. However,SOR+T therapy significantly improved TTP, PFS, and TRR. Treat-ment with sorafenib alone remains the first-line standard ofcare for patients with advanced HCC.

intrahepatic lesions 4 weeks or 3 months, respectively, prior to signing the informed consent		

Methodical Notes

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COI: Employment or leadership position: none.
Consultant or advisory role: Joong-Won Park, BMS, Ono, Bayer, Eisai, Midatech, Roche, Cue; Yoon Jun Kim, Gilead, Bayer, Ono, AbbVie
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Patents, Roy-alties, and Licenses: none.
Other Remunerations: none.

Randomization: block randomization method (block sizes 2 or 4).

Blinding: no blinding reported

Dropout Rate/ITT-Analysis: - A total of 17 patients from Arm C and 2 from Arm S who did not receive cTACE or sorafenib were excluded from the full analysis set
- outcomes were analyzed by the intention-to-treat principle.

Notes:
evidence level 2: randomized controlled trial

Pressiani, T. et al. Sorafenib in patients with Child-Pugh class A and B advanced hepatocellular carcinoma: a prospective feasibility analysis. Ann Oncol. 24. 406-11. 2013

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 3 **Study type:** multicentre, phase II, open-label trial **Number of Patient:** 300 patients were enrolled in the study **Recruitung Phase:** between April 2007 and July 2008 **Inclusion Criteria:** patients who - had cyto-histologically confirmed advanced	**Intervention:** - During the first phase, all patients received continuous oral treatment with sorafenib 400 mg twice daily until radiological progression (as defined by RECIST), symptomatic progression or deterioration of PS, unacceptable toxic effects or patientwithdrawal. **Comparison:** none	**Primary:** progression-free survival (PFS) **Secondary:** overall survival (OS) Time to progression (TTP) **Results:** <u>basics</u> - 297 patients were evaluated: 234 (78.8%) Child-Pugh A, 44 (14.8%) Child-Pugh B7, 14 (4.7%) Child-Pugh B8, 5 (1.7) Child-Pugh B9 - treatment duration was 3.3 (0.03–32.3) months ranging from 4.2 (0.03–32.3) to 1.9 (0.03–19.44) in patients with CP class A and B, respectively ($p<0.001$). - median follow-up was 41.6 (0.4–49.1) months during which 272 patients (91.6%) died. - Adverse events for the two CP groups were similar. <u>progression-free survival (PFS)</u> - median PFS for the total patient population was

HCC unsuitable for resection or loco-regional therapy, - Barcelona Clinic Liver Cancer (BCLC) stage B or C, - CP liver function class A or B, - Eastern Cooperative Oncology Group (ECOG) performance status (PS) score≤2 - adequate haematological, hepatic (according to CP status) and renal function and a life expectancy of≥12 weeks. - Patients must be untreated with targeted therapies and have at least one measurable target lesion according to the Response Evaluation Criteria in Solid Tumours (RECIST) v.1.0. **Exclusion Criteria:** no specification		3.9 (0.1–35.3) months. - PFS for patients with CP class A or B was 4.3 (0.1–35.3) and 2.1 (0.3–27.3) months, respectively (log-rank,P< 0.001). - multivariate analysis: greater risk of disease progression or death for CP class B patients (HR 1.87, 95% CI: 1.41–2.48,P< 0.001); reduced risk in PFS for patients <68 years compared with those ≥68 years (HR 0.77, 95% CI: 0.60–0.97,P=0.026) Time to progression (TTP) - Data on TTP available in 240 patients (80.8%; 206 CP class A and 34 CP class B) - median TTP was 4.1 (0.03–16.0) months for the total patient population - not statistically different according to CP status: TTP for CP class A patients 4.2 (0.03–31.7) and for CP class B patients 3.8 (range 1.3–16.0) months (log-rank,P< 0.102) overall survival (OS) - median OS was 9.1 (0.4–49.1) months for the total patient population - statistically significant greater risk of death for CP class B patients (HR 3.23, 95% CI: 2.38–4.39,P< 0.001). - The median OS was 10.0 (0.5–49.1) for CP class A patients and 3.8 (0.4–27.3) months for CP class B patients (log-rank,P< 0.001) - statistically significant differences in OS according to AST baseline values (log-rank,P=0.008),vascular invasion (log-rank,P=0.049) and HCC disease extent(log-rank,P=0.025) - Patients with extrahepatic spread had a greater risk of death than those with intrahepatic disease (HR 1.55, 95% CI: 1.15–2.08,P=0.026). **Author's Conclusion:** In conclusion, although limited by the statistical design of our study, tolerability data suggest that CP class B patients might be safely treated with sorafenib. However, its activity in this patient population remains to be defined, bearing in mind that it is not a homogeneous group. Further prospective trials specifically designed to investigate the efficacy and safety of sorafenib in CP class B subgroups, particularly in those patients with less compromised liver function (CP score 7), are warranted. While waiting for the results of these studies, the administration of sorafenib in CP class B patients with advanced HCC remains open to discussion and in our opinion could be feasible in carefully selected patient groups.

Methodical Notes

Funding Sources: This work was supported in part by Bayer Italy. The study was designed by the lead investigator (AS, Humanitas Cancer Center). Bayer Italy, the manufacturer of sorafenib, provided the investigational drug and supported the study with a grant, but had no role in data analysis or in the decision to publish the results.

COI: - CP received research grants from Bayer-Schering Pharma and acted as consultant and speaker for the same company.
- CB participated in a board for Sanofi.
- SF conducted a trial sponsored by Bayer.
- AS was a consultant for Bayer.
- The remaining authors have declared no conflicts of interest.

Randomization: none

Blinding: none

Dropout Rate/ITT-Analysis: - of 300 patients initially enrolled, 3 patients never received sorafenib and only data relevant to 297 patients are presented
- Data on TTP were available in 240 patients (80.8%; 206 CP class A and 34 CP class B), 57 patients did not present a radiological evaluation post-enrolment due to death (15.8%), AEs (36.8%) and other reasons (47.4%).

Notes:
evidence level 3: prospective, single-arm, interventional trial

Zhu, A. X. et al. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial. Lancet Oncol. 19. 940-952. 2018

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 3 **Study type:** non-randomised, multicentre, open-label, phase 2 trial **Number of Patient:** 169 patients were assessed for eligibility. Of these patients, 64 (38%) were deemed ineligible. One (1%) patient was enrolled in error. Finally 104 enrolled patients were treated with at least one dose of pembrolizumab and were included in the primary analysis. **Recruitung Phase:** We enrolled participants between June 22, 2016 and Feb 20, 2017. **Inclusion Criteria:** - aged at least 18 years - had a histologically or cytologically confirmed diagnosis of hepatocellular carcinoma - had documented radiographic progression of disease after treatment with sorafenib or intolerance to sorafenib (defined as any grade ≥2 drug-related adverse event) - had Barcelona Clinical Liver	**Intervention:** - 200 mg pembrolizumab intravenously every 3 weeks, on day 1 of each 3-week cycle, for up to 35 cycles (for about 2 years) or until disease progression, unacceptable toxicity, patient withdrawal of consent or investigator decision - Response was assessed every 9 weeks, measured according to RECIST version 1.1 **Comparison:** none	**Primary:** Objective Response Rate (ORR) **Secondary:** Duration of Response (DOR) Disease Control Rate (DCR) Time To Progression (TTP) Progression-Free Survival (PFS) Overall Survival (OS) adverse events (AE) **Results:** Objective Response Rate (ORR) - objective response was recorded in 18 (17%) of 104 participants (95% CI 11–26) who had received at least one dose of pembrolizumab. - Among 18 responders, overall responses were one (1%) complete response and 17 (16%) partial responses - 46 (44%) participants had stable disease and 34 (33%) participants had progressive disease - Six patients (6%) could not be assessed because they did not have assessment data after baseline Disease Control Rate (DCR) - Disease control was reported in 64 (62%; 95% CI 52–71) of the 104 treated participants Duration of Response (DOR)

Cancer Stage (BCLC) C or B disease that was not amenable to, or refractory after, locoregional therapy or to a curative treatment approach - had at least one measurable lesion as defined by Response Evaluation Criteria in Solid Tumors (RECIST) 19 version 1.1 - an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1 - a predicted life expectancy greater than 3 months - adequate organ function - Child-Pugh class A. - Patients with chronic infections with hepatitis C virus (treated or untreated) and patients with hepatitis B virus who were treated with antiviral therapy and who had a viral load less than 100 IU/mL before receiving their first pembrolizumab dose **Exclusion Criteria:** - treatment with sorafenib up to 2 weeks before the first study dose - previous immunotherapy (anti-PD-1, anti-PD-L1 or anti-PD-L2), - previous systemic therapy for advanced hepatocellular carcinoma other than sorafenib - Patients who were currently participating in and receiving therapy from another study - patients who had previously participated in a study of an investigational drug and received study therapy within 4 weeks of the first dose of treatment - Participants must also have recovered from any associated therapy and from adverse events associated with any previous therapy. - Patients with previous locoregional therapy, major surgery to the liver up to 6 weeks before the first study dose - minor surgery to the liver or other sites up to 1 week before the first study dose - previous solid organ or haematological transplantation - active auto-immune disease that had required systemic treatment in the past 2 years - a diagnosis of immunodeficiency or those who had received systemic steroid therapy or other		- 12 (77%) responders showed a response for at least 9 months and the median time to response was 2.1 months (IQR 2.1–4.1) - As of data cutoff, 12 of the 18 responses were ongoing and the median duration of response was not reached (range 3.1–14.6+ months) Time To Progression (TTP) - The median time to progression was 4.9 months (95% CI 3.9–8.0) Progression-Free Survival (PFS) - median progression-free survival was 4.9 months (95% CI 3.4–7.2) Overall Survival (OS) - median overall survival was 12.9 months (95% CI 9.7–15.5) adverse events (AE) - At least one treatment-related adverse event occurred in 76 (73%) of 104 participants (grade 1–2 in 49 [47%] patients, grade 3 in 25 [24%], grade 4 in one [1%], and grade 5 in one [1%]) and 16 (15%) had a treatment-related serious adverse event - most common treatment-related events of any grade: fatigue (22 [21%] of 104 participants), increased aspartate aminotransferase concentration (14 [13%]), pruritus (12 [12%]), diarrhoea (11 [11%]) and rash (10 [10%]). **Author's Conclusion:** Overall, this study in patients with advanced hepatocellular carcinoma suggests that pembrolizumab provides durable clinical efficacy and a safety profile similar to that of pembrolizumab in other indications and could be a therapeutic option for patients who progress after treatment with or are intolerant of sorafenib.

immunosuppressive therapy up to 7 days before the first study dose - evidence of metastases to the CNS - carcino-matous meningitis - fibrolamellar and mixed hepato-cellular or cholangiocarcinoma subtypes of hepatocellular carcinoma - clinically apparent ascites on physical examination - and clinically diagnosed hepatic encephalopathy or oesophageal or gastric variceal bleeding within the past 6 months - Patients with portal vein invasion at the main portal (Vp4) or inferior vena cava or cardiac involvement of hepatocellular carcinoma (determined by imaging)		

Methodical Notes

Funding Sources: The study was funded, administered, and sponsored by Merck & Co, Inc (Kenilworth, NJ, USA).

COI: - AXZ has served as a consultant for Eisai, Bristol-Myers Squibb, Merck & Co, Novartis, Sanofi, AstraZeneca, Bayer, Exelixis, and Eli Lilly and Company; and reports research funding to his institution from Eli Lilly and Company, Bayer, Bristol-Myers Squibb, Novartis, and Merck & Co.
- RSF has served as a consultant for Pfizer, Bayer, Novartis, Bristol-Myers Squibb, and Merck & Co; and reports research funding to his institution from Pfizer.
- JE has received honoraria from BTG and travel expenses from Amgen and Bristol-Myers Squibb.
- SO has served as a consultant for Bayer and Eisai; and has received honoraria from Bayer and Eisai.
- DP has received honoraria from Bayer, Celgene, NuCana, and Bristol-Myers Squibb; has served as a consultant for Bayer, Celgene, NuCana, and Bristol-Myers Squibb; and has received research funding from Bayer and NuCana.
- CV has served as a consultant for Bayer, Ipsen, and Novartis; and has received research funding from Ipsen and Bayer.
- VZ has served as a consultant for Merck Sharp & Dohme, Bristol-Myers Squibb, and Celgene; has been on a speakers' bureau for Bayer, Roche, Pfizer, and Janssen; and has received travel fees from Merck Sharp & Dohme, Roche, and Bayer.
- AV has served as a consultant for Novartis, Delcath Systems, Eli Lilly and Company, Roche, Amgen, Bayer, and Baxalta; has received travel expenses from Bayer, Roche, and Ipsen; has received honoraria from Novartis, Roche, Bayer, Sanofi, Amgen, Delcath Systems, Eli Lilly and Company, Bristol-Myers Squibb, and Merck Sharp & Dohme; and has received research funding from Novartis.
- DS has served as a consultant for Eisai, Baxalta, Novartis, and Blueprint Medicines; has received travel expenses from Bayer, Ipsen and MiNA Therapeutics; and has received honoraria from Pfizer, Bayer, and Ipsen.
- SLC has served as a consultant for Novartis, Merck Sharp & Dohme, and MedImmune (AstraZeneca); has received honoraria from Bayer; and has received research funding from Novartis and Sirtex Medical.
- JK has served as a consultant for Eli Lilly and Company and Merck & Co; has received honoraria from Novartis; and has received research funding from AstraZeneca.
- BD has served as a consultant for Eisai and Bayer; has received honoraria from Bayer, Merck Sharp & Dohme, Merck Serono, Eli Lilly and Company, and Bristol-Myers Squibb; and has received travel grants from Janssen, Celgene, and Bristol-Myers Squibb.
- ALW, SWE, JM, and ABS are employees of Merck Sharp and Dohme, a subsidiary of Merck & Co, Kenilworth, NJ, USA; and own stock or stock options in the company.
- A-LC has served as a consultant for Merck Sharp & Dohme, Exillixis, Merck KGaA, Bristol-Myers Squibb, Bayer, BeiGene, and Ono Pharmaceuticals; has served on advisory board for Novartis, and has received honoraria from Bayer and Merck KGaA.
- MK has served as a consultant for Kowa, Merck Sharp & Dohme, Bristol-Myers Squibb, Bayer, Chugai

Pharma, and Taiho Pharmaceuticals; has received honoraria from Bayer, Eisai, Merck Sharp & Dohme, and Ajinomoto; and has received research funding from Chugai Pharma, Otsuka, Takeda Pharmaceuticals, Taiho Pharmaceuticals, Sumitomo Dainippon Pharma, Daiichi Sankyo, Merck Sharp & Dohme, Eisai, Bayer, and AbbVie.
- SC, LF, and GV declare no competing interests.

Randomization: none

Blinding: none

Dropout Rate/ITT-Analysis: One (1%) patient was enrolled in error. 104 enrolled patients were treated with at least one dose of pembrolizumab and were included in the primary analysis.

Notes:
evidence level 3: non-randomized, single-arm interventional phase 2 trial

Zhu, A. X. et al. Ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma following first-line therapy with sorafenib (REACH): a randomised, double-blind, multicentre, phase 3 trial. Lancet Oncol. 16. 859-70. 2015

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** Randomized, controlled, double-blind, phase 3 study **Number of Patient:** 565 patients were enrolled, of whom 283 were assigned to ramucirumab and 282 were assigned to placebo. **Recruitung Phase:** Between Nov 4, 2010, and April 18, 2013 **Inclusion Criteria:** - aged 18 years or older, - had a diagnosis of hepatocellular carcinoma and Barcelona Clinic Liver Cancer stage C or stage B that was refractory or not amenable to locoregional therapy, and had Child-Pugh A liver disease. - Diagnosis of hepatocellular carcinoma was based on histopathological findings from tumour tissue, or in the absence of histological confirmation, patients had clinical findings consistent with a diagnosis of liver cirrhosis and a liver mass measuring at least 2 cm with characteristic vascularisation seen on either triphasic CT scan or MRI with gadolinium	**Intervention:** ramucirumab 8 mg/kg (ImClone Systems Corporation, Branchburg, NJ, USA) intravenously over 1h every 2 weeks until disease progression, unacceptable toxicity or withdrawal of consent. - Up to two reductions to the dose of ramucirumab or placebo (to 6 mg/kg every other week and subsequently to 5 mg/kg every other week) were allowed **Comparison:** placebo	**Primary:** overall survival **Secondary:** progression-free survival time to tumour progression response (according to RECIST) objective response (complete response and partial response) disease control (complete response, partial response and stable disease) adverse events **Results:** <u>overall survival</u> - Median overall survival in the ramucirumab group was 9.2 months (95% CI 8.1–10.6) compared with 7.6 months (6.0–9.3) in the placebo group (HR 0.87 [95% CI 0.72–1.05]; p=0.14) - In the prespecified subgroup of patients with a baseline α-fetoprotein concentration of 400 ng/mL or greater, median overall survival was 7.8 months (95% CI 5.8–9.3) for the ramucirumab group versus 4.2 months (3.7–4.8) for the placebo group - <u>progression-free survival</u> - Median progression-free survival was 2.8 months (95% CI 2.7–3.9) in the ramucirumab group versus 2.1 months (1.6–2.7) in the placebo group (HR 0.63 [95% CI 0.52–0.75]; p<0.0001) <u>time to tumour progression</u> - Median time to tumour progression in the ramucirumab group was 3.5 months (95% CI 2.8–4.5) versus 2.6 months (1.6–2.8) in the placebo group (HR 0.59 [95% CI

undertaken and reviewed locally. - Patients were previously treated with and discontinued sorafenib at least 14 days before randomisation and had radiographically documented disease progression during sorafenib therapy or after discontinuation of sorafenib therapy. -Patients were required to have an Eastern Cooperative Oncology Group performance status 0 or 1 and adequate haematological and biochemical parameters **Exclusion Criteria:** - major surgery or hepatic locoregional therapy within 28 days before randomisation, - previous systemic therapy with VEGF or VEGFR inhibitors other than sorafenib, - ongoing therapeutic anticoagulation or antiplatelet therapy, - history of or current hepatic encephalopathy or current clinically meaningful ascites, - arterial thrombotic event within 6 months before randomisation, - high bleeding risk from oesophageal or gastric varices, and uncontrolled arterial hypertension. - In the original protocol, patients with Child-Pugh B disease were eligible but had to be excluded from future enrollment during the study due to an imbalance between treatment groups of adverse liver events		0.49–0.72]; p<0·0001) objective response - An objective response was noted in 20 patients (7%; 95% CI 4.6–10.7) in the ramucirumab group compared with two patients (<1%; 0.2–2.5) in the placebo group (p<0.0001). disease control - 159 patients (56%; 95% CI 50.4–61.8)achieved disease control in the ramucirumab group compared with 129 patients (46%; 40.0–51.6) in the placebo group (p=0.011). adverse events - Grade 3 or greater adverse events occurring in 5% or more of patients in either treatment group were ascites (13 [5%] of 277 ramucirumab-patients vs 11 [4%] of 276 placebo-patients), hypertension (34 [12%] vs 10 [4%]), asthenia (14 [5%] vs 5 [2%]), malignant neoplasm progression (18 [6%] vs 11 [4%]), increased aspartate aminotransferase concentration (15 [5%] vs 23 [8%]), thrombocytopenia (13 [5%] vs 1 [<1%]), hyperbilirubinaemia (three [1%] vs 13 [5%]) and increased blood bilirubin (5 [2%] vs 14 [5%]). - most frequently reported (≥1%) treatment-emergent serious adverse event of any grade or grade 3 or more was malignant neoplasm progression. **Author's Conclusion:** Second-line treatment of advanced hepatocellular carcinoma has been an area of high unmet need, and so far no drugs have clearly shown a survival benefit after sorafenib. Although we failed to demonstrate an improvement in overall survival with the use of ramucirumab after first-line sorafenib, the effects of the drug in patients with elevated baseline α-fetoprotein concentrations of 400 ng/mL may warrant further investigation.

Methodical Notes

Funding Sources: Eli Lilly and Co.
The funder provided the study drug and collaborated with investigators on the protocol and were involved in the study design, data collection, analysis, interpretation, and writing and preparation of this report. AXZ prepared the first draft in collaboration with the study funder and other coauthors. AXZ had full access to the study data and all authors approved submission for publication. All authors had responsibility to submit the report for publication.

COI: - AXZ reports grants from Eli Lilly during the conduct of the study.
- J-FB reports personal fees from Eli Lilly during the conduct of the study.
- ADB reports personal fees from Eli Lilly, Bristol-Myers Squibb, and Genentech outside of the submitted work.
- TEFP reports grants from Eli Lilly during the conduct of the study and personal fees from Eli Lilly outside of the submitted work.
- TO reports grants and personal fees from Eli Lilly during the conduct of the study; personal fees from Eli Lilly; grants from Takeda Bio Development Center Ltd, Otsuka Pharmaceutical Co Ltd and grants from

Glaxo Smith Kline K K; grants and personal fees from Kowa K K, Nippon Boehringer Ingelheim Co Ltd, Dainippon Simitomo Pharma Co Ltd, Pfizer Jana Inc, Taiho Pharmaceutical Co, Bayer Yakuhin Ltd, Chugai Pharmaceutical Co Ltd, Novartis Pharma K K, Yakuruto Honsha Co Ltd, Ono Pharmaceutical Co Ltd, Eisai Co Ltd, AstraZeneca K K, Merck Serono Co Ltd, Sceti Medical Labo K K, OncoTherapy Science Inc, and Kyowa Hakko Kirin Co Ltd outside of the submitted work.
- JT reports speaker and advisory board participance for Eli Lilly.
- JS reports personal fees from Roche, Merck, Bayer, Amgen, and Eli Lilly outside of the submitted work.
- IC reports personal fees from Eli Lilly during the conduct of the study; grants from Merck-Serono, personal fees from Bayer, personal fees from Bristol-Myers Squibb, personal fees from Gilead Science, personal fees from Taiho, and grants and personal fees from Roche outside of the submitted work.
- S-CC, PBA, and LY were employees and stockholders of Eli Lilly during the conduct of the study and have a provisional patent relevant to the work.
- JDS was an employee and stockholder of Eli Lilly during the conduct of the study. - All other authors declare no competing interests.

Randomization: - Patients were randomised (1:1) via a call-in interactive web response system to receive either ramucirumab or placebo.
- Randomisation was stratified by geographic region (North and South America, Europe, or East Asia) and cause of liver disease (hepatitis B, hepatitis C, or other) with a stratified permuted block method.

Blinding: - Patients, medical staff, investigators and the funder were masked to treatment assignment.
- Study group assignment could be unmasked in emergency situations where knowledge of the patient's treatment assignment was needed to ensure his or her wellbeing.

Dropout Rate/ITT-Analysis: - The intention-to-treat population consisted of all eligible randomised patients, regardless of study drug administration
- 79 patients with Child-Pugh B disease (41 received ramucirumab and 38 received placebo) were enrolled before the protocol amendment, and were subsequently excluded from the intention-to-treat population; these patients were replaced in the intention-to-treat population with patients with Child-Pugh A disease.

Notes:
evidence level 2: randomized, controlled, double-blind trial

Zhu, Andrew X. et al. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased ?-fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet Oncology. 20. 282-296. 2019

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** randomised, double-blind, placebo-controlled, phase 3 trial **Number of Patient:** 292 patients were randomly assigned, 197 to the ramucirumab group and 95 to the placebo group. **Recruitung Phase:** Between July 26, 2015 and Aug 30, 2017 **Inclusion Criteria:** - diagnosis of hepatocellular	**Intervention:** intravenous ramucirumab (8 mg/kg) or placebo for 1h every 14 days until disease progression, unacceptable toxicity, or withdrawal of consent. **Comparison:** placebo	**Primary:** overall survival **Secondary:** progression-free survival objective response disease-related symptoms **Results:** <u>basics</u> - 281 patients were off treatment, and 11 patients in the ramucirumab group were still receiving therapy at day of cut-off (March 15, 2018). - 206 (71%) of 292 had disease progression and 221 (76%) had died. Median duration of follow-up for overall survival was 7.6 months (IQR 4.0–12.5) <u>overall survival</u> - Median overall survival was significantly improved in the ramucirumab group compared with the placebo group (8.5 months [95% CI 7.0–10.6] vs 7.3 months [5.4–9.1]; HR 0.710 [95% CI 0.531–0.949];

carcinoma - Barcelona Clinic Liver Cancer (BCLC) stage B or C disease that was refractory or not amenable to locoregional therapy, - Child-Pugh class A liver disease, - Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, - serum α-fetoprotein concentrations of 400 ng/mL or higher (as measured by a local laboratory), - adequate haematological and biochemical parameters, - aged 18 years or older, - Sorafenib was the only previous systemic treatment for hepato-cellular carcinoma that was allowed, and it had to have been discontinued at least 14 days before randomisation because of intolerance or disease progression, - at least one measurable lesion as per the Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1) and adequate organ function **Exclusion Criteria:** - hepatic locoregional therapy after sorafenib, - major surgery in the 28 days before randomisation, - a history of or current hepatic encephalopathy, - previous liver transplantation, - oeso-phageal or gastric varices requiring endoscopic treatment, - uncontrolled arterial hypertension. - clinically meaningful ascites (ie, worse than grade 1 on the US National Cancer Institute's Common Terminology Criteria for Adverse Events [CTCAE; version 4.0]) resulting from cirrhosis		p=0·0199) progression-free survival - Median progression-free survival was significantly longer in the ramucirumab group than the placebo group (2.8 months [95% CI 2.8–4.1] vs 1.6 months [1.5–2.7]; HR 0.452 [95% CI 0.339–0.603]; p<0.0001) objective response - the proportion of patients with an objective response did not differ between groups (nine [5%] vs one [1%]; p=0.1697). - The proportion of patients with disease control (ie, an objective response or stable disease) was significantly higher in the ramucirumab group than in the placebo group (118 [59.9%; 95% CI 53.1–66.7] of 197 vs 37 [38.9%; 95% CI 29.1–48.8] of 95; p=0.0006) safety - Treatment discontinuation because of any adverse events (35 [18%] of 197 vs 10 [11%] of 95) or because of treatment-related adverse events (21 [11%] vs three [3%]) occurred more often in the ramucirumab group than in the placebo group - most frequently reported treatment-emergent adverse events of any grade in the ramucirumab group were fatigue (54 [27%]), peripheral oedema (50 [25%]), hypertension (49 [25%]) and decreased appetite (46 [23%]) Grade 3 or worse treatment-emergent adverse events that occurred in at least 5% of patients in either group were hypertension (25 [13%] in the ramucirumab group vs five [5%] in the placebo group), hyponatraemia (11 [6%] vs 0) and increased aspartate aminotransferase (six [3%] vs five [5%] - Serious adverse events of any grade and cause were recorded in 68 (35%) participants in the ramucirumab group and 28 (29%) in the placebo group, whereas treatment-related adverse events of any grade were recorded in 21 (11%) and five (5%) patients, respectively. - Three patients in the ramucirumab group died from treatment-emergent adverse events **Author's Conclusion:** The efficacy and safety results of the pivotal REACH-2 study show that ramucirumab could be a well-tolerated second-line treatment for patients with advanced hepatocellular carcinoma and increased α-fetoprotein concentrations. To our knowledge, REACH-2 is the first successful phase 3 study in a biomarker-selected patient population with advanced hepatocellular carcinoma. The safety profile also makes ramucirumab a good potential candidate for assessment in combination with other agents, including immune checkpoint inhibitors, and in previous lines of therapy.

Methodical Notes

Funding Sources: - This study was funded by Eli Lilly.
- The study funder had roles in study design of REACH and REACH-2, and was involved in data collection, analysis, and interpretation, and writing of the report. The corresponding author had full access to all study data and had final responsibility for the decision to submit for publication

COI: - AXZ reports grants from Bayer, Bristol-Myers Squibb, Eli Lilly, Merck, and Novartis, and consultancy and advisory roles for AstraZeneca, Bayer, Bristol-Myers Squibb, Eisai, Eli Lilly, Exelsix, Merck, Novartis, and Sanofi.
- Y-KK reports personal fees from Ono, BMS, Eli Lilly, Roche, Daehwa, and Taiho.
- RSF reports consultancy for AstraZeneca, Bayer, Bristol-Myers Squibb, Eli Lilly, Pfizer, Merck, Novartis, Roche, and Genentech.
- PRG reports advisory board and lecture fees from Bayer, Bristol-Myers Squibb, MSD, Merck, Sirtex, AstraZeneca, Sillajen, and Eli Lilly.
- JML reports grants from Bayer Healthcare, Bristol-Myers Squibb, Eisai, Ipsen, Blueprint, and Incyte, and personal fees from Eli Lilly, Bayer Healthcare, Bristol-Myers Squibb, Eisai, Blueprint, Incyte, Celsion, Exelixis, Glycotest, Ipsen, Merck, Navigant, Leerink Swann, Midatech, Fortress Biotech, Spring Bank Pharmaceuticals, and Nucleix.
- IO reports personal fees from Merk Serono and Taiho.
- PM reports grant from Onxeo, and has served on advisory boards for Bayer, Ipsen, Exelixis, and Onxeo.
- BD reports personal fees from Bayer, Bristol-Myers Squibb, Ipsen, Eisai, Eli Lilly, MSD, and Merck, and non-financial support from Bayer and Bristol-Myers Squibb.
- J-BH reports personal fees from Gilead, Abbvie, Intercept, and Bayer.
- TO reports grants and personal fees from Eli Lilly, Boehringer Ingelheim, Dainippon Simitomo, Pfizer, Bayer Yakuhin, Chugai, Yakuruto Honsha, Ono, Eisai, AstraZeneca, Merck Serono, Baxter, Nano Carrier, Zeria, and Nobelpharma, grants from OncoTherapy Science, Kyowa Hakko Kirin, Shizuoka Industry, and GlaxoSmith Kline, and personal fees from Bristol-Myers Squibb, Nipponchemofa, EA Pharma, Fujifilm RI, Astellas, Nippon Kayaku, Daiichi Sankyo, Celgene, MSD, and Teijin Pharma.
- YH and PBA are employees of, shareholders in, and have patents pending with, Eli Lilly.
- MK reports grants from Chugai, Otsuka, Takeda, Taiho, Sumitomo Dainippon, Daiichi Sankyo, MSD, Eisai, Bayer, Abbvie, Medico's Hirata, Astellas, and Bristol-Myers Squibb, and has served on advisory boards for Bayer, Eisai, MSD, Ajinomoto, Kowa, Bristol-Myers Squibb, Chugai, Taiho, Eisai, and Ono.
- All other authors declare no competing interests.

Randomization: - Investigators enrolled patients, who were subsequently randomly allocated (2:1) to treatment with ramucirumab or placebo via an interactive web-response system with a computer-generated random sequence.
- Randomisation was stratified by geographical region (region 1 [Americas, Europe, Australia, Israel] vs region 2 [Asia, excluding Japan] vs region 3 [Japan]), macrovascular invasion (yes vs no), and ECOG performance status (0 vs 1).

Blinding: - Patients, investigators and the sponsor were masked to treatment assignment
- Ramucirumab was visibly indistinguishable from placebo

Dropout Rate/ITT-Analysis: all efficacy outcomes were assessed in the intention-to-treat population.

Notes:
- evidence level 2: randomized controlled trial
- this study was not included in the original literature search

NEWCASTLE - OTTAWA Checklist: Cohort: *3 Bewertung(en)*

Daniele, B. et al. Impact of sorafenib dosing on outcome from the European patient subset of the GIDEON study. Future Oncol. 11. 2553-62. 2015

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 3 **Study type:** prospective, open-label, noninterventional study (sub-analysis of European population)	**Funding sources:** The study was supported and funded by Bayer HealthCare Pharmaceuticals and Onyx Pharmaceuticals, an Amgen subsidiary. **Conflict of Interests:** - B. Daniele received consultancy fees from Bayer, lectureship fees from Bayer, Daiichi Sankyo and Novartis, and is a board member of Bayer and Daiichi Sankyo. - A Croitoru received consultancy and lectureship fees, and research support from Bayer, Roche, Merck, Novartis, Ipsen and Lilly. - C Papandreou received honoraria from, and holds an advisory role with Bayer. - JP Bronowicki received consultancy and educational fees from Bayer, and a research grant from Bayer was received by the CHU de Nancy. - P Mathurin received speaking fees from Roche, MSD, Gilead Sciences, Bristol-Myers Squibb, Jansenn-Cilag and Bayer, and is an investigator for Roche, Schering-Plough, Bristol-Myers Squibb, Gilead Sciences, Janssen-Cilag, Boeringher, Novartis and Bayer, is also a member of the French boards of experts in Hepatology for Roche, MSD, Gilead Sciences, Boeringher, Bayer and Bristol-Myers Squibb and holds a consultancy role with Roche, Schering-Plough, MSD, Abbott, Bristol-Myers Squibb, Gilead Sciences, Janssen-Cilag, Boeringher, Novartis and Bayer. - F Serejo declared no conflicts of interest. - P Ståℓ received consultancy and lectureship fees from Bayer. - J Turnes received consultancy and lectureship fees from Bayer. - V Ratziu holds an advisory role with Bayer. - G Bodoky received honoraria from Bayer, Roche, Pfizer, Janssen, Novartis, Lilly and Taiho and holds an advisory role with Bayer, Roche, Novartis, Pfizer and Lilly.	**Total no. patients:** - A total of 3371 patients from 39 countries were enrolled - The European subset comprised 1113 patients from 180 sites in 22 countries. **Recruiting Phase:** between January 2009 and November 2010 **Inclusion criteria:** patients - with histologically/cytologically documented or radio-graphically confirmed unresectable HCC, - with a life expectancy of at least 8 weeks, - who had not undergone previous sorafenib therapy, - were candidates for systemic therapy, - in whom the decision to treat with sorafenib had been made, - must have signed an informed consent form. **Exclusion criteria:** Exclusion criteria followed the approved local product information.	**Interventions:** sorafenib 400 mg/day **Comparison:** nonesorafenib 800 mg/day

	- The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. **Randomization:** none **Blinding:** none **Dropout rates:** - intent-to-treat population comprised all patients who entered the study and received at least one dose of sorafenib		
Notes:	evidence-level 3: prospective, open-label, non-interventional study **Author's conclusion:** In summary, the AE profiles are comparable across the dosing groups. The data suggest that patients receiving the recommended dose of 800 mg/day sorafenib can continue on treatment longer with a better survival outcome than those receiving 400 mg/day. It is important to acknowledge, however, that a greater percentage of the patients who started on the lower dose (n = 171) were older (median age: 69 vs 66 years) and had a worse ECOG performance status (63.2 vs 49.1% were performance status 1–3) and Child-Pugh disease status (25.7 vs 18.8% were status B). Nonetheless, it is not unreasonable to suggest, based on the available data, that the current recommended dose of 800 mg/day should be the starting dose for all patients and reduced on an individual basis depending on the appearance and severity of any AEs observed.		
Outcome Measures/results	**Primary** safety **Secondary** overall survival (OS) time to progression (TTP)	**Results:** <u>Sorafenib dosing</u> - 171 patients recieved 400 mg/d, 917 patients recieved 800 mg/d sorafenib, 25 patients received an alternative dose of sorafenib - Patients who received 800 mg/day sorafenib experienced fewer dose interruptions (23.7 vs 26.9%), dose modifications (43.3 vs 57.9%), dose increases (12.1 vs 39.8%), more dose reductions (39.1 vs 25.7%) - median duration of treatment and days on the study drug were greater for the 800 mg/day group (18.0 vs 13.0 weeks) <u>safety</u> - higher rate of AEs (all grades) in the 400 mg/day patient group (95.9 vs 87.8%), plus higher rates of drug-related AEs (73.7 vs 68.8%) and serious AEs (57.3 vs 44.5%) - most common AEs (all grades, drug-related and drug-related grade 3/4) were diarrhea, fatigue and hand–foot skin reaction (HFSR) (Tab le 5). - Overall, 2.2% of the population died as a result of drug-related AEs. At the time of analysis, 60% of patients were dead in the 400 mg/day group and 52% in the 800 mg/day group. <u>Overall survival</u> - Patients in the 800 mg/day group appeared to	

		have a longer median OS (12.1 months; 95% CI: 10.5–13.8) than those in the 400 mg/day group (9.4 months; 95% CI: 6.3–12.6) time to progression (TTP) - Median TTP was similar for both patient groups (6.5 vs 6.2 months).

Ganten, T. M. et al. Sorafenib in Patients with Hepatocellular Carcinoma-Results of the Observational INSIGHT Study. Clin Cancer Res. 23. 5720-5728. 2017

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 3 **Study type:** observational cohort study, noninterventional, prospective, multicenter.	**Funding sources:** "This study was supported by Bayer Vital GmbH. The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact." **Conflict of Interests:** "T.M. Ganten and E. Schott report receiving speakers bureau honoraria from and are consultant/advisory board members for Bayer. P.R. Galle reports receiving speakers bureau honoraria from Bayer and is a consultant/ advisory board member for Bayer, Bristol-Myers Squibb, Lilly, MSD, Sillajen, and Sirtex. R. Koschny reports receiving commercial research support from Bayer. No potential conflicts of interest were disclosed by the other authors." **Randomization:** - **Blinding:** - **Dropout rates:** 4 lost to follow up.	**Total no. patients:** 788 **Recruiting Phase:** 2008-2014 **Inclusion criteria:** Patients with HCC who were diagnosed according to the American Association for the Study of Liver Diseases (AASLD) guidelines 2005, and the subsequent 2011 update, were aged 18 years or older, and were candidates for systemic therapy with sorafenib. **Exclusion criteria:** -	**Interventions:** Sorafenib was administered orally with the dose and duration chosen at the discretion of the treating physician, complying with daily. Although dosing was generally 800mg some patients were also started on a lower daily dose of 200, 400, or 600 mg. The observation period for each patient was the time between the initial visit, where sorafenib therapy was commenced, and the time point of disease progression (according to RECIST criteria), death or unacceptable AEs leading to sorafenib discontinuation. **Comparison:** -
Notes:	Evidence level 3. Non-randomized controlled cohort **Author's conclusion:** "Sorafenib treatment was shown to be effective in a real-life setting, in agreement with previously reported clinical trial data. Disease stage (BCLC classification), liver function (Child–Pugh stadium), and performance status (ECOG score) correlated with longer overall survival and time to progression. The therapy was found to have an acceptable safety profile, with predominantly mild to moderate side effects. The data obtained in this observational study agree		

	well with those of previously reported clinical trials, validating the results in a real-life setting."	
Outcome Measures/results	**Primary** Overall survival, time to progression **Secondary** -	**Results: Population:** The end of the study observation period was a result of disease progression for 284 patients (36.0%), death for 212 patients (26.9%), and unacceptable AEs leading to treatment discontinuation in 122 patients (15.5%).The mean age of the efficacy set was 66.7 years (±9.6), and the mean body mass index was 26.9 kg/m2 (±4.6); 14.6% were female. The majority of patients had Child–Pugh A liver cirrhosis (56.7%), predominantly due to chronic alcohol abuse (43.5%) or hepatitis B (11.6%) or C (13.9%). Most tumors were at Barcelona Clinic Liver Cancer (BCLC) stage C (50.1%), with 53.2% limited to the liver. A small proportion of patients were treated with sorafenib even though it was not indicated in the EASL guidelines. **Results:** Median overall survival for the total population was 15.1 months, while time to progression was 4.2 months. Median overall survival for patients at BCLC stage A was 29.2 months. Median overall survival decreased to 19.6, 13.6, and 3.1 months for BCLC stages B, C, and D, respectively (P < 0.0001). Time to progression also significantly differed between the different BCLC stages (P = 0.0001). For patients with HCC and Child–Pugh A liver cirrhosis (n = 443), the median overall survival was 17.6 months. Overall survival for patients with Child-Pugh B (n = 182) and C (n = 26) significantly decreased, at 8.1 and 5.6 months, respectively (P < 0.0001). Time to progression was also dependent on Child–Pugh status, with values of 5.3, 3.3, and 2.5 months noted for patients with Child–Pugh A, B, and C, respectively (P < 0.0001)

Kambhampati, S. et al. Nivolumab in patients with advanced hepatocellular carcinoma and Child-Pugh class B cirrhosis: Safety and clinical outcomes in a retrospective case series. Cancer. 125. 3234-3241. 2019

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 4 **Study type:** retrospective case series	**Funding sources:** Support for the University of California at San Francisco Hepatobiliary Tissue Bank and Registry was received from the Bili Project Foundation Inc. **Conflict of Interests:** see article for extensive list. **Randomization:** - **Blinding:** -	**Total no. patients:** 18 **Recruiting Phase:** treatment with nivolumab from 2015-2018. **Inclusion criteria:** Enrollment in the UCSF Hepatobiliary Tissue Bank and Registry (IRB 12-09576). Age ≥18 years, radiographic and/ or histologic diagnosis of incurable HCC and Child-Pugh class B cirrhosis; treatment with nivolumab as a standard therapy for HCC, ineligibility for therapeutic clinical trials, and availability of nivolumab infusion records and oncology clinic	**Interventions:** Nivolumab treatment **Comparison:**

	Dropout rates: --	notes for chart review. **Exclusion criteria:** -	
Notes:	Evidence level 4: case series **Author's conclusion:** In the current study of a cohort of patients with HCC with CPB liver dysfunction, nivolumab was noted to have acceptable safety and similar rates of treatment related AEs compared with other solid tumor studies, although the rates of unrelated AEs and SAEs attributed to comorbid liver disease and advanced tumor burden were high. A subset of patients experienced a prolonged and robust treatment response. Nivolumab warrants further study in patients with CPB HCC, which is a growing population with a poor prognosis and limited standard treatment options.		
Outcome Measures/results	**Primary Safety.** AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events. Safety outcomes included all-cause and treatment-related grade ≥3 AEs, all-cause and treatment-related SAEs, immune-related AEs (irAEs) of any grade, irAEs requiring steroids, irAEs requiring hospitalization, and irAEs resulting in the discontinuation of treatment. **Secondary** -	**Results: Population:** A total of 18 patients were included, with 72% of them (13 of 18 patients) previously treated with sorafenib. Mean age 66.5 years (26-86) and 72% male participants. **Results: Primary: Safety:** The majority of patients (94%; 17 of 18 patients) experienced a grade ≥3 AE, with treatment-related grade ≥3 AEs reported in 28% of patients (5 of 18 patients). irAEs were reported to occur in approximately 50% of patients (9 of 18 patients), and 28% (5 of 18 patients) required steroids. Treatment-related AEs required discontinuation in 4 patients (22%). **Secondary:** The median time on treatment was 2.3 months (95% CI, 1.9 months to upper bound not estimable). The objective response rate was 17% (3 of 18 patients), including 2 partial responses and 1 complete response. The median overall survival from the time of nivolumab initiation was 5.9 months (95% CI, 3 months to upper bound not estimable), with a median progression-free survival of 1.6 months (95% CI, 1.4-3.5 months).	

Schlüsselfrage:

HCC/ICC

Inhalt: *5 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Brouwer, W. P. 2017	4	retrospective prognostic study
Ito, T. 2015	3	Prognostic, observational study
Kim, J. H. 2018	4	Retrospective, prognostic study
Song, B. G. 2018	4	Retrospective, prognostic study.
Toyoda, H. 2015	4	Prognostic, retrospective study.

OXFORD (2011) Appraisal Sheet: Prognostic Studies: *5 Bewertung(en)*

Brouwer, W. P. et al. Prediction of long-term clinical outcome in a diverse chronic hepatitis B population: Role of the PAGE-B score. J Viral Hepat. 24. 1023-1031. 2017

Population	Intervention	Outcomes/Results
Evidence level: 4 **Study type:** retrospective prognostic study **Number of Patient:** 557 patients (323 excluded) mono -infected treatment -naïve CHB (HBsAg positive for >6 months) patients; tertiary care centre in Rotterdam, the Netherlands. **Recruitung Phase:** consecutively biopsied in the period of 1985– 2012 **Inclusion Criteria:** mono -infected treatment -naïve CHB (HBsAg positive for >6 months). **Exclusion Criteria:** In case of a history of antiviral therapy for the duration of > 1 month prior to or at the time of biopsy, a current or past co-infection with hepatitis C, D, E or human immunodeficiency virus, presence of auto -immune liver disease, primary biliary cirrhosis, Wilson's disease, hemochromatosis or any other co -existing primary liver disease, or treatment with immune suppressive medication for more	**Intervention:** Risk scores: -PAGE-B - REACH-B - FIB4 - Log APRI - GAG-HCC - CU-HCC **Comparison:** -	**Primary:** The occurrence of liver failure (defined as an episode of jaundice, ascites, hepatic encephalopathy or gastro-duodenal bleeding due to varices), HCC development, liver transplantation and all -cause mortality was studied. **Secondary:** - **Results:** Mean follow up time was: 10.1 years (interquartile range 5.7 – 15.9, maximum 27.3 years). **Events during follow up:** 40 patients experienced a clinical event: - 10 patients developed liver failure, - 15 patients were diagnosed with HCC, - 7 patients underwent liver transplantation, and - 31 patients died (ten patients died of a liver - related cause (7 due to HCC, and 3 as a result of liver failure), 8 died of liver -unrelated causes (of which 1 patient had a n HCC) and for 13 patients the cause of death was unknown. The overall 5, 10 and 20 -year event -free

than 6 months prior to or at the time of biopsy.		survival was 97.6%, 94.0% and 86.8%, respectively. **Factors associated with long-term clinical outcome:** By multivariable analysis, factors independently associated with clinical outcome were the PAGE -B score (HR 1.27, 95%CI: 1.2 – 1.4, p<0.001) and the Ishak fibrosis stage (HR 1.38, 95%CI: 1.1– 1.7,p=0.003). **Non-invasive scores versus liver biopsy for the prediction of clinical outcome:** **PAGE-B** score for the prediction of any clinical event was 0.86(95%CI: 0.80– 0.92), and was 0.83 (95%CI: 0.76– 0.91) for reduced transplant-free survival and 0.91 (95%CI: 0.82 – 0.9 9) for HCC development (overall highest C-statistic compared to the other non-invasive scores). The other non -invasive prognostic measures showed a lower C-statistic for all respective outcomes. When the Ishak stage was combined with the PAGE-B, the prediction for any clinical event improved(C-statistic 0.87, 95%CI: 0.82– 0.93). Within patients with advanced fibrosis or Asian patients the C -statistics were comparable to the FIB -4 and REACH -B. Prediction of HCC development in Asian patients (who received antiviral therapy after liver biopsy) C -statistics obtained with the PAGE-B was higher than the REACH -B: 0.75(95%CI: 0.53– 0.97) for the PAGE-B versus 0.69 (95%CI: 0.61 – 0.78) for the REACH-B, respectively. **Additional prognostic value of the Ishak stage combined with PAGE-B.** Within the first 10 years of follow -up, the PAGE -B score alone correctly classified all patients who developed HCC into the intermediate–high HCC risk group (PAGE-B >10 corresponding to an HCC risk >0.2% at year 5 [4/4 cases] and >0.6% at year 10 [10/10 cases]) and no patients were incorrectly reclassified (NRI=0). **Author's Conclusion:** In conclusion, we have shown that the PAGE-B score was the best performing non-invasive score to predict the clinical outcome of CHB patients of different origin and within different subgroups. The Ishak stage did not clinically improve the risk prediction of the PAGE -B score. When

		further validated, this score could additionally be used to assess the need for antiviral therapy and HCC surveillance.

Methodical Notes

Funding Sources: Foundation for Liver Research (SLO), Rotterdam, the Netherlands. This study was supported by the Virgo consortium, funded by the Dutch government project number FES0908, and by the Netherlands Genomics Initiative (NGI) project number 050-060-452.

COI: The institution of Adriaan J. van der Meer received financial compensation for lecture activities from MSD. Andre Boonstra received grants from Bristol Myers Squibb, Roche, Tibotec and Janssen -Cilag. Harry L.A. Janssen received grants from and is a consultant for: Bristol Myers Squibb, Gilead Sciences, Novartis, Roche and Merck. The other authors have nothing to disclose.

Randomization: none

Blinding: Biopsies were re-scored by a single experienced hepato-pathologist who was blinded to the patient characteristics and outcome.

Dropout Rate/ITT-Analysis: Survival and HCC status was available for 515 (92.6%) patients, 41 (7.2%) patients emigrated and were censored at the last follow -up visit, ; follow -up data of 1 patient (0.2%) could not be retrieved.

Notes: CEBM Level 4 (Retrospective, observational study).

Ito, T. et al. Utility of the FIB-4 Index for hepatocarcinogenesis in hepatitis C virus carriers with normal alanine aminotransferase levels. J Viral Hepat. 22. 777-83. 2015

Population	Intervention	Outcomes/Results
Evidence level: 3 **Study type:** Prognostic, observational study **Number of Patient:** from 4620 patients tested 516 patients fulfill all inclusion parameters. **Recruitung Phase:** September 1995 and August 2004. **Inclusion Criteria:** Patients tested positive for HCV, positive for HCV RNA for at least 2 time points with a >6 month interval, had no evidence of hepatitis B virus (HBV) infection, had no other potential causes of chronic liver disease (i.e. alcohol consumption < 80 g/day, no history of hepatotoxic drug use and negative tests for autoimmune hepatitis, primary biliary cirrhosis, hemochromatosis and Wilson's disease), had a follow-up period >3 years, had no evidence of HCC at study entry and for at	**Intervention:** FIB-4 index (was calculated at the start of follow-up) and a new scoring system that combines the FIB-4 index and AFP. The total score was the sum of the FIB-4 index and AFP scores. We estimated the incidence of hepatocarcinogenesis with this new scoring system. **Comparison:** AFP (AFP was measured in 477 patients at the start of follow-up period).	**Primary: HCC incidence:** - time integral of the ALT level ('integration value') would be more useful for predicting the incidence of HCC. - Ultrasonography (US) and blood tests including the tumour marker AFP were performed every 3 to 6 months for HCC surveillance. The diagnosis of HCC was confirmed through histological examination or via typical radiological findings. **Secondary:** Factors associated with incidence of HCC. **Results:** The median follow-up period was 11.3 years. **Incidence of HCC**: HCC developed in 60 of 516 patients (11.6%). The incidence rate of HCC at 5 and 10 years were 2.6% and 17.6%, respectively. **Factors associated with the incidence of hepatocarcinogenesis** (multivariate analysis): FIB-4 index >2.0 (hazard ratio (HR), 7.690 [95%

least 3 years from the start of the follow-up period, had no antiviral therapy involving interferon and/or ribavirin, had ALT measurements taken more than twice annually and had ALT values < 40 IU/L. **Exclusion Criteria:**		confidence interval (CI), 2.636–22.438]; P < 0.001) and FIB-4 index >4.0 (HR, 8.991 [95% CI, 3.088– 26.178]; P < 0.001), AFP >5 ng/mL (HR, 2.742 [95% CI, 1.497–5.023]; P < 0.001) and AFP >10 ng/mL (HR, 4.915 [95% CI, 2.353–10.267]; P < 0.001) and total bilirubin >1.2 mg/dL (HR, 2.142 [95% CI, 1.115–4.117]; P = 0.022). **Relationship between the FIB-4 index and AFP:** There were no significant correlation between the FIB-4 index and AFP based on Spearman's rank correlation (r = 0.023, P = 0.63). **Incidence of hepatocarcinogenesis based on the combined FIB-4 index and AFP score** 5 categories in the scoring system that combines the FIB-4 index and AFP level (2–6 points). The incidence rate of HCC increased as the score increased (2 vs 3, P < 0.001; 3 vs 4 points, P = 0.070; 4 vs 5 points P = 0.011; and 5 vs 6 points; P = 0.270). This scoring system reflected patient survival well. **Author's Conclusion:** In conclusion, the FIB-4 index was closely associated with the risk of HCC in hepatitis C virus carriers with normal ALT levels. Furthermore, we showed that the risk of HCC could be well stratified according to a scoring system that combines the FIB-4 index and AFP.

Methodical Notes

Funding Sources: none

COI: none

Randomization: n.s.

Blinding: n.s.

Dropout Rate/ITT-Analysis: -

Notes: CEBM Level of Evidence: 3 oder 4 (prognostic observational study)

Authors limitation:
-histological confirmations for liver fibrosis were obtained in partial patients.
-study did not investigate the changes of FIB-4 index over the years.

Kim, J. H. et al. Validation of modified fibrosis-4 index for predicting hepatocellular carcinoma in patients with compensated alcoholic liver cirrhosis. Medicine (Baltimore). 97.

e13438. 2018

Population	Intervention	Outcomes/Results
Evidence level: 4 **Study type:** Retrospective, prognostic study **Number of Patient:** 924 consecutive Asian patients with compensated ALC. **Recruitung Phase:** January 1, 2007 and December 31, 2015. **Inclusion Criteria:** Patients listes in the inpatient and outpatient database at Kangwon National University Hospital (Chuncheon, Korea); the time limit of abstinence accepted for inclusion criteria was 2 years. We included the patients who had compensated cirrhosis when the non-invasive fibrosis tests were performed at baseline. **Exclusion Criteria:** 1. aged <18 or >85 years; 2. developed HCC within 12 months from the date of cirrhosis diagnosis; 3. diagnosed with HCC before study enrollment; 4. diagnosed with infection of hepatitis B, hepatitis C, and other hepatotropic viruses or human immunodeficiency virus; or 5. had a medical history indicating active alcoholism, liver transplantation, or decompensated cirrhosis. Patients with decompensated cirrhosis at baseline (n=32) were excluded.	**Intervention:** - fibrosis-4 (FIB4) index, - the aspartate aminotransferase (AST)-to-platelet ratio index (APRI), - modified fibrosis-4 index (mFIB-4), - the easy liver fibrosis test (eLIFT) **Comparison:** see intervention.	**Primary:** Compare the **performance** of the mFIB-4 index, eLIFT score, FIB-4 index, and APRI for **HCC development** at 3 years of follow-up. Patients regularly underwent clinical examinations and liver function tests every 6 months. The primary modality for HCC surveillance in this study was ultrasonography in combination with serum alpha-fetoprotein levels in accordance with current guidelines of South Korea. **Secondary:** - **Results:** Follow-up period (median 58 month). **HCC development:** - patients who developed HCC (n=83, 9.0%) - patients who did not (n=841, 91.0%). Age, serum creatinine levels, mFIB-4 index, FIB-4 index, and APRI were significantly higher in patients who developed HCC than in those without HCC (all values: P<.05 however serum albumin levels and platelet counts were significantly lower in patients who developed hcc than those without values: p> Predictive performances of four risk prediction models for HCC development (3 years): Highest: mFIB-4 index, AUROC=0.71, 95% confidence interval [CI]: 0.64–0.78, followed by: FIB-4 index, AUROC=0.69, 95% CI: 0.63– 0.75), - APRI, AUROC=0.61, 95% CI: 0.56–0.66, and - eLIFT score, AUROC=0.56, 95% CI: 0.50–0.62. The AUROCs of the mFIB-4 index were significantly higher than those of APRI and eLIFT scores at 3 years (all P<.05 no significant difference in aurocs was found between the mfib-4 and fib-4 indexes at years multivariable analysis revealed that older age ci: p=".001)" index were independent predictors of hcc development.>Sensitivities of non-invasive tests based on tumor size: The mFIB-4 index tended to show higher sensitivities irrespective of tumor size compared with other non-invasive tests. Predictive performance: mFIB-4 better for tumors ≤ 5 cm in size, for tumors >5 cm in size, the FIB-4 index tended to better predict HCC development than other non-invasive tests. **Author's Conclusion:** In conclusion, the

		mFIB-4 index, a newly developed noninvasive marker of liver fibrosis, can predict HCC and stratify HCC risk in patients with ALC. This result indicates that this index can help clinicians make surveillance strategies based on individual risk.

Methodical Notes

Funding Sources: This study was supported by a grant from 2017 Kangwon National University Hospital, a fund from Gangwon branch of the Korean
Association for the Study of the Liver, 2015 Research Grant from the Kangwon National University (grant number: 520150354), a research grant from Hanmi Pharmaceutical Co, Ltd, and a grant from Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (grant number: 2017R1D1A1B03031499).

COI: none.

Randomization: none.

Blinding: n.s.

Dropout Rate/ITT-Analysis: none.

Notes: CEBM Level of evidence: 4 (retrospective, prognostic study).

Song, B. G. et al. Additional role of liver stiffness measurement in stratifying residual hepatocellular carcinoma risk predicted by serum biomarkers in chronic hepatitis B patients under antiviral therapy. Eur J Gastroenterol Hepatol. 30. 1447-1452. 2018

Population	Intervention	Outcomes/Results
Evidence level: 4 **Study type:** Retrospective, prognostic study. **Number of Patient:** 4046 consecutive TE exams were screened, 1045 patients fulfilled the inclusion criteria. After exclusion of 31 patients due to the exclusion criteria, finally 1015 adult chronic HBV monoinfected patients without malignancy at baseline who were taking NUCs for at least a year and had at least 6 months of followup were analyzed. **Recruitung Phase:** March 2012 and December 2014 **Inclusion Criteria:** Patients at Samsung Medical Center, Seoul, Korea. (i) adults aged 18 years and older; (ii) chronic HBV infection confirmed by hepatitis B surface antigen positivity for more than 6	**Intervention:** The follow-up period started at the time of LS measurement to the development of HCC or last follow-up, whichever came first. Exposures were the fibrosis markers: LS, APRI, and FIB-4. **Comparison:** -	**Primary:** Diagnosis of HCC during the follow-up. Patients receiving NUCs therapy were monitored on a regular basis, typically every 3–6 months, for biochemical response, virological response, and side effects. HCC surveillance was usually performed with ultrasonography and a serum α-fetoprotein measurement at 6-month intervals. **Secondary:** - **Results:** Follow up: median of 3.9 years (range: 0.5–5.3 years). **HCC was newly diagnosed** in 37 (3.6%) patients. These 37 patients had significantly different characteristics from patients who were not diagnosed with HCC. They were older, more likely to be male, had higher AST levels, and lower platelet counts. The fibrosis markers, LS, APRI, and FIB-4 were all significantly higher for those who developed HCC. Hepatocellular carcinoma risk by serum

months or compatible clinical history; (iii) no history or current malignancy; (iv) no co-infection with hepatitis C virus or HIV; (v) under NUCs therapy for at least a year at the time of LS measurement; and (vi) a reliable liver stiffness measurement (LSM), as defined by at least 10 valid measurements, a success rate of at least 60%, and an interquartile range-to-median ratio of less than 30%. **Exclusion Criteria:** 31 patients (of the 1045 patients) were excluded as they developed HCC within 6 months (n=9) or had follow-up duration less than 6 months after LS measurement (n=22).		noninvasive predictors of liver fibrosis: The **HCC incidence rate at 3 years** was higher for those with a higher degree of liver fibrosis, as estimated by the APRI (2.0 vs. 6.9% for APRI< 0.5 vs. ≥0.5, P< 0.001) and FIB-4 (1.3 vs. 5.2% for FIB-4< 1.45 vs. ≥1.45, P< 0.001) scores, respectively. The HCC risk was significantly higher for those with both high APRI and FIB-4 compared with those with both low APRI and FIB-4 scores. **Hepatocellular carcinoma risk stratified by serum biomarker and liver stiffness values** The HCC incidence rate at 3 years was higher for those with higher LS values (1.4 vs. 5.3% for LS<6 vs. ≥6, P<0.001). The combination of the LS values and serum biomarkers showed better performance for stratifying HCC risk. **Author's Conclusion:** This study showed that TE can further stratify the CHBrelated HCC risk over the serum biomarkers in patients under AVT. The combined use of TE and serum biomarkers provided an additional benefit compared with the combination of only the serum biomarkers. Therefore, TE may be useful for improving current HCC surveillance strategies by further subdividing the HCC risk.

Methodical Notes

Funding Sources: n.s.

COI: none.

Randomization: n.s.

Blinding: n.s.

Dropout Rate/ITT-Analysis: -

Notes: CEBAM Level of evidence: EL 4 (Retrospective, prognostic study).

Limitations: by authors
- follow up duration (short)
- patients population developing hcc small (3,6%)

Toyoda, H. et al. Risk factors of hepatocellular carcinoma development in non-cirrhotic patients with sustained virologic response for chronic hepatitis C virus infection. J Gastroenterol Hepatol. 30. 1183-9. 2015

Population	Intervention	Outcomes/Results

Evidence level: 4 **Study type:** Prognostic, retrospective study. **Number of Patient:** 1285 patients with chronic HCV infection underwent IFN-based antiviral therapy. Out of these 522 patients achieved SVR. **Recruitung Phase:** 1990 and 2012 **Inclusion Criteria:** Patients with chronic HCV infection underwent IFN-based antiviral therapy (with SVR). Patients of Ogaki Municipal Hospital, Japan. **Exclusion Criteria:** Patients were excluded if they had antibodies against human immunodeficiency virus or hepatitis B virus surface antigen or other forms of liver disease (e.g., autoimmune hepatitis, alcoholic liver disease, or hemochromatosis). Patients with cirrhosis were not included because IFN-based antiviral therapy is not permitted by the Japanese National Medical Insurance System for patients who had cirrhosis at the start of the antiviral therapy.	**Intervention:** FIB-4, APRI **Comparison:** Liver biopsy was performed in 494 patients prior to the start of antiviral therapy. Liver histology was classified according to the METAVIR score. Patients continued to follow-up every six months after SVR with laboratory testing and ultrasonography at every visit.	**Primary:** The **diagnosis of HCC** was based on appropriate imaging characteristics according to criteria in the guidelines of the American Association for the Study of Liver Diseases with the findings of arterial hypervascularity and venous or delayed phase washout by contrast-enhanced dynamic computed tomography or magnetic resonance imaging. In addition, HCC was confirmed histologically based on the resected specimen when patients underwent surgical resection as a treatment. **Secondary:** risk factors **Results:** Median follow-up of 7.2 years (range, 1.0-22.9 years). HCC was diagnosed in 18 patients. The **incidence** of HCC at five and ten years was 1.2 % and 4.3 %, respectively. **Risk factors:** Presence of diabetes mellitus (RR 2.08; P = 0.0453) and higher FIB-4 index at SVR24 (RR 1.73; P = 0.0198) were selected as a factor significantly associated with a higher likelihood of HCC according to the multivariate analysis. **FIB-4 Index:** Patients were classified as having a FIB-4 index of < 2.0 or ≥ 2.0. The incidence of HCC in patients with a FIB-4 index ≥ 2.0 was significantly higher than that of patients with FIB-4 index < 2.0 (P = 0.0001). <u>Characteristics of Patients Who Developed Hepatocellular Carcinoma after SVR:</u> *AFP level* increased significantly at HCC development, compared to the baseline AFP level (P = 0.0437). *APRI* at HCC development was significantly lower than that at SVR24 (P = 0.0424), no significant decrease was observed in FIB-4 index between at SVR24 and at HCC development (P = 0.1750). *Liver fibrosis progressed* to cirrhosis at the development of HCC in 6 of 15 patients (40.0%) who underwent surgical resection as a treatment of HCC and non-cancerous liver tissue at HCC development was available. **Author's Conclusion:** In conclusion,

		the incidence of HCC was 1.2 % at five years and 4.3 % at ten years in non-cirrhotic patients with chronic HCV infection who achieved the eradication of HCV with IFN-based antiviral therapy in Japan. The risk of HCC after SVR was not associated with the antiviral treatment regimen that eradicated HCV. Presence of diabetes mellitus and the elevation of FIB-4 index at SVR24 are at risk factors of HCC after SVR.

Methodical Notes

Funding Sources: None

COI: None

Randomization: no

Blinding: no

Dropout Rate/ITT-Analysis: 51 of 522 patients (9.8%) were lost for follow-up during the study period after 2.3-18.2 years' follow-up, who were treated as censored cases.

Notes: CEBM Level of Evidence: 4 (Study is retrospective based on the laboratory data and medical record).

Limitations:
Study population = number of patients developing HCC was small: 18 patients (=4.3% after 10 years).

Schlüsselfrage:

Ergänzende Literaturrecherche Downstaging

Inhalt: 16 Literaturstellen

Literaturstelle	Evidenzlevel	Studientyp
Affonso, B. B. 2019	3	Prospective cohort study
Agopian, V. G. 2015	4	Retrospective Cohort Study
Chapman, W. C. 2017	4	Retrospective Cohort Study
Degroote, H. 2020	1	Retrospective multicentric validation study
Kardashian, A. 2020	4	Retrospective Cohort Study
Kulik, L. 2018	1	Systematic review and meta-analysis. Effectiveness of LRT in the management of HCC patients on the LT waitlist.
Lai, Q. 2020	4	Retrospective Cohort Study
Mazzaferro, V. 2020	2	Randomised controlled phase 2b/3 trial
Mehta, N. 2020	4	Retrospective Cohort Study
Parikh, N. D. 2015	1	Systematic Review and Meta-Analysis (of cohort studies)
Ravaioli, M. 2019	4	Retrospective observational study
Sapisochin, G. 2016	3	Prospective cohort study
Sinha, J. 2019	3	Prospective cohort study
Toso, C. 2019	4	Retrospective cohort study
Victor, D. W., 3rd 2020	4	Retrospective Cohort Study
Yao, F. Y. 2015	3	Prospective Cohort Study

OXFORD (2011) Appraisal Sheet: Systematic Reviews: 2 Bewertung(en)

Kulik, L. et al. Therapies for patients with hepatocellular carcinoma awaiting liver transplantation: A systematic review and meta-analysis. Hepatology. 67. 381-400. 2018			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References

Evidence level: 1 **Study type: Systematic review and meta-analysis.** **Effectiveness of LRT in the management of HCC patients on the LT waitlist.** **Databases: Ovid Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, and Scopus** **Search period: inception to April 25, 2016.** **Inclusion Criteria: studies that enrolled adults with cirrhosis awaiting LT and treated with bridging or down-staging therapies before transplant. Therapies included TACE,transarterial radioembolization (TARE), ablation, and radiotherapy. We included both comparative and noncomparative studies with no language restrictions.** **Exclusion Criteria: studies with patients enrolled before 1996, case reports, cohorts with fewer than 5 patients, reviews, letters, errata, commentaries, and studies published only as abstracts.**	**Population:** **Three research questions** **1.) Adults with cirrhosis awaiting LT andT1 HCC** **2.)Adults with cirrhosis awaiting LT and T2 HCC** **3.)Adults with cirrhosis awaiting LT and beyond Milan (T3) HCC** **63 studies were included (comparative and non-comparative).** **Intervention:** **three research questions.** **1.) Observation versus any therapy (TACE,TARE, ablation, or radiotherapy)** **2.)Transplant alone versus transplant with any bridging therapy (TACE, TARE, ablation, or radiotherapy)** **3.) Transplant without down-staging versus transplant following down-staging to within Milan (T2)** **Comparison: -**	**Primary: Waitlist dropout due to progression beyond transplant criteria, post-LT survival, recurrence.** **Secondary: -** **Results: 1.): For adults with T1 HCC and waiting for LT, there were only 2 nonrandomized comparative studies, both with a high risk of bias. In one series, the rate of dropout from all causes at 6 months in T1 HCC patients who underwent LRT was 5.3%, while in the other series of T1 HCC patients who did not receive LRT, the dropout rate at median follow-up of 2.4 years and the progression rate to T2 HCC were 30% and 88%, respectively.** **2: For adults with T2 HCC awaiting LT, transplant with any bridging therapy showed a nonsignificant reduction in the risk of waitlist dropout due to progression (relative risk [RR], 0.32; 95%CI, 0.06-1.85; I2 5 0%) and of waitlist dropout from all causes (RR, 0.38; 95% CI, 0.060-2.370; I2 5 85.7%) compared to no therapy based on three comparative studies. The quality of evidence is very low due to high risk of bias, imprecision, and inconsistency.** **There were five comparative studies which reported on posttransplant survival rates and 10 comparative studiesvwhich reported on posttransplant recurrence, and there was no significant difference seen in either of these endpoints.** **3.)For adults initially with stage T3 HCC who received LRT, there were three studies reporting on transplant with any downstaging therapy versus no downstaging, and this showed a significant increase in 1-year (two studies, RR, 1.11; 95% CI,1.01-1.23) and 5-year (1 study, RR, 1.17; 95% CI, 1.03-1.32) post-LT survival rates for patients who received LRT. The quality of evidence is very low due to serious risk of bias and imprecision** **Author's Conclusion: "In patients with HCC listed for LT, the use of LRT is associated with a non-significant trend toward improved**	**see article, 63 references.**

		waitlist and posttransplant outcomes, though there is a high risk of selection bias in the available evidence."	

Methodical Notes

Funding Sources: not stated.

COI: "Potential conflict of interest: Dr. Kulik advises Bayer."

Study Quality: Modified Newcastle-Ottawa Scale was used to assess the risk of bias in observational studies. Quality of evidence was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methods.
Quality of evidence was rated very low for all outcomes.

Heterogeneity: "There was significant heterogeneity among the three studies that looked at down-staging for T3 HCC compared to transplant for T3 HCC without downstaging in terms of the comparative group"

Publication Bias: Not investigated

Notes:
Publication bias not investigated.

Parikh, N. D. et al. Downstaging hepatocellular carcinoma: A systematic review and pooled analysis. Liver Transpl. 21. 1142-52. 2015

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 **Study type: Systematic Review and Meta-Analysis (of cohort studies)** **Databases: MEDLINE and Embase** **Search period: 01.1996 - 03.2015** **Inclusion Criteria: Cohort studies (retrospective or prospective); evaluating downstaging in patients with cirrhosis and HCC; studies in which downstaging was performed using surgical resection, RFA, TACE, TARE, SBRT, or a combination of therapies; and studies that reported rates of success for downstaging patients to within Milan criteria using imaging criteria and/or posttransplant outcomes (including recurrence rates and/or survival) among those who were downstaged to within Milan criteria.**	**Population: Patients with cirrhosis and HCC: Child-Pugh class A disease (54%), Child-Pugh class B (36%)Child-Pugh class C (8%).** **15 obeservational Studies. 13 studies with 950 patients described the success of downstaging patients to within Milan criteria and 15 studies with 320 patients which described posttransplant recurrence rates among patients who were downstaged.** **Intervention: downstaging was performed using surgical resection, RFA, TACE, TARE, SBRT, or a combination**	**Primary: Success rate of downstaging to within Milan criteria and HCC (decrease of tumor burden to within Milan)** **Recurrence rates after LT.** **Secondary: Post-LT Survival** **Results: Primary: Downstaging success:** **13 Studies n=950: Aggregate success rate of 0.48% (95% CI, 0.39%-0.58%). High heterogeneity (I^2 5 84.8%).** **Studies that included patients with tumor thrombus had the lowest success rates;** **when these studies were excluded, the pooled success rate was 0.54% (95% CI, 0.45%-0.63%).** **Studies with prospectively designed protocols for downstaging also yielded a significantly higher success rate compared to retrospective studies**	**Green 2013** **Pracht 2013** **Tohme 2013** **Bova 2013** **Inarrairaegui 2012** **Barakat 010** **Jang 2010** **De Luna 2009** **Lewandowski 2009** **Chapman 2008** **Otto 2006** **Yao 2015** **Ravaioli 2008**

Exclusion Criteria: We excluded articles that evaluated investigational procedures; evaluated systemic chemotherapeutic agents; used explant data for evaluation of downstaging success; had incomplete data for primary outcomes of interest; included less than 5 patients; and/or used surgical resection as the only method for downstaging patients.	**Comparison: Other methods**	**(0.68% versus 0.44% P < 0.001;). There was no significant difference in the success rate of TACE and TARE for downstaging (0.48% versus 0.37%; P 5 0.51; however, the highest downstaging success rates were reported in cohorts undergoing multimodal therapy for downstaging.** **Primary: Post-LT Recurrence:** **12 Studies n=320 patients. In total 58 (0.16; 95% CI, 0.11-0.23) patients had HCC recurrence after LT; There was no significant difference in recurrence rates between TACE and TARE (P = 0.33).** **Secondary: Post-LT survival could not be aggregated because of heterogeneity** **Author's Conclusion: "We have shown that downstaging patients outside of Milan can be achieved in approximately half of all patients; however, post-LT recurrence is higher than what has been reported in patients who present within Milan.** **It is important to note that in well-designed studies with downstaging protocols, equivalent posttransplant results between downstaged patients and those who present within Milan criteria can be achieved."**	

Methodical Notes

Funding Sources: "This work was conducted with support from the Agency for Health Research and Quality Center for Patient-Centered Outcomes Research (R24 HS022418)."

COI: Nothing to report.

Study Quality: Study quality was rated by 1 investigator using the modified Newcastle-Ottawa scale NOS. Quality ranged from 5-9 points.

Heterogeneity: "There was heterogeneity in downstaging success rate among included studies (I^2 = 84.8%)".
"One of the most notable findings of our systematic review is the substantial heterogeneity and limitations of data evaluating downstaging."

Publication Bias: "Publication bias was assessed by visual inspection of a funnel plot. "Our funnel plots showed no evidence of bias; however, this may reflect the large number of small studies

included in this meta-analysis." **Notes:** **Evidence level 1:Systematic review** **High heterogeneity in the main analysis (Downstaging success).**

OXFORD (2011) Appraisal Sheet: RCT: 1 Bewertung(en)

Mazzaferro, V. et al. Liver transplantation in hepatocellular carcinoma after tumour downstaging (XXL): a randomised, controlled, phase 2b/3 trial. Lancet Oncol. 21. 947-956. 2020

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type: Randomised controlled phase 2b/3 trial** **Number of Patient: 74** **Recruitung Phase: March 1, 2011 to March 31, 2015** **Inclusion Criteria: Patients aged 18–65 years with hepatocellular carcinoma beyond the Milan criteria, absence of macrovascular invasion or extrahepatic spread, 5-year estimated post-transplantation survival of at least 50%, and good liver function (Child-Pugh A-B7)** **Exclusion Criteria: General contraindications to transplantation, other previous or concurrent malignant diseases, and HIV infection were exclusion criteria. The main tumour-related exclusion criteria were presence of extrahepatic spread on CT scan or MRI,** **presence of hepatic hilum lymph nodes with short axis greater than 2 cm, portal vein tumour thrombosis or invasion, and life expectancy of less than 3 months owing to hepatocellular carcinoma or less than 6 months owing to any other disease.**	**Intervention: Liver transplantation** **Comparison: Non-transplantation best available tumour treatment**	**Primary: 5-year tumour event-free survival for phase 2b and overall survival for phase 3.** **Secondary:** **Results: <u>5-year tumour event-free survival</u>** **5-year tumour event-free survival was 76,8% (95% CI 60,8–96,9) in the transplantation group versus 18·3% (7,1–47,0) in the control group (hazard ratio [HR] 0·20, 95% CI 0·07–0·57; p=0·003).** **<u>5-year overall survival</u>** **5-year overall survival was 77,5% (95% CI 61,9–97,1) in the transplantation group versus 31,2% (16,6–58,5) in the control group (HR 0,32, 95% CI 0,11–0,92; p=0,035).** **Author's Conclusion: Although results must be interpreted with caution owing to the early closing of the trial, after effective and sustained downstaging of eligible hepatocellular carcinomas beyond the Milan criteria, liver transplantation improved tumour event-free survival and overall survival compared with non-transplantation therapies Postdownstaging tumour response could contribute to the expansion of hepatocellular carcinoma transplantation criteria.**
Methodical Notes		

Funding Sources: Italian Ministry of Health

COI: Not stated

Randomization: After an observation period of 3 months, during which sorafenib was allowed, patients with partial or complete responses according to modified Response Evaluation Criteria in Solid Tumors were randomly assigned (1:1) by an interactive web-response system to liver transplantation or non-transplantation therapies (control group). A block randomisation (block size of 2), stratified by centre and compliance to sorafenib treatment, was applied.

Blinding: Open-label trial

Dropout Rate/ITT-Analysis: Statistical analyses were done according to the intention-to-treat population

Notes:
Level of evidence 2: Randomized controlled trial

- A national programme for expansion of the donor pool was implemented progressively. These major changes, not considered in the study design, forced the trial monitoring committee to recommend study closure on March 31, 2015. Owing to the study closure, the required number of tumoural events or deaths was not met.
- Open-label trial, no blinding

OXFORD (2011) Appraisal Sheet: Diagnostic Studies: 1 Bewertung(en)

Degroote, H. et al. Extended criteria for liver transplantation in hepatocellular carcinoma. A retrospective, multicentric validation study in Belgium. Surg Oncol. 33. 231-238. 2020

Evidence level/Study Types	Population	Outcomes/Results
Evidence level: 1 Study type: Retrospective multicentric validation study	Number of patients / samples: 526 Reference standard: Milan Criteria (MC) Validation: Blinding: Blinding was not stated Inclusion of clinical information: Dealing with ambiguous clinical findings:	Results: Overall survival (OS) and recurrence (RR) rates were similar between patients within MC and all extended criteria. Five-year OS within MC was 71.3% compared to 70.9% for Asan Criteria (AC), 71.4% for Up-to-7 Criteria (UT7), 69.7% for French alpha-foetoprotein (AFP model) and 71.0% for Metroticket 2.0 (MT2.0) criteria. Five-year RR within MC was 12.3% compared to 13.5% for AC, 13.0% for UT7, 14.3% for AFP-model and 13.2% for MT2.0 criteria. Patients beyond MC but within the extended criteria had tendency towards higher recurrence. Author conclusions: All validated extended criteria (AC, UT7, AFP-model and MT2.0) could be proposed as alternatives to the MC with similar outcome. Prospective data are awaited to assess recurrence beyond MC.
Methodical Notes		

Funding Sources: None

COI: None

Notes: Level 4: Retrospective Studies without reference standard or without blinding

OXFORD (2011) Appraisal Sheet: Prognostic Studies: 1 Bewertung(en)

Lai, Q. et al. Identification of an Upper Limit of Tumor Burden for Downstaging in Candidates with Hepatocellular Cancer Waiting for Liver Transplantation: A West-East Collaborative Effort. Cancers (Basel). 12. . 2020

Population	Intervention	Outcomes/Results
Evidence level: 4 **Study type: Retrospective Cohort Study** **Number of Patient: 3325** **Recruitung Phase: January 2000 - March 2017** **Inclusion Criteria: patients with a radiological diagnosis of HCC at the time of first referral for LT** **Exclusion Criteria: patients with mixed hepatocellular-cholangiocellular cancer, cholangiocarcinoma misdiagnosed as HCC and incidental HCC**	**Intervention: This study aimed at developing an intention-to-treat model through a competing-risk analysis.** **Comparison:**	**Primary: Posttransplant HCC-related death, upper limit of tumor burden** **Secondary:** **Results: Twelve centers in Europe, United States, and Asia created a Derivation (n = 2318) and a Validation Set (n = 773) of HCC patients listed for LT between January 2000–March 2017.** **In the Derivation Set, the competing-risk analysis identified two independent covariables predicting post-transplant HCC-related death: combined HCC number and diameter (SHR = 1.15; p < 0.001) and alpha-fetoprotein (AFP) (SHR = 1.80; p < 0.001). WE-DS Model showed good diagnostic performances at internal and external validation. The identified upper limit of tumor burden for downstaging was AFP 20 ng/mL and up-to-twelve as sum of HCC number and diameter; AFP = 21–200 and up-to-ten; AFP = 201–500 and up-to-seven; AFP = 501–1000 and up-to-five.** **Author's Conclusion: In conclusion, the WE-DS Model, based on both morphologic and biologic data obtained at first referral in a large international (Western-Eastern) cohort of HCC patients listed for LT, allowed identifying an upper limit of tumor burden for downstaging beyond which successful LT, following downstaging, results in a futile transplantation**

Methodical Notes

Funding Sources: None

COI: None

Randomization:

Blinding: was not described

Dropout Rate/ITT-Analysis:

Notes: Level of Evidence 4: Retrospective Cohort Study

NEWCASTLE - OTTAWA Checklist: Cohort: 11 Bewertung(en)

Affonso, B. B. et al. Long-term outcomes of hepatocellular carcinoma that underwent chemoembolization for bridging or downstaging. World J Gastroenterol. 25. 5687-5701. 2019			
Evidence level	**Methodical Notes**	**Patient characteristics**	**Interventions**
Evidence level: 3 **Study type: Prospective cohort study**	**Funding sources:** **Conflict of Interests: None** **Randomization:** **Blinding: Not described** **Dropout rates:**	**Total no. patients: 200** **Recruiting Phase: April 2011 to June 2014** **Inclusion criteria: For the Bridging-Group: Patients who were within MC or UNOS T2** **For the Downstaging-Group:** **Group 1 = 1 lesion > 5 and ≤ 8 cm** **Group 2 = 2 or 3 lesions at least one > 3 and ≤ 5 cm with the sum of the maximal tumor diameters ≤ 8 cm** **Group 3 = 4 or 5 lesions each ≤ 3 cm with the sum of the maximal tumor diameters ≤ 8 cm** **Group 4 = 2 or 3 lesions at least one > 5cm with the sum of the maximal tumor diameters ≤ 8 cm** **Group 5 = total tumor diameter > 8 cm** **Absence of vascular invasion based on cross-sectional MRI or CT** **Absence of lymph node involvement by tumor or extra-hepatic tumor spread.** **Criteria for successful downstaging:** **Residual tumor(s) within MC for deceased donor liver transplant** **In patients with 4 or 5 tumors, successful downstaging requires complete necrosis (based on cross-sectional MRI or CT) of at least 1 to 2 tumor(s), respectively, so that there will be no more**	**Interventions: DEB-TACE procedures were performed under local anesthesia with lidocaine 2%, sedation and analgesia, with venous administration of midazolam and fentanyl.** **Comparison:**

		than 3 lesions with viable tumor each ≤ 3 cm to meet MC Exclusion criteria: Progression of tumor(s) to beyond inclusion criteria for downstaging and bridging based on tumor size and number Vascular invasion based on cross-sectional MRI or CT Lymph node involvement by tumor or extra-hepatic spread of tumor	
Notes:	**Evidence Level 3: Prospective cohort study -Blinding was not described in this study Author's conclusion: Tumors initially exceeding the MC down-staged after DEB-TACE, can achieve post-transplant survival and HCC recurrence-free probability, at five years, just like patients within MC in patients undergoing DEB-TACE**		
Outcome Measures/results	**Primary Five-year post-transplant overall survival, Recurrence-free Survival, Radiological response Secondary**	**Results: After TACE, only patients within MC were transplanted. More patients underwent LT in bridging group 65.9% (P = 0.001). Downstaging population presented: higher number of nodules 2.81 (P = 0.001); larger total tumor diameter 8.09 (P = 0.001); multifocal HCC 78% (P = 0.001); more post-transplantation recurrence 25% (P = 0.02). Patients with maximal tumor diameter up to 7.05 cm were more likely to receive LT (P = 0.005). Median time on the waiting list was significantly longer in downstaging group 10.6 mo (P = 0.028). <u>Five-year posttransplant overall survival:</u> Five-year posttransplant overall survival was 73.5% in downstaging and 72.3% bridging groups (P = 0.31) <u>Recurrence-free survival:</u> Recurrence-free survival was 62.1% in downstaging and 74.8% bridging groups (P = 0.93). <u>Radiological response:</u> complete response was observed more frequently in bridging group (P = 0.004).**	

Agopian, V. G. et al. Complete pathologic response to pretransplant locoregional therapy for hepatocellular carcinoma defines cancer cure after liver transplantation: analysis of 501 consecutively treated patients. Ann Surg. 262. 536-45; discussion 543-5. 2015

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 4 Study type: Retrospective Cohort Study	Funding sources: Conflict of Interests: The authors declare no conflicts of interest. Randomization: Blinding: Dropout rates:	Total no. patients: 501 Recruiting Phase: 1994 - 2013 Inclusion criteria: Not described Exclusion criteria: Not described	Interventions: HCC recipients with complete pathologic response (cPR) (n = 126) Comparison: HCC recipients without cPR (n = 375)
Notes:	Level of Evidence 4: Retrospective Cohort Study -Single center experience Author's conclusion: Achieving cPR in patients with HCC receiving LRT strongly predicts tumor-free survival. Factors predicting cPR are identified, allowing for differential prioritization of HCC recipients based on their variable risks of post-LT recurrence. Improving LRT strategies to maximize cPR would enhance posttransplant cancer outcomes.		
Outcome Measures/results	Primary Post-transplant survival, HCC recurrence Secondary	Results: Of 501 patients, 272, 148, and 81 received 1, 2, and 3 or more LRT treatments. The overall, recurrence-free, and disease-specific survival at 1-, 3-, and 5 years was 86%, 71%, 63%; 84%, 67%, 60%; and 97%, 90%, 87%. Compared with recipients without cPR, cPR patients had significantly lower laboratory model for end-stage liver disease scores, pretransplant alpha fetoprotein, and cumulative tumor diameters; were more likely to have 1 lesion, tumors within Milan/University of California, San Francisco (UCSF) criteria, LRT that included ablation, and a favorable tumor response to LRT; and had superior 1-, 3-, and 5-year recurrence-free survival (92%, 79%, and 73% vs 81%, 63%, and 56%; P = 0.006) and disease-specific survival (100%, 100%, and 99% vs 96%, 89%, and 86%; P<0.001) with only 1 cancer-specific death and fewer recurrences (2.4% vs 15.2%; P < 0.001). Multivariate predictors of cPR included a favorable post-LRT radiologic/alpha fetoprotein tumor response, longer time interval from LRT to LT, and lower model for end-stage liver disease score and maximum tumor diameter (C-statistic 0.75).	

Chapman, W. C. et al. Liver Transplantation for Advanced Hepatocellular Carcinoma after Downstaging Without Up-Front Stage Restrictions. J Am Coll Surg. 224. 610-621. 2017

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 4 Study type: Retrospective Cohort Study	Funding sources: Not described Conflict of Interests: None	Total no. patients: 284 Recruiting Phase: January 1, 2002 - December 31, 2014	Interventions: Patients with HCC beyond Milan criteria who underwent LT after successful

	Randomization: Blinding: Not described Dropout rates:	Inclusion criteria: age older than 18 years at HCC diagnosis; a single nodule >5 cm, 2 to 3 nodules at least 1 >3 cm, corresponding to stage III of the ALTSG Classification, or 4 nodules of any size (stage IVA1 of the ALTSG classification), or HCC with any tumor stage plus intrahepatic portal or hepatic vein involvement(stage IVA2 of the ALTSG classification) Exclusion criteria: Patients with regional lymph nodes or metastatic disease (including extrahepatic main portal or hepatic vein involvement), stage IVB of ALTSG classification, were excluded from this study.	downstaging to within Milan criteria Comparison: Patients initially within Milan criteria. who received transplants in the same time period
Notes:	Level of Evidence 4: Retrospective Cohort Study Author's conclusion: Patients with beyonde Milan criteria HCC who are otherwise candidates for LT should undergo aggressive attempts at downstaging without a priori exclusion. This highly selective approach allows for excellent long-term results, similar to patients presenting with earlier stage disease.		
Outcome Measures/results	Primary Overall Survival, Recurrence of HCC Secondary Disease-specific survival, Death and hepatocellular carcinoma-related deaths, disease-free survival	Results: Sixty-three of 210 (30%) eligible patients were downstaged and underwent transplantation; 14 additional downstaged and listed patients were withdrawn for the following reasons: death while waiting (n = 4), disease progression (n = 8), development of other malignancy (n = 1), and declined LT (n ¼ 1). Twelve patients underwent resection after downstaging and did not require LT. <u>Overall Surival</u> Survival for patients who were downstaged was similar to those who were within Milan criteria initially (94.4%, 94.4%, 85.8%, and 62.6%; and 93.2%, 83.0%, 74.1%, and 61.9%, respectively)(p = 0.29) <u>Recurrence of HCC</u> Recurrence of HCC at 5 years was similar between groups (10.9% vs 10.8%; p = 0.84).	

Kardashian, A. et al. Liver Transplantation Outcomes in a U.S. Multicenter Cohort of 789 Patients with Hepatocellular Carcinoma Presenting Beyond Milan Criteria. Hepatology. . . 2020

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 4 Study type: Retrospective Cohort Study	Funding sources: None Conflict of Interests: None	Total no. patients: 4359 Recruiting Phase: 2002-2013 Inclusion criteria: Adults aged 18 years or older with	Interventions: Examine post-LT outcomes, including HCC recurrence and survival, and the impact of pre-transplant LRT on the rate of

	Randomization: **Blinding:** **Dropout rates:**	**HCC who underwent LT from 2002 to 2013 regardless of tumor size, requirement for MELD exception points, follow-up time, or non-HCC-related death** **Exclusion criteria: Patients who had cholangiocarcinoma, mixed hepatocellular cholangiocarcinoma, fibrolameller HCC, or hepatoblastoma**	**successful downstaging in LT patients presenting with beyond-MC tumors** **Comparison: LT recipients transplanted within these study period whose tumors were radiographically within MC**
Notes:	**Level of Evidence 4: Retrospective Cohort Study** **-Blinding was not described** **Author's conclusion: In LT recipients with HCC presenting beyond MC, successful downstaging is predicted by wait time, alpha-fetoprotein response to LRT, and tumor burden, and results in excellent post-LT outcomes, justifying expansion of LT criteria. In LRT-NoDS patients, higher HCC-R compared to NoLRT-NoDS cannot be explained by clinicopathologic differences, suggesting a potentially aggravating role of LRT in patients with poor tumor biology that warrants further investigation.**	
Outcome Measures/results	**Primary Overall survival (OS), recurrence-free survival (RFS), HCC recurrence (HCC-R)** **Secondary**	**Results: <u>OS, RFS, HCR</u>** **Five-year post-LT OS and RFS was higher in Milan Criteria (MC) (71.3% and 68.2%) compared to downstaged (DS) (64.3% and 59.5%), and lowest in NoDS (n=324; 60.2% and 53.8%; overall P<0.001). DS patients had superior RFS (60% vs 54%,P=0.043) and lower 5-year HCC-R (18% vs 32%,P<0.001) compared to NoDS, with further stratification by maximum radiologic tumor diameter (5-year HCC-R of 15.5% in DS/< 5cm and 39.1% in NoDS/>5cm,P<0.001). Multivariate predictors of downstaging included alpha-fetoprotein response to LRT, pathologic tumor number and size, and wait time >12 months. LRT-NoDS had greater HCC-R compared to NoLRT-NoDS (34.1% vs 26.1%,P<0.001), even after controlling for clinicopathologic variables (HR=2.33,P<0.001) and inverse probability of treatment weighted propensity matching (HR=1.82,P<0.001).**	

Mehta, N. et al. National Experience on Down-Staging of Hepatocellular Carcinoma Before Liver Transplant: Influence of Tumor Burden, Alpha-Fetoprotein, and Wait Time. Hepatology. 71. 943-954. 2020

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 4 **Study type: Retrospective Cohort Study**	**Funding sources: Supported by the Clinical and Translational Core of the UCSF Liver Center** **Conflict of Interests: Nothing**	**Total no. patients: 3819** **Recruiting Phase: April 2012 - September 2015** **Inclusion criteria: Patients in the UNOS database (Standard Transplant Analysis and Research files**	**Interventions: Patients with HCC always within Milan criteria** **Comparison: Two different down-staging groups classified by initial tumor burden**

	to report Randomization: Blinding: Not described Dropout rates:	released in December 2016) aged 18 years and older who received MELD exception for HCC and underwent LT between April 2012 and September 2015. Exclusion criteria: Patients without evidence of HCC on explant who had not received LRT prior to LT (HCC misdiagnosis) as well as patients with either intrahepatic cholangiocarcinoma or mixed HCC/ cholangiocarcinoma on explant were excluded.	meeting UNOS-DS criteria and "all-comers" down-staging (AC-DS) group with initial tumor burden beyond UNOS-DS criteria.
Notes:	Level of Evidence 4: Retrospective Cohort Study Author's conclusion: Our results validated UNOS-DS criteria based on comparable 3-year survival between UNOS-DS and Milan groups. Additional refinements based on AFP and wait time may further improve post-LT outcomes in downstaging groups, especially given that reported 3-year recurrence was higher than in those always within Milan criteria.		
Outcome Measures/results	Primary Post-LT survival Secondary Post-LT HCC recurrence	Results: <u>Post-LT survival</u> Kaplan-Meier 3-year post-LT survival was 83.2% for Milan, 79.1% for UNOS-DS (P = 0.17 vs. Milan), and 71.4% for AC-DS (P = 0.04 vs. Milan). Within down-staging groups, risk of post-LT death in multivariable analysis was increased in SWR or MWR (hazard ratio [HR], 3.1; P = 0.005) and with alpha-fetoprotein (AFP) ≥ 100 ng/mL at LT (HR, 2.4; P = 0.009). <u>Post-LT HCC recurrence</u> The 3-year HCC recurrence probability was 6.9% for Milan, 12.8% for UNOS-DS, and 16.7% for AC-DS (P < 0.001). In down-staging groups, AFP ≥ 100 (HR, 2.6; P = 0.02) was the only independent predictor of HCC recurrence.	

Ravaioli, M. et al. Long term results of down-staging and liver transplantation for patients with hepatocellular carcinoma beyond the conventional criteria. Sci Rep. 9. 3781. 2019

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 4 Study type: Retrospective observational study	Funding sources: Conflict of Interests: The authors declare no competing interests. Randomization: Blinding: Not described Dropout rates:	Total no. patients: 308 Recruiting Phase: 2003 - 2013 Inclusion criteria: Patients with HCC listed for LT Exclusion criteria: AFP higher than 400 ng/dL and the absence of macro-vascular or biliary invasion.	Interventions: Comparison:

Notes:	**Level of Evidence 4: Retrospective observational study** **Author's conclusion: In conclusion, our study measured the price to be paid by transplant patients outside conventional HCC criteria (and within the Bologna criteria) after effective or ineffective down-staging procedures. The long-term outcome of down-staging candidates was poorer than that achievable with the conventional criteria, particularly for cases not meeting the protocol. Nevertheless, it can be considered acceptable since it is much better than that obtained with non-LT treatments.**	
Outcome Measures/results	**Primary** **Recurrence rate, post-LT survival, average treatment effect (ATE)** **Secondary**	**Results: <u>Recurrence rate</u>** **After LT, the tumor recurrence rate was significantly different: MC 7.6%, Down-Achieved 20.9%, Down-not Achieved 31.6%, and No-Down 30.4% ($p < 0.001$).** **<u>Post-LT survival</u>** **The survival rates at 5 years were: 63% in Down-Achieved, 62% in Down-not Achieved, 63% in No-Down, and 77% in MC (p = n.s.). The only variable related to a better outcome was the effective down-staging to T2 at the histological evaluation of the explanted liver: recurrence rate = 7.8% vs. 26% ($p < 0.001$) and 5-year patient survival = 76% vs. 67% ($p < 0.05$).** **The ATE estimation showed that the mean survival of T3-LT candidates was significantly better than that of T3 patients ineligible for LT [83.3 vs 39.2 months (+44.6 months); $p < 0.001$].**

Sapisochin, G. et al. The extended Toronto criteria for liver transplantation in patients with hepatocellular carcinoma: A prospective validation study. Hepatology. 64. 2077-2088. 2016

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 3 **Study type: Prospective cohort study**	**Funding sources:** **Conflict of Interests: Nothing to report** **Randomization:** **Blinding:** **Dropout rates: "Herein, we validate our original data with a new prospective cohort and report the long-term follow-up (10-years) using an intention-to-treat analysis."**	**Total no. patients: 362 patients in cohort 1 (January 1996 - August 2008), 243 patients in cohort 2 (September 2008 - December 2012)** **Recruiting Phase: January 1996 - December 2012** **Inclusion criteria: 1. Tumor confined to the liver—i.e., no pulmonary or nodal metastases** **2. No radiologic evidence of venous or biliary tumor thrombus** **3. No cancer-related symptoms. These symptoms were defined as a weight loss over 10 kg and/or an increase in the Eastern Cooperative Oncology Group score of 1 point over a period of 3 months. Also, patients had to have a performance status of 0.(1)** **4. A mandatory percutaneous tumor biopsy of the largest lesion (per protocol) that determined the lesion to be not poorly differentiated as determined by one of the two expert liver pathologists at our institution**	**Interventions:** **Patients with exceeded tumors beyond Milan criteria (M+)** **Comparison:** **Patients with tumors within Milan criteria**

		(no interobserver pathological evaluation was performed). Biopsy was only required for those patients who exceeded the Milan criteria but were within the ETC and was done percutaneously in all cases. Those patients with tumors that exceeded the Milan criteria who had massive ascites and/or coagulopathy that precluded a biopsy of the tumor were not included on the waiting list. Even though a biopsy was not required to undergo LT in the M group, some tumors were biopsied due to uncertainty in the diagnosis and others were referred for transplant with a biopsy already performed elsewhere Exclusion criteria:	
Notes:	Level of Evidence 3: Prospective Cohort Study Author's conclusion: Tumor differentiation and cancer-related symptoms of HCC can be used to select patients with advanced HCC who are appropriate candidates for liver transplantation; alpha-fetoprotein level limitations should be incorporated in the listing criteria for patients within or beyond the Milan criteria.		
Outcome Measures/results	Primary Actuarial survival from transplant Secondary	Results: <u>Actuarial survival</u> For the validation cohort 2, the actuarial survival from transplant for the M+ group was similar to that of the M group at 1 year, 3 years, and 5 years: 94%, 76%, and 69% versus 95%, 82%, and 78% (P = 0.3). For the combined cohorts 1 and 2, there were no significant differences in the 10-year actuarial survival from transplant between groups. On an intention-to-treat basis, the dropout rate was higher in the M+ group and the 5-year and 10-year survival rates from listing were decreased in the M+ group. An alpha-fetoprotein level >500 ng/mL predicted poorer outcomes for both the M and M+ groups.		

Sinha, J. et al. Are There Upper Limits in Tumor Burden for Down-Staging of Hepatocellular Carcinoma to Liver Transplant? Analysis of the All-Comers Protocol. Hepatology. 70. 1185-1196. 2019

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 3 Study type: Prospective cohort study	Funding sources: Biostatistics Core of the UCSF Liver Center (National Institute of Diabetes and Digestive and Kidney Diseases P30 DK026473) Conflict of Interests: Drs Mehta and Yao received institutional	Total no. patients: 133 patients enrolled in the UCSF-Group, 74 patients enrolled in the AC-group Recruiting Phase: January 2005 - January 2015 Inclusion criteria: <u>UCSF-DS Group</u> HCC exceeding UNOS T2 criteria but meeting one of the following:	Interventions: Outcomes for DS in patients with initial tumor burden beyond the UCSF-DS criteria, defined as “all-comers” (AC) Comparison: Outcomes for patients meeting UCSF-DS criteria

	research grant from FUJIFilm Wako. Randomization: Blinding: Dropout rates: "We compared the intention-to-treat (ITT) outcomes of DS in 74 patients in the AC group and 133 patients in the UCSF-DS group."	1. Single lesion ≤ 8 cm 2. 2 or 3 lesions each ≤ 5 cm with the sum of the largest tumor diameters ≤ 8 cm 3. 4 or 5 lesions each ≤ 3 cm with the sum of the largest tumor diameters ≤ 8 cm Absence of vascular invasion based on cross-sectional imaging <u>AC-Group</u> HCC exceeding UCSF-DS protocol by any of the following: 1. HCC tumor number 2. HCC tumor size 3. Total HCC tumor diameter Absence of vascular invasion based on cross-sectional imaging Exclusion criteria: <u>UCDS-Group</u> 1. Progression of tumor(s) beyond inclusion criteria for DS based on tumor size and number 2. Any evidence of extrahepatic, lymphatic, or vascular tumor spread <u>AC-Group</u> 1. Progression of tumor burden beyond Milan criteria after initial successful DS 2. Development of a new HCC lesion(s) 3. Any evidence of extrahepatic, lymphatic, or vascular tumor spread	
Notes:	Level of Evidence 3: Mixed prospective and retrospective cohort study Patients in the AC protocol for DS were prospectively enrolled, clinical data were collected retrospective. Author's conclusion: We observed a significantly lower LT probability and inferior ITT survival with DS in the AC group versus the UCSF-DS group. Our results suggest that an upper limit in tumor burden exists beyond which successful LT after DS becomes an unrealistic goal.		
Outcome Measures/results	Primary Downstaging results, Posttransplant survival, HCC	Results: <u>Downstaging</u> Successful DS to Milan was observed in 64.8% of the AC group versus 84.2% of the UCSF-DS group (P < 0.001). The sum of tumor number and largest tumor diameter was significantly associated with successful DS (hazard	

	recurrence Secondary	ratio [HR] 0.87, P < 0.05). The cumulative probability of dropout within 1 year and 3 years was 53.5% and 80.0%, respectively, for AC versus 25.0% and 36.1%, respectively, for UCSF-DS (P < 0.0001). Factors predicting dropout included sum of tumor number and largest tumor diameter greater than 8 (HR 1.79, P = 0.049) and Child class B and C (HR 2.54, P = 0.001). The AC group also had a significantly lower liver transplant (LT) rate (13.5% versus 59.0%, P < 0.001). <u>Posttransplant survival</u> ITT survival at 1 year and 5 years was 77.4% and 21.1%, respectively, in AC versus 85.5% and 56.0%, respectively, in UCSF-DS (P < 0.001). <u>HCC recurrence</u> The AC group also had a significantly lower 5-year recurrence- free probability compared with the UCSF-DS group (40.0% versus 86.1%, P < 0.01). Three of 10 patients in the AC group who underwent LT developed HCC recurrence

Toso, C. et al. Downstaging prior to liver transplantation for hepatocellular carcinoma: advisable but at the price of an increased risk of cancer recurrence - a retrospective study. Transpl Int. 32. 163-172. 2019

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 4 Study type: Retrospective cohort study	Funding sources: The authors have declared no funding. Conflict of Interests: The authors have declared no conflicts of interest. Randomization: Blinding: Dropout rates:	Total no. patients: 455 patients were listed, 286 were transplanted Recruiting Phase: February 2004 - October 2017 Inclusion criteria: Patients with total Tumour Volume (TTV) continuously ≤115 cm3 and alpha fetoprotein (AFP) continuously ≤400 ng/ml, and those with originally more advanced HCC (with no size, number, nor AFP limit) successfully downstaged and stable within TTV115/AFP400 for more than 3 months. Of note, patients entered into the database when they fulfilled TTV115/AFP400 according to mRECIST criteria (modified Response Evaluation Criteria in Solid Tumours) with no macro-vascular invasion or extra-hepatic metastasis. Exclusion criteria: Patients not reaching TTV115/AFP400 after downstaging, patients with macro-vascular invasion or extra-hepatic metastasis	Interventions: Comparison:
Notes:	Level of Evidence 4: Retrospective Cohort Study Author's conclusion: Overall, despite an expected increase in post-transplant HCC recurrence, similar survivals can be achieved with and without downstaging, using the TTV115/AFP400		

	transplantation criteria, and including patients with advanced original HCCs. Downstaging should continue to be performed.	
Outcome Measures/results	Primary Disease free survival (DFS), HCC recurrence Secondary	Results: Patients downstaged to TTV115/AFP400 (n = 29) demonstrated similar disease-free survivals (DFS, 74% vs. 80% at 5 years, P = 0.949), but a trend to more recurrences (14% vs. 5.8%, P = 0.10) than those always within TTV115/AFP400 (n = 257). Similarly, patients downstaged to Milan criteria (n = 80) demonstrated similar DFS (76% vs. 86% at 5 years, P = 0.258), but more recurrences (11% vs. 1.7%, P = 0.001) than those always within Milan (n = 177). Among patients downstaged to Milan, those originally beyond TTV115/AFP400 (n = 27) had similar outcomes as those originally beyond Milan, but within TTV115/AFP400 (n = 53). However, the likelihood of being within Milan at transplant was lower for patients with more advanced original HCCs (P < 0.0001).

Victor, D. W., 3rd et al. Outcomes of Liver Transplantation for Hepatocellular Carcinoma Beyond the University of California San Francisco Criteria: A Single-center Experience. Transplantation. 104. 113-121. 2020

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 4 Study type: Retrospective Cohort Study	Funding sources: The authors declare no funding. Conflict of Interests: The authors declare no conflict of interests. Randomization: Blinding: Dropout rates:	Total no. patients: 220 Recruiting Phase: April 2008 - June 2017 Inclusion criteria: Age >18, pretransplant diagnosis of HCC, no evidence of extrahepatic disease, and histologically proven HCC in the explant liver. Exclusion criteria: Patients with radiographic evidence of tumor thrombus, extrahepatic disease, mixed tumors or multiple organ involvement on explant pathology were excluded.	Interventions: Comparison:
Notes:	Level of Evidence 4: Retrospective Cohort Study -Single center study, relatively small number of patients involved Author's conclusion: Selective patients outside of traditional size criteria can be effectively transplanted with equivalent survival to patients with smaller tumors, even when pathologic tumor burden is considered. Tumor stability over time can be used to help select patients for transplantation.		
Outcome Measures/results	Primary Patient survival at 1, 3, and 5 years after OLT. Secondary HCC recurrence	Results: Patient survival at 1, 3, and 5 years after OLT. Two hundred twenty HCC patients were transplanted, 138 inside Milan, 23 inside UCSF, and 59 beyond UCSF criteria. Patient survival was equivalent at 1, 3, or 5 years despite pathologic tumor size. The 1-year survival for the Milan cohort was 92%, UCSF 100%, and beyond UCSF 97%. Three-year survival was also not significantly different with the groups showing 87%, 88%, and 87%, respectively. Even 5-year survival was closely mirrored in all groups with 81%, 88%, and 80% survivals (Figure 1). DFS was noted to be similar among groups with 1-year survival for Milan 100%, inside	

		UCSF 95.5%, and outside UCSF at 91.1%. DFS at 5 years revealed 92% survival for Milan, 88.6% inside UCSF, and 85.4% outside UCSF (P = 0.53; Figure 2). **<u>HCC recurrence</u>** **In patients outside UCSF, tumor recurrence was equivalent to Milan and UCSF criteria recipients who waited >9 months from LRT. Although tumor recurrence was more likely in outside of UCSF patients (3% versus 9% versus 15%; P = 0.02), recurrence-free survival only trended toward significance among the groups (P = 0.053).**

Yao, F. Y. et al. Downstaging of hepatocellular cancer before liver transplant: long-term outcome compared to tumors within Milan criteria. Hepatology. 61. 1968-77. 2015

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 3 **Study type: Prospective Cohort Study**	**Funding sources: This work is supported in part by a grant from the National Institute of Health to the University of California, San Francisco Liver Center (P01DK26743)** **Conflict of Interests: Not stated** **Randomization:** **Blinding:** **Dropout rates: Intention-to-treat analysis was performed**	**Total no. patients: 122 patients in the down staging group, 488 patients in the retrospective control group** **Recruiting Phase: March 2002 - January 2012** **Inclusion criteria: HCC exceeding UNOS T2 criteria but meeting one of the following criteria:** **1. Single lesion ≤ 8 cm** **2. 2 or 3 lesions each ≤ 5cm with the sum of the maximal tumor diameters ≤ 8 cm.** **3. 4 or 5 lesions each ≤ 3cm with the sum of the maximal tumor diameters ≤ 8 cm.** **Absence of vascular invasion based on cross-sectional imaging** **Exclusion criteria: 1 Progression of tumor(s) to beyond inclusion criteria for down-staging based on tumor size and number.** **2 Invasion of a major hepatic vessel based on cross-sectional imaging or Doppler ultrasonography of the abdomen.** **3 Lymph node involvement by tumor or extra-hepatic spread of tumor.**	**Interventions: Patients with HCC undergoing down-staging to within Milan/UNOS T2 criteria before liver transplantation** **Comparison: Patients with HCC meeting T2 criteria without requiring down-staging**
Notes:	**Level of evidence 3: Prospective Cohort Study** **-A retrospective component of this study was the collection of data in a control group of patients with HCC meeting T2 criteria without requiring down-staging.** **-Single center study** **Author's conclusion: Successful down-staging of HCC to within T2 criteria was associated with a low rate of HCC recurrence and excellent post-transplant survival, comparable to those meeting T2 criteria without down-staging. Due to**		

	the small number of patients with 4–5 tumors, further investigations are needed to confirm the efficacy of down-staging in this subgroup.	
Outcome Measures/results	**Primary Post-transplant survival, HCC recurrence** **Secondary**	**Results: In the down-staging group, 64 patients (54.2%) had received LT, and 5 (7.5%) developed HCC recurrence. Two of the 5 patients with HCC recurrence had 4–5 tumors at presentation. The 1- and 2-year cumulative probabilities for dropout (competing risk) were 24.1% and 34.2% in the down-staging group, versus 20.3% and 25.6% in the T2 group (p=0.04). The Kaplan-Meier 5-year post-transplant survival and recurrence-free probabilities were 77.8% and 90.8%, respectively, in the down-staging group, versus 81% and 88%, respectively, in the T2 group (p=0.69 and p=0.66, respectively). The 5-year intention-to-treat survival was 56.1% in the down-staging group, versus 63.3% in the T2 group (p=0.29).**

Schlüsselfrage:

Ergänzende Literaturrecherche Senkt Kaffeekonsum das Risiko der HCC-Entstehung?

Inhalt: 2 Literaturstellen

Literaturstelle	Evidenzlevel	Studientyp
Aleksandrova, K. 2015	4	Prospective nested case-control study using data from the EPIC cohort.
Bravi, F. 2017	1	Systematic review and meta-analysis. (11 studies for HCC, 6 for CLD)

OXFORD (2011) Appraisal Sheet: Systematic Reviews: 1 Bewertung(en)

Bravi, F. et al. Coffee and the risk of hepatocellular carcinoma and chronic liver disease: a systematic review and meta-analysis of prospective studies. Eur J Cancer Prev. 26. 368-377. 2017

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: Systematic review and meta-analysis. (11 studies for HCC, 6 for CLD) Databases: Medline/Pubmed and Embase Search period: Inception? - June 2015 Inclusion Criteria: (a) were based on original prospective cohort studies onhumans; (b) were focused on primary HCC (or liver cancer, when separate estimates for HCC were not available), or CLD; (c) provided information on the association between coffee consumption and one of the outcomes of interest, including	Population: In the present meta-analyses, we combined results from 12 studies on HCC and 6 studies on CLD, including 3414 cases of liver cancer (2154 of which were specified as HCC) and 1463 cases of CLD, respectively. Intervention: Exposure to coffee. Comparison: Non-exposure to coffee.	Primary: HCC or CLD risk. Secondary: - Results: Primary: Meta-analysis of coffee consumption and risk of HCC: The summary RRs for HCC were 0.66 [95% confidence interval (CI): 0.55–0.78] for regular, 0.78 (95% CI: 0.66–0.91) for low, and 0.50 (95% CI: 0.43–0.58) for high coffee consumption, respectively. The summary RR for an increment of one cup per day was 0.85 (95% CI: 0.81–0.90). Secondary: Meta-analysis of coffee consumption and risk of CLD. The summary RRs forCLD were 0.62 (95% CI: 0.47–0.82) for regular, 0.72 (95% CI: 0.59–0.88) for low, 0.35 (95% CI: 0.22–0.56) for high, and 0.74 (95% CI: 0.65–0.83) for an increment of one cup per day. Author's Conclusion: "The present meta-analysis provides	Bamia et al. 2015, Int J Cancer 136:1899–1908. Hu et al. 2015, Hepatology 48:129–136. Inoue et al. 2005, J Natl Cancer Inst 97:293–300. Inoue et al. 2009, Cancer Epidemiol Biomarkers Prev 18:1746–1753. Johnson et al. 2011, Cancer Causes Control 22:503–510. Kurozawa et al. 2005, Br J Cancer 93:607–610. Lai et al. 2013, Br J Cancer 109:1344–1351. Ohishi et al. 2008, Cancer Epidemiol Biomarkers Prev 17:846–854. Petrick et al. 2015,

estimates of the RR, with the corresponding CIs, or sufficient information to calculate them; and (d) were published as full-length papers in English. Case–control studies nested in a prospective cohort were also included this type of study. Exclusion Criteria: not meeting inclusion criteria.		a precise quantification of the inverse relation between coffee consumption and the risk of HCC, and adds evidence to the presence of an even stronger negative association with CLD. Thus, the apparent consistency of these results among prospective studies and with results from case–control studies (Bravi et al., 2013), as well as across different populations, the presence of dose–response relations, the strength of the RR, especially among heavy coffee drinkers, and the biological plausibility support the hypothesis that the inverse relation between coffee drinking and HCC is causal. The evidence for CLD goes in the same direction, but it is based on a smaller number of studies and cases, requiring more data before a conclusion in terms of causality can be drawn."	Cancer Epidemiol Biomarkers Prev 24:1398–1406. Setiawan et al. 2015, Gastroenterology 148:118–125. Shimazu et al .2005, Int J Cancer 116:150–154. CLD articles not listed here

Methodical Notes

Funding Sources: not described.

COI: P.B. has acted as an expert in coffee-related ligation. All other authors have no conflicts of interests to disclose.

Study Quality: The Newcastle–Ottawa Scale was used to assess the quality of individual studies. "The quality score ranged between 5 and 8 for studies on HCC and between 4 and 8 for studies on CLD (with a median score of 7 for both outcomes). We decided not to exclude any of the studies from the analyses for a low quality score."

Heterogeneity: Meta-analysis using random effect models (DerSimonian and Laird, 1986). Heterogeneity investigated using the χ2-test (Greenland and Longnecker, 1992) and quantified using the I2-statistic, which represents the percentage of the total variation across studies that is attributable to heterogeneity rather than chance (Higgins and Thompson, 2002). Heterogeneity was defined as a P-value less than 0.10.

Publication Bias: "We evaluated the presence of publication bias through visualization of the funnel plot."
No asymmetry was evident in the funnel plot and Egger's test was not statistically significant, thus reassuring against a major role of publication bias.

Notes:
Oxford level of evidence: 1 Systematic review and meta-analysis.
Notes: High heterogeneity between studies, I2 estimates not displayed in the forest plots. The authors claim that among other factors the data for adjusting for HepB,C are not availabe in many studies.

NEWCASTLE - OTTAWA Checklist: Case Control: 1 Bewertung(en)

Aleksandrova, K. et al. The association of coffee intake with liver cancer risk is mediated by

<table>
<tr><td colspan="4">biomarkers of inflammation and hepatocellular injury: data from the European Prospective Investigation into Cancer and Nutrition. Am J Clin Nutr. 102. 1498-508. 2015</td></tr>
<tr><td>Evidence level</td><td>Methodical Notes</td><td>Patient characteristics</td><td>Interventions</td></tr>
<tr><td>Evidence level: 4

Study type: Prospective nested case-control study using data from the EPIC cohort.</td><td>Funding sources: Serveral governmental grants including a grant from the German Research Foundation (DFG NO446/7-1),

Conflict of Interests: None of the authors reported any conflicts of interest related to the study.

Randomization: -

Blinding: Lab workers were blinded regarding status.

Dropout rates: -</td><td>Total no. patients: 125 incident HCC cases matched to 250 controls

Patient characteristics: EPIC was designed to identify nutritional, lifestyle, metabolic, and genetic risk factors for cancer. In brief, in the period 1992– 2000, ca. 520,000 apparently healthy men and women aged 35– 75 y from 10 European countries (Denmark, France, Germany, Greece, Italy, Netherlands, Norway, Spain, Sweden, and the United Kingdom) enrolled in the study.

Inclusion criteria: Lacking description for EPIC cohort in the article.
Lacking description for inclusion in the current study: Assuming the deevelopment of HCC over specified period.

Exclusion criteria: Exclusion of cases with other types of cancer before the index case (n = 18), metastatic cases (n = 23) or cases with ineligible histological subtypes (n = 31),</td><td>Interventions: Exposure to Coffee. Coffe intake was evaluated using questionnaires.

Comparison: Non-exposure to Coffee.</td></tr>
<tr><td>Notes:</td><td colspan="3">Oxford level of evidence: 4 Case control study.
NOS Scale: 6/9:
Comments:
Unclear or missing description of inclusion criteria or validation for HCC cases. Unsure if cases are representative or not. Significant differences between groups (smoking, anthropometric, hepatitis status). These were adjusted in the multivariable model. Coffee consumption was ascertained with questionnaires, not blinded interviews.

Author's conclusion: "In conclusion, the association of coffee intake with HCC risk in this large European cohort study was statistically accounted for by biomarkers of inflammation and hepatocellular injury. Because of difficulties in conducting long-term randomized trials to test these relations, our findings may provide important insights into the current knowledge on the prevention of HCC—one of the
most lethal tumors in the world."</td></tr>
<tr><td>Outcome Measures/results</td><td>Primary Hepatocellular carcinoma.

Secondary Investigation of mediatiors on the association between coffee consumption</td><td colspan="2">Results: Population Characteristics:
125 HCC cases were identified that occurred over a median of 5 y following recruitment (range:+ 2.4–6.8 y). With the use of risk set sampling, 2 controls per case were selected at random from all cohort members who had
donated blood and were alive and cancer-free at the time of liver cancer diagnosis of the index case and were matched to the case on study center, sex, age</td></tr>
</table>

	and HCC risk (metabolic, inflammatory, liver injury, and iron metabolism).	**(±12 mo), date of blood collection, fasting status, and time of day at blood collection. Women were additionally matched according to menopausal status [premenopausal, perimenopausal (or unknown), or postmenopausal] and exogenous hormone use (yes, no, or missing) at blood donation. 32% female patients, age 60.1±6.6 years in both groups. Significant group differences in the group distribution regarding smoking, antropomorphic factors and many biomarkers, but were adjusted in the association. Results: <u>Primary:</u> The multivariable-adjusted RR of having ≥4 cups (600mL)coffee/d compared with <2 cups (300 mL)/d was 0.25 (95% CI: 0.11,0.62; P-trend = 0.006). <u>Secondary:</u> In the multivariable linear regresision coffee intake was positively associated with C-peptide and inversely with IL-6, GLDH, ALT, AST, GGT, alkaline phosphatase, total bilirubin, and AFP. Medation analysis: A statistically significant attenuation of the association between coffee intake and HCC risk and thereby suspected mediation was confirmed for the inflammatory biomarker IL-6 and for the biomarkers of hepatocellular injury glutamate dehydrogenase, alanine aminotransferase, aspartate aminotransferase (AST), g-glutamyltransferase (GGT), and total bilirubin, which—in combination—attenuated the regression coefficients by 72% (95%CI: 7%, 239%). Of the investigated biomarkers, IL-6, AST, and GGT produced the highest change in the regression coefficients: 40%, 56%, and 60%, respectively.**

Schlüsselfrage:

Nachgereichte Literatur 26.05.20

Inhalt: 8 Literaturstellen

Literaturstelle	Evidenzlevel	Studientyp
Abdel-Rahman, O. M. 2016	2	Systematic Review
Endo, K. 2018	3	Retrospective Cohort Study
Finn, R. S. 2020	2	global, multicenter, open-label, phase 3 randomized trial
Ioannou, G. N. 2019	3	Prognostic Cohort Study
Liu, H. 2016	2	Randomized controlled trial
Papatheodoridis, G. 2016	2	9 center cohort study. Prognostic study to develop and validate a risk prediction score (PAGE-B) for the development of HCC in Caucasian CHB patients on 5-year antiviral therapy.
Peng, Z. W. 2013	2	Retrospective randomized controlled trial
Tzartzeva, K. 2018	1	Systematic review and meta-analysis.

OXFORD (2011) Appraisal Sheet: Systematic Reviews: 2 Bewertung(en)

Abdel-Rahman, O. M. et al. Yttrium-90 microsphere radioembolisation for unresectable hepatocellular carcinoma. Cochrane Database Syst Rev. 2. Cd011313. 2016

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 2 Study type: Systematic Review Databases: Cochrane Hepato-Biliary Controlled Trials Register, Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, Science Citation Index Expanded Search period: Up to	Population: All trial participants with histologically or radiologically diagnosed unresectable hepatocellular carcinoma who were older than 18 years. Intervention: Y-90 microsphere radioembolisation either as a monotherapy or in	Primary: • All-cause mortality. • quality of life (as reported by the participants and as assessed by standard grading systems (e.g., Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep 2015)). • Serious adverse events as defined by the International Conference on Harmonisation of Technical Requirements for Registration of	Kolligs F, Bilbao J, Jakobs T, Iñarrairaegui M, Nagel J, Rodriguez M, et al. Pilot randomized trial of selective internal radiation therapy vs. chemoembolization in unresectable hepatocellular carcinoma. Liver International 2015; Vol. 35, issue 6:1715-21. Ricke J, Bulla K,

December 2015 Inclusion Criteria: All randomised clinical trials comparing Y-90 microsphere radioembolisation either as a monotherapy or in combination with other systemic or locoregional therapies versus placebo, no treatment, or other similar systemic or locoregional therapies for unresectable hepatocellular carcinoma. We did notlimit our search for randomised clinical trials in terms of language or year of publication. If the searches had found quasi-randomised studies or other observational studies,then we would have considered such studies for reports of harm only. Exclusion Criteria:	combination with other systemic or locoregional therapies Co-interventions were allowed if administered equally to all trial intervention groups. Comparison: Placebo, no treatment, or other systemic or locoregional therapies.	Pharmaceuticals forHuman Use (ICH) Guidelines for Good Clinical Practice as any untoward medical occurrence that at any dose resulted in death, was life-threatening, required hospitalisation or prolongation of existing hospitalisation, or resulted in persistent or significant disability or incapacity, or was a congenital anomaly/birth defect, or any medical event that might have jeopardised the person, or required intervention to prevent it (ICH-GCP 1997). Secondary: • Cancer-related mortality. • Time to progression of the tumour (reported as median time to progression). • Tumour response assessments (as recommended by the response evaluation in solid tumours criteria) (Eisenhauer 2009). * Complete response: disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to less than 10 mm. * Partial response: at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. * Progressive disease: at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this included the baseline sum if that was the smallest on study). In addition to the relative increase of 20%, the sum must also have demonstrated an absolute increase of at least 5 mm (note: the appearance of one or more new lesions was also considered as progression).	Kolligs F, Peck-Radosavljevic M, Reimer P, Sangro B, et al. Safety and toxicity of radioembolization plus sorafenib in advanced hepatocellular carcinoma: analysis of the European multicentre trial SORAMIC. Liver International 2015;35:620-6

		*** Stable disease: neither suLicient shrinkage to qualify for partial response nor suLicient increase to qualify for progressive disease, taking as reference the smallest sum diameters while on study.** *** In addition,we planned to considert he European Association for the Study of the Liver disease response evaluation criteria and the positron emission tomography Response Criteria in Solid Tumors whenever appropriate (Riaz 2011; MaLione 2013).** **• Non-serious adverse events: any medical occurrences not necessarily having a causal relationship with the treatment but that did, however, cause a dose reduction or discontinuation of the treatment** **Results: Study characteristics:** **The review authors found two small randomised clinical trials, in which 68 people with advanced liver cancer were randomised. One trial compared radioembolisation with chemoembolization. The other trial presented the safety analysis of a study that compared radioembolisation plus sorafenib versus sorafenib alone. These two small trials suggested that this intervention may be as safe as other standard therapies for this disease. We identified five ongoing randomised clinical trials, the results of which have not been finalised.** **Author's Conclusion: Quality of the evidence and conclusions** **The evidence obtained from the two low quality randomised trials was insufficient to reach conclusions on the**	

		potential beneficial and harmful effects of yttrium-90 microsphere radioembolisation for people with advanced hepatocellular carcinoma. More randomised clinical trials are needed.	

Methodical Notes

Funding Sources: None

COI: None

Study Quality: We assessed the overall evidence as very low quality using the GRADE approach (GRADEpro 2008 ; Balshem 2011). Generation of the allocation sequence was unclearly reported in both trials while allocation concealment was clearly reported in Kolligs 2015 and unclearly reported in Ricke 2015. In addition, high risk of performance bias and reporting bias existed in both trials, while detection bias was unclearly reported in both trials.

Heterogeneity:

Publication Bias: Publication bias might be an issue here; however, due to the fact that there were only two trials for this comparison, it was not possible to assess this formally

Notes:
Article retrieved by hand search after consensus conference
Oxford Level of Evidence: 2 (Down grading of the systematic review due to methodological weakness)
The authors assessed the included evidence as very low quality. High risks of bias were reported. Furthermore only two randomised clinical trials with 68 participants were included in this systematic review.

Tzartzeva, K. et al. Surveillance Imaging and Alpha Fetoprotein for Early Detection of Hepatocellular Carcinoma in Patients With Cirrhosis: A Meta-analysis. Gastroenterology. 154. 1706-1718.e1. 2018

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 **Study type: Systematic review and meta-analysis.** **Databases: MEDLINE and SCOPUS** **Search period: 1990 through August 2016.** **Inclusion Criteria: Studies thatevaluated abdominal imaging (ultrasound, CT, or MRI) with or without AFP for HCC surveillance in a cohort of patients with cirrhosis.** **Surveillance was defined as the repeated use of the test at a regular interval over time to detect a previously undiagnosed lesion. Studies**	**Population: Cirrhosis patients.** **Intervention: Ultrasound surveillance only** **Comparison: Additional surveillance using AFP marker, CT or MRI**	**Primary: HCC detection sensitivity, specificity** **Secondary: -** **Results: Study characteristics:** **32 studies including a total n=13367 patients,1877 of which developed HCC. 15 studies (n=4480) reported data on early HCC; of 516 patients who developed HCC, 319 (61.8%) were detected at an early stage. 28 studies (n=10743) exclusively included patients with cirrhosis, with four studies including some patients with significant fibrosis. Most studies (n=23) were**	**Bolondi L, et al. Gut. 2001;48:251–9.** **Caturelli E, et al. Am J Gastroenterol. 2002;97:397–405.** **Chalasani N, et al. Am J Gastroenterol. 1999;94:2988–93.** **Chen TH, et al. Int J Cancer. 2002;98:257–61.** **Giardina MG, et al. Cancer. 1998;83:2468–74.** **Henrion J, et al. Acta Gastroenterol Belg. 2000; 63:5–9.** **Izzo F, et al. Ann Surg. 1998; 227:513–8.** **Larcos G, et al. AJR**

evaluating imaging for screening or diagnostic purposes instead of surveillance were not included in the analysis. Exclusion Criteria: Studies performed exclusively in a non-cirrhotic cohort, such as patients with chronic hepatitis, were excluded. If the study cohort included both patients with cirrhosis and chronic hepatitis, only data regarding cirrhosis patients were included when possible. If data could not be extracted for the subset of patients with cirrhosis, we only included those studies in which a majority of patients had cirrhosis. Studies in which <50% of patients had cirrhosis, or those in which the proportion of patients with cirrhosis was not detailed, were excluded. Studies using sequential test combinations, such as ultrasound testing in patients based on AFP levels, were excluded because information bias from the initial study could have unpredictable effects on the ultrasound operating characteristics. Studies were required to report the number of discovered HCC and number of missed HCC for each surveillance test, as lack of data for false negative results (i.e. patients with missed lesions) precluded sensitivity calculations. Studies that reported the proportion of HCC discovered by surveillance, but not stratified by test, were excluded. Additional exclusion criteria included non-English language, non-human data, and lack of original data. If duplicate publications used the same cohort of patients, the data from the most recent manuscript were included		prospective in design, although 9 collected data on surveillance test performance retrospectively. 7 studies were conducted in the USA, 14 in Europe, 7 in Asia, and 4 in other countries. Most studies evaluated ultrasound as the surveillance imaging modality; however, two evaluated CT-based surveillance and two evaluated MRI-based surveillance. Results: Ultrasound alone: detected any stage HCC with 84% sensitivity (95% CI, 76%–92%), but early-stage HCC with only 47% sensitivity (95% CI, 33%–61%). ultrasound with vs without AFP measurement, ultrasound detected any stage HCC with a lower level of sensitivity than ultrasound plus AFP measurement (relative risk [RR], 0.88; 95% CI, 0.83–0.93) and early-stage HCC with a lower level of sensitivity than ultrasound plus AFP measurement (RR, 0.81; 95% CI, 0.71–0.93). However, ultrasound alone detected HCC with a higher level of specificity than ultrasound plus AFP measurement (RR, 1.08; 95% CI, 1.05–1.09). Ultrasound with vs without AFP detected early-stage HCC with 63% sensitivity (95% CI, 48%–75%) and 45% sensitivity (95% CI, 30%–62%), respectively (P=.002). CT and MRI for HCC Detection: Only 4 studies evaluated computed tomography or magnetic resonance image-based surveillance, which detected HCC with 84% sensitivity (95% CI, 70%–92%). Author's Conclusion: In summary, we demonstrated ultrasound has suboptimal sensitivity for early HCC detection, highlighting the need for alternative surveillance strategies. There are currently insufficient data	Am J Roentgenol. 1998; 171:433–5. Lok AS, et al. Gastroenterology. 2010; 138:493–502. Luo K, et al. J Viral Hepat. 2010; 17:511–7. Mok TS, et al, J Clin Oncol. 2005; 23:8041–7. Oka H, et all Hepatology. 1990; 12:680–7. Pateron D, et al. J Hepatol. 1994; 20:65–71. Paul SB, et al. Indian J Gastroenterol. 2007; 26:274–8. Pocha C, et al. Aliment Pharmacol Ther. 2013; 38:303–12. Qian MY, et al. AJ Gastroenterol Hepatol. 2010; 25:951–6. Sangiovanni A, et al.Gastroenterology. 2004; 126:1005–14. Santagostino E, et al. Blood. 2003; 102:78–82. Sato T, et al. Hepatol Int. 2009; 3:544–50. Shah TU, et al. Am J Gastroenterol. 2006; 101:533–40. Shimauchi Y, et al. Oncol Rep. 2000; 7:249–56. Singal AG, Cancer Epidemiol Biomarkers Prev. 2012; 21:793–9. Solmi L, et al. Am J Gastroenterol. 1996; 91:1189–94. Tong MJ, et al. J Gastroenterol Hepatol. 2001; 16:553–9. Tradati F, et al. Blood. 1998; 91:1173–7. Trinchet JC, Hepatology. 2011; 54:1987–97. Van Thiel DH, et al. Liver Transpl. 2004; 10:631–7. Mancebo A, et al.

		to support routine use of CT- or MRI-based surveillance in all patients with cirrhosis. Using AFP in combination with ultrasound significantly increases early HCC detection, suggesting this may be the preferred surveillance strategy for patients with cirrhosis until superior surveillance strategies are available.	Clin Gastroenterol Hepatol. 2013; 11:95–101. Frey RS, et al. Swiss Med Wkly. 2015; 145:w14200. Pinero F, et al. Eur J Gastroenterol Hepatol. 2015; 27:355–60. Chang TS, et al. Am J Gastroenterol. 2015; 110:836–44. Kim SY, et al. JAMA Oncol. 2017; 3:456–463.

Methodical Notes

Funding Sources: inancial support: This work was conducted with support from NCI RO1 CA212008 and Cancer Prevention Research Institute of Texas (CPRIT) RP150587. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

COI: "None of authors have relevant conflicts of interest"

Study Quality: Two authors (K.T. and A.S.) independently assessed study quality by a modified checklist based upon the Quality Assessment Tool for Diagnostic Accuracy (QUADAS2) guidelines with discrepancies resolved by consensus. Results: see article.

Heterogeneity: Estimates of effect were pooled using the DerSimonian and Laird method for a random effects model. The heterogeneity of diagnostic test parameters was initially evaluated graphically by examination of forest plots and statistically by the inconsistency index, with values >50% consistent with the possibility of substantial heterogeneity. Sensitivity analysis, in which one study is removed at a time from the model, was performed to determine if there was possible undue influence of a single stud

Publication Bias: Publication bias was initially evaluated graphically by funnel plot analysis and then statistically using Begg's test.
There was no evidence of publication bias by Begg's test (p=0.85).

Notes:
Article retrieved by hand search after consensus conference
Evidence level 1: systematic review and meta-analysis.
No major methodology limitations. Authors described that the majority of studies report detection of HCC at any, instead of early stage, which could possibly lead to overstimation of the effect. In addition the primary studies often lack the comparison with gold standards or lack information which affects ultrasound quality (f.e operator experience).

OXFORD (2011) Appraisal Sheet: RCT: 3 Bewertung(en)

Finn, R. S. et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med. 382. 1894-1905. 2020

Population	Intervention - Comparison	Outcomes/Results

Evidence level: 2 **Study type: global, multicenter, open-label, phase 3 randomized trial** **Number of Patient: n=501 treated with atezolizumab plus bevacizumab n=336 treated with sorafenib n=165** **Recruitung Phase: 15.03.2018 - 30.01.2019** **Inclusion Criteria: patients with unresectable hepatocellular carcinoma who had not previously received systemic treatment** **Exclusion Criteria: history of autoimmune disease coinfection with hepatitis B or hepatitis C virus, and untreated or incompletely treated esophageal or gastric varices with bleeding or high risk of bleeding**	**Intervention: atezolizumab plus bevacizumab** **Comparison: sorafenib**	**Primary: overall survival progression-free survival median follow-up 8.6 month** **Secondary:** **Results: <u>Study characteristics:</u> - Between March 15, 2018, and January 30, 2019, a total of 501 patients at 111 sites in 17 countries were randomly assigned to receive atezolizumab plus bevacizumab (336 patients, 82% male sex) or sorafenib (165 patients, 83% male sex) - median age was 64 years (atezolizumab plus bevacizumab) vs. 66 years (sorafenib) - Participants came from Asia (40 % atezolizumab plus bevacizumab/ 41 % sorafenib) and the rest of the world (60 % atezolizumab-bevacizumab/ 59 % sorafenib) <u>Efficacy</u> - a total of 197 patients (58.6%) receiving atezolizumab–bevacizumab and 109 patients (66.1%) receiving sorafenib had disease progression or died [95% CI, 4.0 to 5.6]; stratified hazard ratio for progression or death, 0.59; 95% CI, 0.47 to 0.76; P<0.001) - progression-free survival at 6 months was 54.5% in the atezolizumab–bevacizumab group and 37.2% in the sorafenib group. - the confirmed objective response rates were 27.3% (95% CI, 22.5 to 32.5) with atezolizumab–bevacizumab and 11.9% (95% CI, 7.4 to 18.0) with sorafenib, according to independent assessment with RECIST 1.1 (P<0.001), and 33.2% (95% CI, 28.1 to 38.6) and 13.3% (95% CI, 8.4 to 19.6) - complete response: n=18 (5.5%) atezolizumab-bevacizumab vs. n=0 sorafenib treatment - disease control rate(objective response plus stable disease): 73.6 % with atezolizumab-bevacizumab and 55.3 % with sorafenib <u>Safety</u> - Adverse events of any grade regardless of causality: n=323 (98.2%) atezolizumab–bevacizumab vs. n=154 (98.7%) sorafenib - Serious adverse events : 125 patients (38.0%) atezolizumab–bevacizumab vs. n=48 (30.8%) sorafenib - most common adverse events grade 3 or 4: atezolizumab–bevacizumab hypertension (15.2%) - discontinued treatment because of adverse effects: 15.5% atezolizumab–bevacizumab vs. 10.3% sorafenib Author's Conclusion: "Treatment with atezolizumab plus bevacizumab was associated with significantly better overall survival and progression-free survival outcomes than sorafenib in patients with advanced unresectable hepatocellular carcinoma not previously treated with systemic therapy. Serious toxic effects were noted in 38% of the Patients who received the combination therapy;however, no new or unexpected toxic effects were observed. The combination therapy also resulted in a longer time to deterioration of patientreported quality of life and functioning than sorafenib."**

Methodical Notes
Funding Sources: Supported by F. Hoffmann–La Roche/Genentech **COI: numerous, see article** **Randomization: Randomization was performed through an interactive voice-response or Web-response system in permuted blocks, stratified by geographic region (Asia excluding Japan vs. the rest of the world), macrovascular invasion or extrahepatic spread of disease (presence vs. absence), baseline alphafetoprotein level (<400 vs. ≥400 ng per milliliter), and ECOG performance status (0 vs. 1)** **Blinding: To minimize the potential bias associated with the open-label design, a blinded independent review of imaging for progressionfree survival was selected for the coprimary endpoint.** **Dropout Rate/ITT-Analysis:** **Notes:** **Article retrieved by hand search after consensus conference** **Oxford Level of Evidence: 2 RCT** **limitations: open-label design, trial was conducted in a patient population that had preserved liver function (Child–Pugh class A) and a decreased risk of variceal bleeding. The safety of the combination in a broader population warrants further study.**

Liu, H. et al. Randomized clinical trial of chemoembolization plus radiofrequency ablation versus partial hepatectomy for hepatocellular carcinoma within the Milan criteria. Br J Surg. 103. 348-56. 2016

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type: Randomized controlled trial** **Number of Patient: 200 randomized, 100 per group.** **Recruitung Phase: June 2006 to April 2009** **Inclusion Criteria: All patients with HCC swithin the Milan criteria in the Third Department of Hep-atic Surgery at Eastern Hepatobiliary Surgery Hospital were considered for enrolment in the study. The diagnosis of HCC followed the criteria of the American Association or the Study of the Liver Diseases.** **Inclusion criteria were: no previous treatment for cancer; age between 18 and 80 years; a solitary HCC nodule of 5 cm or less, or up to three nodules of 3 cm or less in size; treatable by either partial hepatectomy or TACE plus RFA; Child–Pugh grade A or B.**	**Intervention: Sequential treatment with transcatheter arterial chemo-embolization (TACE) and percutaneous radiofrequency ablation (RFA).** **Comparison: Partial hepatectomy**	**Primary: Overall survival (OS)** **Secondary: Recurrence-free survival (RFS)** **Results: Study poppulation:** **Mean age 49 and 52, 94 and 86% male participants in partial hepatectomy vs TACE/RFA group.** **Follow-up ranged from 5 to 85 (median 56) months. In the hepatectomy group, all 100 patients had a successful partial hepatectomy. Median tumour diameter was 3·0cm,and median distance between tumour and resection marginwas 1·7 cm.** **Results:** **On an ITT analysis, the 1-,3- and 5-year OS rates were 97,0 83,7 and 61,9% partial hepatectomy group, and 96,0, 67,2 and 45,7% in the TACE+RFA group.** **The 1-, 3- and 5-year RFS rates were 94,0 68,2 and 48,4%, and 83,0 44,9 and 35,5% respectively. Using Kaplan–Meier analysis, there was a significant difference between the two groups in both RFS (P=0,026) and OS (P=0,007)**

Exclusion Criteria: Radiological appearance ofmacroscopic vascular invasion or extrahepatic metastases; contraindications to hepatectomy, TACE or RFA.		**Author's Conclusion: "For patients with HCC within the Milan criteria, partial hepatectomy was associated with better overall and recurrence-free survival than sequential treatment with TACE and RFA. "**

Methodical Notes

Funding Sources: "This study was funded by the National Key BasicResearch Programme of China (2014CB542102),State Key Project on Infectious Diseases of China(2012ZX10002010, 2012ZX10002016), Science Fund forCreative Groups, National Natural Science Foundation ofChina (NSFC) (81221061) and NSFC (81071681)".

COI: The authors declare no conflict of interest.

Randomization: Patients were randomized in a 1 : 1 ratio to the two groups, using randomnumbers. The random allocation sequence was generatedfrom a computer by a research assistant who was notinvolved in the study.

Blinding: As different treatment methods were used in this trial,double-blinding was impractical.

Dropout Rate/ITT-Analysis: An intention-to-treat analysis was followed when performing survival analysis. 4 vs 7 lost to follow in each group.

Notes:
Article retrieved by hand search after consensus conference
Oxford level of evidence 2: randomized controlled trial.
Significant group difference in AFP (implication unclear, but discussed as a prognostic risk factor).
Lack of histological diagnosis of HCC in the TACE/RFA group. Authors also mentioned that the included patients predominantly showed HBV related HCC.
Double blinding considered impractical (surgery), single blinding not described.

Peng, Z. W. et al. Radiofrequency ablation with or without transcatheter arterial chemoembolization in the treatment of hepatocellular carcinoma: a prospective randomized trial. J Clin Oncol. 31. 426-32. 2013

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type: Retrospective randomized controlled trial** **Number of Patient: 189** **Recruitung Phase: October 2006 to June 2009** **Inclusion Criteria: (1) age 18 to 75 years (2) a solitary HCC 7.0 cm in diameter, or multiple (three or fewer) HCC lesions,**	**Intervention: TACE combined with RFA (TACE-RFA n=94)** **Comparison: RFA alone (n=95)**	**Primary: Overall survival** **Secondary: Recurrence-free survival** **Results: Study population:** **2,256 patients with HCC who were treated in our hospital, 1,603 did not meet the inclusioncriteria of this study. The reasons for exclusion were portal veinthrombosis (n=256), extrahepatic metastasis (n=156), tumorsize ≥=7 cm or number more than three (n=891), severe liver dysfunction (n=138), and significant coagulopathy (n=162).** **Of the remaining patients, 464 patients refused to participate in this study, and they received surgical resection (n=227), RFA (n=141), and TACE (n=96). Finally, 189 eligible patients consentedto be randomly assigned to the TACE-RFA group (n=94) and theRFA group (n=95;). Two patients (one in each group) withdrew from the trial after randomization. These two patients received partial hepatectomy and were analyzed together in**

each 3.0 cm in diameter (3) no radiologic evidence of invasion into major portal/hepatic venous branches and no extrahepatic metastases (4) lesions visible on ultrasound with an acceptable and safe path between the lesion and skin as shown on ultrasound (5) an Eastern Cooperative Oncology Group performance status of 0 (6) no previous treatment (7)Child-Pugh class A or B cirrhosis. Exclusion Criteria: (1) severe coagulation disorders (prothrombin activity40% or a platelet count of40,000/L) (2) evidence of hepatic decompensation including ascites refractory to diuretics, esophageal or gastric variceal bleeding, or hepatic encephalopathy (3) contraindications to carboplatin, epirubicin, mitomycin, or lipiodol.		theiroriginally assigned groups using the intention-to-treat principle. One patient in the TACE-RFA group was lost to follow-up. There were no significant differences between the two groups of patients for anyof the variables. Results: At a follow-up of 7 to 62 months, 34 patients in the TACE-RFA group and 48 patients in the RFA group had died. Thirty-three patients and 52 patients had developed recurrence in the TACE-RFA group and RFA group, respectively. The 1-, 3-, and 4-year overall survivals for the TACE-RFA group and the RFA group were 92.6%, 66.6%, and 61.8% and 85.3%, 59%, and 45.0%, respectively. The corresponding recurrence-free survivals were 79.4%, 60.6%, and 54.8% and 66.7%, 44.2%, and 38.9%, respectively. Patients in the TACE-RFA group had better overall survival and recurrence-free survival than patients in the RFA group (hazard ratio, 0.525; 95% CI, 0.335 to 0.822; P .002; hazard ratio, 0.575; 95% CI, 0.374 to 0.897; P .009, respectively). There were no treatment-related deaths. On logistic regression analyses, treatment allocation, tumor size, and tumor number were significant prognostic factors for overall survival, whereas treatment allocation and tumor number were significant prognostic factors for recurrence-free survival. Author's Conclusion: TACE-RFA was superior to RFA alone in improving survival for patients with HCC less than 7 cm.

Methodical Notes

Funding Sources: Supported by a grant from the National Natural Science Foundation of China (Grant No. 30872995), the State Key Project on Infectious Diseases of China (Grant No. 2012ZX10002-016), and the 5010 Foundation of Sun Yat-sen University (Grant No. 2007043).

COI: None

Randomization: The randomization was done at a central registry using computer-generated numbers by a nurse who was not part of this research team.

Blinding: Double-blind and double dummy techniques were not used because of the nature of the treatments and their possible adverse effects. However, the radiologists who evaluated the tumor response and the statistician who analyzed the data were blinded to the treatment the patients received.

Dropout Rate/ITT-Analysis: TACE-RFA: withdrew and lost to follow-up n=2
RFA: withdrew n=1

Intention-to-treat analysis in both groups

Notes:
Article retrieved by hand search after consensus conference
Oxford level of evidence 2: randomized controlled trial.

Number of patients in this study is relatively small. Single-center experience, results may not be generalizable to patients with HCC in other countries. Study is not double-blind.

OXFORD (2011) Appraisal Sheet: Prognostic Studies: 2 Bewertung(en)

Ioannou, G. N. et al. Increased Risk for Hepatocellular Carcinoma Persists Up to 10 Years After HCV Eradication in Patients With Baseline Cirrhosis or High FIB-4 Scores. Gastroenterology. 157. 1264-1278.e4. 2019

Population	Intervention	Outcomes/Results

Evidence level: 3 **Study type: Prognostic Cohort Study** **Number of Patient: n=48135 including n=1509 who developed Hepatocellular carcinoma (HCC) >180 d after antiviral treatment initation** **Recruitung Phase: 2000- 2015** **Inclusion Criteria: -patients who achieved Sustained virological response (SVR) after HCV antiviral regimes** **Exclusion Criteria: Patients who** **- had a diagnosis of HCC recorded before antiviral treatment or within 180 days** **- died within 180 days from the start date of antiviral treatment or had fewer than 180 days of available follow-up (n=80)** **- underwent liver transplantation before antiviral treatment (n=826)** **- without baseline Fibrosis-4 (FIB-4) scores (n=1470)**	**Intervention: Non-intervention study** **Comparison: -**	**Primary: - changes in HCC annual incidence over time following HCV eradication** **- fibrosis-4 (FIB-4) scores** **Secondary:** **Results: - among patients with cirrhosis before treatment with direct-acting antivirals (DAAs) (n=9784), those with pre-SVR fibrosis-4 (FIB-4) scores 3.25 had a higher annual incidence of HCC (3.66%/year) than those with FIB-4 scores 3.25 (1.16%/year) (adjusted hazard ratio 2.14; 95% confidence interval 1.66–2.75)** **- in DAA-treated patients with cirrhosis and FIB-4 scores 3.25, annual HCC risk decreased from 3.8%/year in the first year after SVR to 2.4%/year by the fourth year (P=.01)** **- in interferon-treated patients with FIB-4 scores 3.25, annual HCC risk remained above 2%/year, even 10 years after SVR** **- a decrease in FIB-4 scores from 3.25 pre-SVR to <3.25 post-SVR was associated with an approximately 50% lower risk of HCC, but the absolute annual risk remained above 2%/year** **- patients without cirrhosis before treatment (n=38,351) had a low risk of HCC, except for those with pre-SVR FIB-4 scores 3.25 (HCC risk 1.22%/year) and post-SVR FIB-4 scores 3.25 (HCC risk 2.39%/year); risk remained high for many years after SVR** **Author's Conclusion: "Tretreatment FIB-4 score (3.25 vs <3.25), together with the change in FIB-4 score after SVR, can be used as a convenient, readily available method of stratifying HCC risk in patients with HCV who achieve SVR. Changes in FIB-4 score reflect changes in HCC risk. Patients with established cirrhosis appear to have a persistently high risk of HCC even many years after SVR and should continue HCC surveillance indefinitely. Among patients with cirrhosis, only those whose FIB-4 level is <3.25 both before and persistently after SVR have an annual HCC risk <1%. Patients without a pretreatment diagnosis of cirrhosis generally have low HCC risk after SVR, except those with pre-SVR FIB-4 3.25 and especially if post-SVR FIB-4 remains 3.25. These patients should be offered HCC surveillance."**

Methodical Notes

Funding Sources: "This study was funded by National Institutes of Health/National Cancer Institute grant R01CA196692 and VA Clinical Science Research and Development grant I01CX001156 to GNI. The contents do not represent the views of the US Department of Veterans Affairs or the US Government."

COI: "These authors disclose the following: Amit G. Singal has served as a consultant for TARGET, Wako Diagnostics, Roche, Exact Sciences, and Glycotest; he has received research funding from AbbVie and Gilead. Elliot B. Tapper has served as consultant for Novartis and Bausch Health, and has received research grants from Gilead and Valeant. Richard K. Sterling has received research grants from Roche Diagnostics, Abbott, AbbVie, and Gilead, and has served on the DSMB of studies for Pfizer and Baxter. Jordan J. Feld has served as consultant for Abbott, Enanta, Janssen, and Roche, and has received research grants from AbbVie, Gilead, Janssen, Fujifilm/Wako. The remaining authors disclose no conflicts.

Randomization: none

Blinding: none

Dropout Rate/ITT-Analysis: none

Notes: Article retrieved by hand search after consensus conference
Oxford Level of evidence: 3 Cohort study
limitations: predominantly male, VA patient population, diagnosis was not based on uniform histological or other criteria and occult cirrhosis could have been missed

Papatheodoridis, G. et al. PAGE-B predicts the risk of developing hepatocellular carcinoma in Caucasians with chronic hepatitis B on 5-year antiviral therapy. J Hepatol. 64. 800-6. 2016

Population	Intervention	Outcomes/Results
Evidence level: 2 **Study type: 9 center cohort study.** **Prognostic study to develop and validate a risk prediction score (PAGE-B) for the development of HCC in Caucasian CHB patients on 5-year antiviral therapy.** **Number of Patient: 1815 adults (1264 in the derivation, 484 in the validation cohort)** **Recruitung Phase:** **Inclusion Criteria: Two datasets of Caucasian chronic hepatitis B (CHB) from 9 participating centers (8 derivation, 1 validation).** **All patients with CHB followed in the liver clinics of the 9 centers were included if they were adults (≥16 years old), Caucasians and had received treatment with ETV or TDF for ≥12 months. The participating centers were in Greece, Italy, Spain, Netherlands, and Turkey. Patients naive to or previously treated with other NAs were included.** **Exclusion Criteria: Patients with decompensated cirrhosis, HCC diagnosed before the onset of ETV/TDF, patients with co-infection(s) with hepatitis D, hepatitis C or human immunodeficiency virus and liver transplant patients were excluded.**	**Intervention: Non-intervention study.** **Comparison:**	**Primary: PAGE-B perdictive score: We imputed 10 values of the missing predictor for each patient. We applied backwardelimination to each of the 10 completed data sets separately, resulting in 10 setsof selected predictors. The final set comprised those predictors that were selectedin more than 50% of the 10 data sets. Given the finally selected predictors, amodel was fitted in each of the 10 completed data sets. We used Rubin's rulesto combine the estimated regression coefficients and variances from the 10 differ-ent completed data sets. To evaluate the predictive performance of the model, weexamined discrimination and calibration measures. Discrimination was assessedusing Harrell's c-index A calibration plot was used to assess graphically theagreement between the 5-year probability of remaining HCC free as predictedby the modelvs.the Kaplan-Meier estimate (observed probability).** **Secondary: -** **Results: Median follow-up of 50 (31–62) months, HCC was diagnosed in 51 (3.8%) patients in the derivation and 34 (6.9%) patients in the validation dataset. The cumulative 1-, 3- and 5-year rates of HCC were 0.9%, 3.1% and 5.7% in the derivationand 1.2%, 3.9% and 8.4% in the validation dataset, respectively(p= 0.10).** **Primary outcome:** **In the derivation dataset, age, gender, platelets and cirrhosis were independently associated with HCC. The PAGE-B score was developed based on age, gender and platelets (c-index = 0.82, 0.81 after bootstrap validation). The addition of cirrhosis did not substantially improve the discrimination (c-index = 0.84). The predictability of PAGE-B score was similar (c-index = 0.82) in the validation dataset. Patients with PAGE-B ≤9, 10–17, ≥ 18 had 5-year cumulative HCC incidence rates of 0%, 3%, 17% in the derivation and 0%, 4%, 16% in the validation dataset.** **Author's Conclusion: "In conclusion, PAGE-B, which is based only on baseline patients' age, gender and platelets, represents a reliable and simple to use risk score for the prediction of HCC**

		during the first 5 years of ETV or TDF therapy in Caucasians CHB patients. If thesedata are confirmed in other studies, non-cirrhotic patients in thelow risk group by the PAGE-B score who have no or minimal 5-year probability for HCC will not need HCC surveillance, whilepatients in the moderate and particularly in the high risk groupwho are at increased 5-year HCC risk will require close surveil-lance for HCC."

Methodical Notes

Funding Sources: numerous, see article

COI: numerous, see article

Randomization: -

Blinding: -

Dropout Rate/ITT-Analysis: -

Notes: Article retrieved by hand search after consensus conference
Oxford evidence level 2: Inception cohort study.
No comparison to established risk scores or standards. Not all patients were at different stages of the disease (CHB w or wo cirrhosis)

NEWCASTLE - OTTAWA Checklist: Cohort: 1 Bewertung(en)

Endo, K. et al. Efficacy of combination therapy with transcatheter arterial chemoembolization and radiofrequency ablation for intermediate-stage hepatocellular carcinoma. Scand J Gastroenterol. 53. 1575-1583. 2018

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 3 **Study type: Retrospective Cohort Study**	**Funding sources: None** **Conflict of Interests: None** **Randomization: Not stated** **Blinding: Not stated** **Dropout rates: Not stated**	**Total no. patients: 103** **Recruiting Phase: January 2011 to December 2017** **Inclusion criteria: We selected patients with intermediate HCC who met the following eligibility criteria: (1) 20 years of age, (2) receiving initial therapy, (3) 7 tumors, and (4) maximum tumor diameter under 5 cm.** **Exclusion criteria: In order to avoid selection bias, we excluded patients with HCC having more than 8 tumors or maximum diameter exceeding 5 cm based on a previous report.**	**Interventions: TACE + RFA** **Comparison: TACE**
Notes:	**Article retrieved by hand search after consensus conference** **Oxford Level of evidence: 3 Cohort study** **Retrospective, single-center study with a small sample size** **Study limited to intermediate-stage HCC patients who met the inclusion criteria as tumor number <8 and maximal tumor diameter <5cm**		

	Author's conclusion: The addition of RFA to TACE improved cumulative overall and recurrence-free survival in patients with intermediate-stage HCC, especially in patients with AFP <100.	
Outcome Measures/results	**Primary** **Cumulative overall survival rate from initial treatment till the last follow-up or death** **Secondary** **Recurrence-free survival rate from initial treatment until patients experienced tumor recurrence or death**	**Results: Population characteristics:** **439 patientswith HCC received either TACE or TACE+RFA at our hospital.** **336 patients were excluded based upon defined exclusion criteria.** **103 patients met the inclusion criteria. Median follow-up periods were 27.1 months. The median patient age was 74 (46–89) and 73 (71%) patients were male. Infection withthe Hepatitis C virus was the major cause of background liver disease (55%), and 76 (74%) patients had Child-Pughclass A liver function. The median maximal tumor size was33 mm (11–49 mm) and the median tumor number was 3(2–7). According to the BCLC-B sub-classification as reportedby Bolondi et al. [14], 58 (56%), 26 (25%), 5 (5%), and 14(14%) patients were classified as B1, B2, B3, and B4, respect-ively. The maximal tumor size and total bilirubin levels werestatistically different between the two groups.** **Results:** **Among the 103 patients, 92 were selected using PSM. The cumulative overall survival rates at 1, 3, and 5 years for the TACE+RFA group were 97.4%, 70.4%, and 60.4%, respectively, which were significantly higher than those for the TACE group (92.7%, 55.7%, and 22.8%, respectively, p=045). The recurrence-free survival rates at 0.5, 1, and 2 years for the TACE+RFA group were 80.0%, 58.6%, and 33.3%, respectively, which were significantly higher than those for the TACE group (34.5%, 8.8%, and 2.9%, respectively, p<.01 for the sub-group with a-fetoprotein ng tace group demonstrated a significantly improved prognosis than>**