Schlüsselfrage:
AG 1 Risikofaktoren: Wird das Ösophaguskarzinomrisiko (SCC AC) durch einen der folgenden Faktoren beeinflusst?

<table>
<thead>
<tr>
<th>Citation</th>
<th>Evidence Level</th>
<th>Study Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vinogradova, Y. 2013</td>
<td>3b</td>
<td>Series of nested case-control studies</td>
</tr>
<tr>
<td>Levi, Z. 2013</td>
<td>2b</td>
<td>Cohort study</td>
</tr>
<tr>
<td>Pottegard, A. 2013</td>
<td>3b</td>
<td>population-based case-control study</td>
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<tr>
<td>Cooper, S. 2014</td>
<td>3b</td>
<td>Nested-case control study</td>
</tr>
<tr>
<td>Feng, X. S. 2014</td>
<td>2b</td>
<td>Prospective Cohort Study</td>
</tr>
<tr>
<td>Alexandre, L. 2014</td>
<td>3b</td>
<td>Case-control study</td>
</tr>
<tr>
<td>Hvid-Jensen, F. 2014</td>
<td>3b</td>
<td>Nested case-control study</td>
</tr>
<tr>
<td>Masclee, G. M. 2014</td>
<td>2b</td>
<td>dynamic population-based retrospective cohort study</td>
</tr>
<tr>
<td>Jia, N. 2014</td>
<td>2b</td>
<td>Retrospective Cohort Study</td>
</tr>
<tr>
<td>Agrawal, S. 2014</td>
<td>3b</td>
<td>Retrospective case-control study</td>
</tr>
<tr>
<td>Lindkvist, B. 2014</td>
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<td>Prospective cohort study</td>
</tr>
<tr>
<td>Moura, M. A. 2014</td>
<td>3b</td>
<td>case-control study</td>
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<tr>
<td>Cook, M. B. 2015</td>
<td>2b</td>
<td>Prospective Cohort Study</td>
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<tr>
<td>Hazelton, W. D. 2015</td>
<td>2b</td>
<td>Cohort Study</td>
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<tr>
<td>Wiencke, A. 2015</td>
<td>1b</td>
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<tr>
<td>Bhat, G. A. 2015</td>
<td>3b</td>
<td>Case-control study</td>
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<tr>
<td>Buckland, G. 2015</td>
<td>1b</td>
<td>prospective cohort study</td>
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<tr>
<td>Chen, T. 2015</td>
<td>3b</td>
<td>population-based case-control study</td>
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<tr>
<td>Rafiq, R. 2016</td>
<td>3b</td>
<td>Case-control study</td>
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<tr>
<td>Sawram, V. 2016</td>
<td>3b</td>
<td>hospital-based Case-Control Study</td>
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<tr>
<td>Thota, P. N. 2016</td>
<td>1b</td>
<td>Retrospective Cohort Study</td>
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<tr>
<td>Kestens, C. 2016</td>
<td>2b</td>
<td>Retrospective population-based cohort study</td>
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<tr>
<td>Krishnamoorthi, R. 2016</td>
<td>1b</td>
<td>population-based cohort study</td>
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<tr>
<td>Zakaria, D. 2017</td>
<td>2b</td>
<td>Cohort Study</td>
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<tr>
<td>Nguyen, T. 2017</td>
<td>2b</td>
<td>Retrospective cohort study</td>
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<tr>
<td>Ji, J. 2017</td>
<td>2b</td>
<td>Retrospective cohort study</td>
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<tr>
<td>Busby, J. 2017</td>
<td>3b</td>
<td>Nested case-control study</td>
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<tr>
<td>Cook, M. B. 2017</td>
<td>2b</td>
<td>Cohort study</td>
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</tbody>
</table>
Schlüsselfrage: Wird das Ösophaguskarzinomrisiko (SCC AC) durch einen der folgenden Faktoren beeinflusst?

Bewertungsvorlage: NEWCASTLE - OTTAWA Checklist 4: Cohort

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<tbody>
<tr>
<td><strong>Evidence level</strong></td>
<td><strong>Methodical Notes</strong></td>
<td><strong>Interventions</strong></td>
<td></td>
</tr>
<tr>
<td>Study type: prospective cohort study</td>
<td>Recruiting Phase: recruited between 1992 and 2000, mainly from the general population</td>
<td></td>
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<tr>
<td></td>
<td>Inclusion criteria: general population of France, Italy, Spain, United Kingdom, The Netherlands, Greece, Germany, Sweden, Denmark, Norway (Not further described)</td>
<td>Inclusion criteria: healthy lifestyle index (combining smoking status, alcohol consumption, diet quality evaluated on the basis of adherence to the Mediterranean dietary pattern and body mass index)</td>
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<td></td>
<td>Conflict of Interests: not reported</td>
<td>Comparison: -</td>
<td></td>
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<tr>
<td></td>
<td>Randomization: -</td>
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<td></td>
<td>Blinding: -</td>
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<tr>
<td></td>
<td>Dropout rates: Not relevant, drop out was exclusion criteria</td>
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Notes: NOS-rating: 6/8 stars

- part of anthropometric data is based on self-reports (risk of bias)
- dietary questionnaire regarding Mediterranean diet for central/nothern europe countries
- BMI as a factor to assess obesity/overweight without considering body fat percentage

Author's conclusion: Results indicate that following a combination of modifiable healthy lifestyle behaviors could dramatically decrease the burden of gastric cancer. These findings are particularly relevant considering the very poor relative survival rate for GC (25% at 5-years), which is reported to be worse for cardia GC (20% at 5-years) compared to non-cardia GC (31% at 5-years). Understanding the impact of combined lifestyle habits on GC risk further underscores the importance of health promotion strategies to eradicate cigarette smoking, reduce overweight/obesity, limit alcohol consumption if consumed and improve diet quality.

Outcome Measures/results

**Primary** - (Cox proportional hazards regression models and hazard ratios (HR)) associations between healthy lifestyle index and GC

**Secondary** - (Population attributable risk (PAR) fractions) proportion of GC cases that could have been avoided, assuming a causal relationship, if all the studied population had been in the healthiest category for all the healthy lifestyle behaviors within the index

Results: - Never smoking/quitting more than 10 years previously compared with smokers was associated with decreased risk of overall GC (HR 0.64, 95% CI 0.54-0.75), noncardia GC (HR 0.67, 95% CI 0.53-0.86) and cardia GC (HR 0.56, 95% CI 0.41-0.75)
- Strong inverse association between alcohol intake and overall GC, especially noncardia GC (HR 0.74, 95% CI 0.56-0.97), but no association was observed for cardia GC
- High compared with low rMED score (Mediterranean diet) was only significantly related to cardia GC (HR 0.81, 95% CI 0.38-0.97)
- For BMI a normal compared with non-normal weight was not associated with
### Krishnamoorthi, R. et al. Rates and predictors of progression to esophageal carcinoma in a large population-based Barrett’s esophagus cohort. Gastrointest Endosc. 84. 40-46.e7. 2016

<table>
<thead>
<tr>
<th>Evidence level</th>
<th>Methodical Notes</th>
<th>Patient characteristics</th>
<th>Interventions</th>
</tr>
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<tbody>
<tr>
<td>1b Study type</td>
<td>population-based cohort study</td>
<td></td>
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<tr>
<td>Evidence level</td>
<td>Funding sources: Takeda Pharmaceuticals, Inc. Prasad Iyer and Amitabh Chak are members of the National Cancer Institute–supported Barrett’s Esophagus Translational Research Network</td>
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<tr>
<td>Recruiting Phase</td>
<td>Inclusion criteria: All patients with a diagnosis of BE in the GPRD database between May 1991 and April 2010</td>
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<tr>
<td>Exclusion criteria:</td>
<td>Subjects who developed EC within 12 months of the index date -missing data</td>
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<tr>
<td>Dropout rates:</td>
<td>N.r.</td>
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<tr>
<td>NOS-rating:</td>
<td>8/8 stars</td>
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<tr>
<td>Notes:</td>
<td></td>
<td>Increasing age, male sex and increasing BMI were found to be risk factors that predicted progression to EC. PPI and statin use were identified as independent factors that protect against progression to EC. These results remained valid with a number of sensitivity analyses. NSAIDs and metformin use showed a trend toward protection against malignant progression. Subjects with high BMI may constitute a group of subjects who could be targeted by suitable chemopreventive agents. Prospective studies are needed to confirm these associations.</td>
<td></td>
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<tr>
<td>Author’s conclusion:</td>
<td>Increasing age, male gender, and being overweight continued to be independent risk factors predictive of progression to EC.</td>
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<tr>
<td>Outcome Measures/results</td>
<td>Primary Incidence rates of EC in BE cohort</td>
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<tr>
<td></td>
<td>Hazard Ratios of risk of progression to esophageal cancer</td>
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<td></td>
<td>Secondary -</td>
<td></td>
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<tr>
<td>Results:</td>
<td>The overall incidence rate of EC in the cohort was 2.23 per 1000 person years of follow-up -Significant association between increasing age, male gender, overweight (BMI 25-29.9), and progression to EC. -On multivariate analysis (adjusting for age, gender, smoking, BMI, hiatal hernia, DM2, PPI, NSAIDs, Statin, Metformin, Insulin, and OAD), increasing age, male gender, and being overweight continued to be independent risk factors predictive of progression to EC. -Obese-I (BMI 30-34.9) patients showed a trend toward significance as a risk factor for predicting progression (p = 0.08). -Increasing hazard ratios for the 3 BMI groups - overweight, Obese-I and Obese-II (HR= 1.63, 1.72 and 2.24) demonstrated a statistically significant trend across the 3 groups (p = 0.034), suggesting increased risk of progression with higher BMI. -On multivariate analysis (adjusting for age, gender, smoking, BMI, hiatal hernia, DM2, PPI, NSAIDs, Statin, Metformin, Insulin, and OAD), increasing age, male gender, and being overweight continued to be independent risk factors predictive of progression to EC. -Obese-I (BMI 30-34.9) patients showed a trend toward significance as a risk factor for predicting progression (p = 0.08). -Increasing hazard ratios for the 3 BMI groups - overweight, Obese-I and Obese-II (HR= 1.63, 1.72 and 2.24) demonstrated a statistically significant trend across the 3 groups (p = 0.034), suggesting increased risk of progression with higher BMI. -Using PDC (Proportion days covered) to determine exposure to medications during the follow-up intervals, PPI use (HR = 0.43, p &lt;0.0001) and statin use (HR = 0.61, p = 0.002) were protective against progression to EC. Once a day versus twice a day PPI use did not appear to influence the protective effect of PPIs</td>
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<tr>
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</tr>
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<tbody>
<tr>
<td>1b Study type</td>
<td>Retrospective Cohort Study</td>
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<td>Evidence level</td>
<td>Funding sources: not described</td>
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<tr>
<td>Conflict of Interests:</td>
<td>authors report no conflicts of interest</td>
<td></td>
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<tr>
<td>Randomization:</td>
<td>N.r.</td>
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<tr>
<td>Blinding:</td>
<td>N.r.</td>
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<tr>
<td>Dropout rates:</td>
<td>N.r.</td>
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<tr>
<td>Total no. patients:</td>
<td>1239</td>
<td></td>
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</tr>
<tr>
<td>Recruiting Phase:</td>
<td>Inclusion criteria: All patients diagnosed with Barrett’s esophagus (BE) at the Cleveland Clinic Digestive Disease Institute from January 2000 - December 2012 -Patients with at least 1 upper endoscopic evidence of BE and confirmed by the presence of intestinal</td>
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<tr>
<td>Interventions:</td>
<td>-BMI (lower 25, 25-27.4, 27.5-29.9, 30-34.9, 35-39.9 ≥ 40 kg/m²)</td>
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<tr>
<td>Comparison:</td>
<td>-different BMI levels</td>
<td></td>
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<tr>
<td>Notes:</td>
<td>NOS-rating: 6/8 stars</td>
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<tr>
<td>-interpretation of results is not consistent with actual results (authors: “high BMI was associated with higher prevalence of dysplasia (p = 0.002”)</td>
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<tr>
<td>Author's conclusion:</td>
<td>High BMI was associated with higher prevalence of dysplasia in BE. But once in a surveillance program, higher BMI is not associated with progression of dysplasia in NDBE</td>
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<tr>
<td>Outcome Measures/results:</td>
<td>Primary -Prevalence of dysplasia in BE (%)</td>
<td></td>
<td></td>
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<tr>
<td>Secondary -Hazard Ratios (HR) of BMI and progression to dysplasia in non-dysplastic Barrett’s esophagus (NDBE)</td>
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<tr>
<td>Results:</td>
<td>-Lower BMI groups tended to have lower prevalence of dysplasia while higher BMI groups had higher prevalence of dysplasia (p = 0.002)</td>
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<tr>
<td>-BMI or BMI change was not associated with progression to high-grade dysplasia or esophageal adenocarcinoma in NDBE (p = 0.055)</td>
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Cohort study

| Evidence level: | 1b- |
| Study type: | Evidence level Methodical Notes Patient characteristics Interventions |
| Total no. patients: | 2,919 men, 3,007 women (total: 5926) |
| Recruiting Phase: | average age: 54 SD 11.9 (men) and 55 SD 12.3 (women) |
| Inclusion criteria: | men and women aged ≥ 35 years of age diagnosed with different cancer types including squamous cell carcinoma (ICD-O-3 morphology codes 8050) of the esophagus (C15) in Germany in the year 2010 |
| Exclusion criteria: | not reported |

| Notes: | NOS-rating: 5/8 stars |
| -For esophageal cancer, simulations could not be conducted, because confidence intervals for the relative risks were not published for the exposure-specific analysis |
| Author's conclusion: | In Germany, a substantial proportion of cases of common cancers can be attributed to alcohol consumption, even when consumed at moderate levels. Alcohol consumption with concurrent tobacco smoking is especially important for cancers of the UADT. These findings strengthen the rationale for prevention measures that address exposure at all levels. |

Outcome Measures/results: | Primary -Population attributable risk (PAR%) of incident cases by alcohol consumption in Germany, 2010 |
| Secondary - | Results: -PAR was highest for alcohol consumption for esophageal cancer (men: 47.6 %, women: 35.8 %; 2.5th -97.5th percentile) |
| -Regarding estimated prevalence and corresponding population attributable risks for esophageal cancer in Germany by sex and alcohol and tobacco exposure category, highest PARs were found for 15-24 cig/day and 1-24ml/d (8.6% men, 7.9% women) corresponding Prevalences: 15.7% men, 10.0% women |


Cohort study

| Evidence level: | 2b |
| Study type: | Evidence level Methodical Notes Patient characteristics Interventions |
| Total no. patients: | 8929 |
| Recruiting Phase: | KPNK (Kaiser Permanente Northern California) |
| Inclusion criteria: | Patients with BE diagnosed at KPNK at ages 18 years and older during 1995 through 2012 |
| Exclusion criteria: | - any cancer diagnosis (excluding skin cancer) prior to their BE diagnosis |
| -no diagnosis date associated with a cancer diagnosis |
| -no enrolment information |
| -unknown sex |

| Notes: | NOS-rating: 6/8 stars |
| Author's conclusion: | Patients with BE had a persistent excess risk of oesophageal adenocarcinoma over time, although their absolute excess risks for this cancer, any cancer and overall mortality were modest. |

Outcome Measures/results: | Primary -cancer incidence (Standardised incidence ratio (SIR)) |
<p>| Secondary -Mortality (Standardised mortality) |
| Results: | Oesophageal adenocarcinoma risk was increased 24 times in the BE cohort, which translated into an excess absolute risk of 24 cases per 10 000 person years. Although oesophageal adenocarcinoma risk decreased with time since BE diagnosis, oesophageal cancer mortality... |</p>
<table>
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</thead>
<tbody>
<tr>
<td>Cohort Study</td>
<td>Funding sources: This study was funded by the Intramural Program of the National Cancer Institute, National Institutes of Health, Department of Health and Human Services and by the European Research Council-European Union’s Seventh Framework Programme.</td>
<td>Total no. patients: 255,053 individuals (128,330 males, 126,723 females)</td>
<td>Interventions: Childhood BMI (z-scores), childhood height (z-scores)</td>
</tr>
<tr>
<td></td>
<td>Conflict of Interests: The authors declare no conflict of interest.</td>
<td>Recruiting Phase: Inclusion criteria: -boys and girls born 1930 to 1971 -registered in Copenhagen School Health Records Register (CSHRR) -BMI and cancer data available at all ages -having personal ID Number</td>
<td>Comparison: -</td>
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<td></td>
<td>Randomization: Not relevant</td>
<td>Blinding: Not relevant</td>
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<td></td>
<td>Dropout rates: Not relevant</td>
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<td>Exclusion criteria: -emigrated/deseased/lost to follow-up prior to 40 years -Height or BMI measures outlier at all ages</td>
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<tr>
<td>Notes:</td>
<td>NOS rating: 7/8 stars</td>
<td>Results: During more than 5.4 million person-years of follow-up, there were 254 incident oesophageal adenocarcinoma cases (216 males and 38 females). Incidence rates increased with increasing age and with more recent birth cohorts.</td>
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<tr>
<td>Author's conclusion: Childhood BMI was associated with increased risk of oesophageal adenocarcinoma in adulthood. Whether childhood BMI is directly related to oesophageal adenocarcinoma, or associated indirectly through increased likelihood of adult obesity cannot be determined from our data. Nevertheless, our findings support lifestyle interventions targeted towards the growing number of overweight and obese children worldwide.</td>
<td>Hazard ratios of the associations between per unit increase in childhood BMI z-score and oesophageal adenocarcinoma risk: -For females and males: HRs increased from 1.14 (0.99-1.31; 95% CI; N=240,435, 241 cases) at 7 years to 1.31 (1.13-1.51; 95% CI; N= 240,913, 241 cases) per BMI z-score at the age of 13 -For females: HRs increased from 1.30 (0.90-1.87; 95% CI; N= 119,398, 34 cases) at 7 years to 1.68 (1.15-2.44; 95% CI; 120,581, 36 cases) per BMI z-score at the age of 13 -For males: HRs increased from 1.11 (0.95-1.30; 95% CI; N= 121,037, 207 cases) at 7 years to 1.25 (1.06-1.46; 95% CI; N= 120,332, 205 cases) per BMI z-score at the age of 13. HRs were not significantly different between the sexes.</td>
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<tr>
<td>Outcome Measures/results</td>
<td>Primary</td>
<td>Relationship between childhood anthropometric variables and risk of oesophageal adenocarcinoma (Cox proportional hazards regression models using age as the underlying time metric with the baseline hazard)</td>
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<td></td>
<td>Secondary</td>
<td>-birth cohort in 5-year intervals [Hazard ratios (HR)] -sex [Hazard ratios (HR)]</td>
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<tbody>
<tr>
<td>Prospective Cohort Study</td>
<td>Funding sources: The First Affiliated Hospital of Henan University of Science and Technology Endoscopy Center</td>
<td>Total no. patients: 4092</td>
<td>Interventions: Age, Sex, Geographical Area</td>
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<tr>
<td>Conflict of Interests: Not reported</td>
<td>Recruiting Phase: Patients of The First Affiliated Hospital of Henan University of Science and Technology (North China)</td>
<td></td>
<td>Comparison: 10 year age bands (20-29, 30-39, 40-49, 50-59, 60-69, 70-79, 80-89), male vs. female, rural vs. urban area</td>
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<tr>
<td>Randomization: N.r</td>
<td>Inclusion criteria: All the cases of ESCC that were diagnosed by endoscopy and histologically confirmed in the 22 years period from January 1985 to December 2006</td>
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<tr>
<td>Blinding: N.r</td>
<td>Exclusion criteria: Patients with only adenocarcinoma of the esophagogastric junction</td>
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<td>Dropout rates: N.r</td>
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Note: -excess absolute risks as the excess number of cancers per 10,000 BE person-years; risk of OC-death did not vary by time since diagnosis of BE.
### Evidence level

**Cancer Prev.** 26. 119-124. 2017


**Hazelton, W. D. et al.** The Role of Gastroesophageal Reflux and Other Factors during Progression to Esophageal Adenocarcinoma.

### Methodological Notes

**Notes:**
- NOS-rating: 5/8 stars
- Author's conclusion: In summary, our current study is the first to describe the prevalence and distribution status of ESCC in North China with a novel epidemiological approach. We found the prevalence of ESCC is higher in male and rural area patients though the overall rates decline and the median age of onset increases, which suggested that rural areas and male patients are more urgent need for the public health initiatives aimed at reducing risk factors such as unhealthy lifestyles.

### Patient characteristics

- **Primary Measures/results**
  - **Prevalence of ESCC Odds Ratio (female: male; rural: urban)**
  - **Secondary -**

### Interventions

- **Notes:**
  - Men: 77.8% [95% credibility interval (CI), 64.9%-85.6%] of the incidence trend is attributable to OF, 13.4% (95% CI, 11.4%-17.3%) to sGERD, and 8.6% (95% CI, 4.2%-13.7%) to sGERD-OF interactions.
  - Women: 32.6% (95% CI, 27.0%-39.9%) of the trend is attributable to OF, 13.6% (95% CI, 12.5%-15.9%) to sGERD, and 47.4% (95% CI, 30.7%-64.6%) to interactions. The predicted trends were compared with historical trends for obesity, smoking, and proton pump inhibitor use.

### Outcome Measures/results

- **Primary Incidence rates for EAC Odds**
- **Secondary -**

### Results

- Men: 77.8% [95% credibility interval (CI), 64.9%-85.6%] of the incidence trend is attributable to OF, 13.4% (95% CI, 11.4%-17.3%) to sGERD, and 8.6% (95% CI, 4.2%-13.7%) to sGERD-OF interactions.
- Women: 32.6% (95% CI, 27.0%-39.9%) of the trend is attributable to OF, 13.6% (95% CI, 12.5%-15.9%) to sGERD, and 47.4% (95% CI, 30.7%-64.6%) to interactions. The predicted trends were compared with historical trends for obesity, smoking, and proton pump inhibitor use.

### Interventions

- **Total no. patients:**
  - Men: 14 518 patients with esophageal cancer (735 with alcohol use disorders (AUD), 13 783 without)
  - Women: 73 504 patients with gastric cancer (641 with AUD, 72 863 without)

- **Interventions:**
  - Alcohol use
  - Comparison: no alcohol use

Evidence level: 2b
Study type: Retrospective population-based cohort study

Funding sources: PALGA Foundation
Conflict of Interests: The authors disclose no conflicts.
Randomization: N.r.
Blinding: N.r.
Dropout rates: N.r.

Total no. patients: 1579
Recruiting Phase: n=50 no-dysplasia, n=14 indefinite for dysplasia, n=161 Low grade dysplasia, n=2 high grade dysplasia, n=4 unknown

Exclusion criteria: -all histopathology reports (diagnostic codes of BE and LGD) from January 2005 to December 2010, with followup data until July 2014.

Results: - Incidence of esophageal cancer is significantly increased among AUDs compared to those without AUD (SIR = 2.24 [95%CI 2.08-2.41])
- Risk of gastric cancer is decreased in AUDs compared to those without AUD (SIR = 0.73 [95%CI 0.68-0.79] - decrease more prominent for corpus cancer in the stomach compared with cardia cancer)
- Risk of esophageal cancer is somewhat higher in women (SIR = 3.93 [95% CI 3.17-4.81]) compared to men (SIR = 2.11 [95% CI 1.95-2.28])


Evidence level: 2b
Study type: Prospective cohort study

Funding sources: Onderzoek Fonds Onverzorgde F10
Conflict of Interests: The authors declare that they have no competing of interests.
Randomization: N.r.
Blinding: N.r.
Dropout rates: N.r.

Total no. patients: 578 700
Recruiting Phase: 289 866 men 288 834 women

Incidence rate
- Incidence rate in patients with ND BE at the first follow-up endoscopy after an initially confirmed LGD diagnosis was significantly lower 2.32 (95% CI, 1.08–4.50; p < .0001) and 1.45 (95% CI, 0.53–3.21; p = .007) for HGD/EAC and EAC, respectively than in patients with confirmed and persistent LGD. In addition, patients with 2 consecutive endoscopies showing ND BE after a confirmed LGD diagnosis (29%, n = 46) developed no HGD/EAC during a follow-up of 117 patient-years.
- In patients with ND BE after an unconfirmed LGD diagnosis (n = 765) (median follow-up, 4.35 years; IQR, 2.99–5.95), the incidence rate was significantly lower 0.99 (95% CI, 0.70–1.37; P < .001) and 0.38 (95% CI, 0.21–0.63; P < .0001) per 100 person-years, respectively than in patients with unconfirmed persistent LGD diagnosis.
- History of no-dysplasia BE did not affect risk of developing HGD/EAC.

Notes: NOS-rating: 6/8 stars

Author's conclusion: We demonstrate that confirmed and persistent LGD identifies a subgroup of patients with an increased risk of malignant progression. In addition, in half of these patients LGD was no longer detected during follow-up, and one-fourth of them exhibited persistent ND BE. Therefore, we believe that endoscopic treatment of LGD BE is indicated in patients with confirmed and persistent LGD. In patients in whom confirmed LGD does not persist, it may well be that a wait and see policy is justified.
## Authors' conclusion
High BMI was associated with an increased risk of EAC and a decreased risk of ESCC. An association between high blood pressure and risk of ESCC was observed but alcohol consumption is a potential confounding factor that we were not able to adjust for in the analysis. The Metabolic Syndrome was associated with EAC but not ESCC. However this association was largely driven by the strong association between BMI and EAC. We hypothesize that this association is more likely to be explained by factors directly related to obesity than the metabolic state of the MetS, considering that no other metabolic factor than BMI was associated with EAC.

### Outcome Measures/results

<table>
<thead>
<tr>
<th>Primary</th>
<th>Relative risks (RR) for esophageal cancer related to different metabolic risk factors in quintiles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary</td>
<td>-</td>
</tr>
</tbody>
</table>

#### Results:
- **EAC:**
  - Association between BMI and risk of EAC. Highest adjusted RR for EAC were Quintiles 4 (5.19 95% CI 2.00-13.42) and 5 (7.34 95% CI 2.88-18.68)
  - Mid BP, glucose, cholesterol and triglycerides were not associated with the risk of EAC.
  - Association between the composite Metabolic Syndrome score and the risk of EAC (RR 1.56 (95% CI 1.19-2.05) per one unit increase of the composite MetS score.
- **ESCC:**
  - Association between BMI and risk of ESCC. Highest adjusted RR for ESCC were Quintiles 2 (0.50 95% CI 0.32-0.79) and 3 (0.76 95% CI 0.51-1.12)
  - Higher BMI was associated with a decreased risk of ESCC (adjusted RR for top versus bottom quintile of BMI: 0.38, 95% CI 0.23-0.62)
  - Higher mid BP was associated with an increased risk of ESCC. The adjusted RR for ESCC was 2.60 (95% CI 1.54-4.39) for top versus bottom quintile of mid BP.
  - There was no association between glucose, cholesterol and risk of ESCC
- Marginal significant association between triglycerides and risk of ESCC (RR 1.9 (95% CI, 1.01-1.40)

### Notes:
NOS-rating: 8/8 stars

**Author's conclusion:** This work is funded in part by National Institutes of Health grant NCI R01 116845 and the Texas Digestive Disease Center. MCJMS is coordinating a research group that has started working for the medical board of Erasmus University. EJK has since completion of this research.

### Funding sources:
None

### Conflict of Interests:
None

### Study type:
2b retrospective population-based study

### Evidence level:
2b

### NOS-rating:
8/8 stars

### Patients characteristics

<table>
<thead>
<tr>
<th>Total no. patients:</th>
<th>12,312 (all incident cases)</th>
</tr>
</thead>
</table>

### Interventions:

<table>
<thead>
<tr>
<th>Interventions:</th>
<th>age, sex</th>
</tr>
</thead>
</table>

### Comparisons:

<table>
<thead>
<tr>
<th>Comparison:</th>
<th>age categories (&lt;40, 40-60, &gt;60), female vs. male</th>
</tr>
</thead>
</table>


### Evidence level

<table>
<thead>
<tr>
<th>Evidence level</th>
<th>Methodical Notes</th>
<th>Patient characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>2b</td>
<td></td>
<td>Total no. patients: 12,312</td>
</tr>
</tbody>
</table>

### Conflict of Interests:
None

### Study type:
Retrospective dynamic cohort study

### Inclusion criteria:

- Patients with a diagnosis of oesophageal or stomach cancer at any time before study entry
- Patients with a diagnosis of stomach cancer within 6 months after BO diagnosis

### Exclusion criteria:

- Patients diagnosed with oesophageal adenocarcinoma at least 1 year after diagnosis of BO, demonstrating a 1-year risk of 0.09%. The observed current increase in the OAC incidence among BO patients probably reflects the increase in the incidence of BO a decade ago.

### Results:

- From the BO cases, we identified 40 (0.3%) incident OAC cases in the UK and 5 (0.4%) incident OAC cases in the NL.
- Forty-five patients in the UK (0.4%) and two patients in the NL (0.1%) were diagnosed with OAC within 1 year of BO diagnosis and were considered prevalent OAC and therefore excluded in the analysis.
- Mean age of BO diagnosis in the incident OAC cases was 67.0 years (s.d. 10.3) and mean time from BO diagnosis until OAC diagnosis was 4.2 years (s.d. 2.5).
- In the NL, incident OAC cases were diagnosed with BO at a mean age of 63.5 years (s.d. 11.3) and mean time to OAC diagnosis was 3.5 years (s.d. 0.8).
- The overall IR of OAC was 22.6/100 000 PYs in the UK and 20.1/100 000 PYs in the NL.
- In 2000, the IR of OAC was 8.9/100 000 PYs and increased 4-fold up to 38.1/100 000 PYs in 2010.
- The 1-year risk of OAC after BO diagnosis, excluding OAC cases within 1 year after BO diagnosis, was 0.086% (95% CI: 0.04–0.17) overall, 0.11% (95% CI: 0.05–0.23) for males and 0.06% (95% CI: 0.02–0.24) for females.

### Notes:
NOS-rating: 8/8 stars

**Author's conclusion:** In conclusion, the incidence rate of Barrett's oesophagus in the UK and the Netherlands has increased substantially in both males and females at the beginning of the millennium but has remained stable since then. The rise in incidence was not explained by an increase in gastroscopies. Around 0.3% of BO patients are diagnosed with oesophageal adenocarcinoma at least 1 year after diagnosis of BO, demonstrating a 1-year risk of 0.09%. The observed current increase in the OAC incidence among BO patients probably reflects the increase in the incidence of BO a decade ago.

### Outcome Measures/results

<table>
<thead>
<tr>
<th>Primary</th>
<th>Incidence Rates (IR) of BO in population of UK and the Netherlands</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary</td>
<td>-</td>
</tr>
</tbody>
</table>

| Secondary | - |

### Results:

- The annual risk of Esophageal Adenocarcinoma does not decrease over time in patients with Barrett's Esophagus.

### References:

**Cohort Study**

Center NIH DK58338. Dr El-Seraf.

**Measures/results**

**Outcome**

Notes: NOS-rating: 7/8 stars

**Author's conclusion:** “Persistence of non-neoplastic BE on multiple consecutive endoscopies was not associated with lower EAC risk. These findings argue against discontinuation of endoscopic surveillance in patients with persistent nondysplastic BE after multiple negative endoscopies.”

**Outcome Measures/results**

Primary: “The outcome of this study was the development of incident EAC a er the BE index date. We used Poisson regression models to calculate incidence rates, rate ratios, and corresponding 95% confidence intervals (CI) for EAC according to number of successive follow-up endoscopies, number of follow-up years since the index BE diagnosis date (independent of the number of follow-up endoscopies), and calendar year of BE diagnosis (FY 2004–2009).”

Secondary --

Results: **EAC incidence rates**: Among 28,561 male patients with BE, 406 developed EAC during 140,499 person-years of follow-up (median 4.9 years). EAC incidence rates increased with each additional endoscopy following a previous negative endoscopy (RR per additional endoscopy, 1.43; 95% CI, 1.25–1.64). Compared to the EAC incidence rate at the 1st follow-up EGD, the EAC incidence rate at the 5th follow-up EGD was ninefold higher (adjusted RR, 8.82; 95% CI, 4.90–15.9). EAC incidence was highest at the first year of follow-up (5.34 per 1,000 person-years); however, EAC rates starting from the second follow-up year increased during successive years of follow up. Compared to the EAC incidence rate in the 2nd year of follow-up, the EAC incidence rate was 1.5-fold higher in EGDS conducted 35 years after the index BE date (adjusted RR, 1.49; 95% CI, 1.07–2.10). In contrast, we found no significant change in EAC incidence rates by calendar year.”

**Notes:**

NOS-rating: 8/8 stars

**Author's conclusion:** In conclusion, we found significant differences in age at onset and multiple primary cancers between ESCC patients with or without a positive family history of the cancer. Younger onset age possibly stands for genetic and environmental interaction, but multiple primary cancers represent only genetic predisposition.

**Levi, Z. et al.**

**Body mass index and socioeconomic status measured in adolescence, country of origin, and the incidence of gastroesophageal adenocarcinoma in a cohort of 1 million men.**

Cancer. 119. 4086-93. 2013

**Evidence level**

2b-Cohort study

**Measures/results**

**Notes:**

NOS-rating: 8/8 stars

**Author's conclusion:** In conclusion, we found significant differences in age at onset and multiple primary cancers between ESCC patients with or without a positive family history of the cancer. Younger onset age possibly stands for genetic and environmental interaction, but multiple primary cancers represent only genetic predisposition.

**Outcome Measures/results**

Primary Incident rates (%) --

Secondary --

Results: -Of the 2 542 ESCCs analyzed, 30.13% (766/2 542) were associated with a positive and 69.87% (1 776/2 542) associated with a negative family history of ESCC and/or GCA.

- Average onset age of ESCCs associated with a positive family history (n= 766) is 51.38 years old, younger than that of 53.49 years old associated with ESCCs with a negative family history (n= 1 776).

**Notes:**

- Acquisition of family history data by self-report (risk of bias)
- No definition of negative family history of cancer

**Evidence level**

2b- Study type: Retrospective Cohort Study

**Notes:**

NOS-rating: 8/8 stars

**Author’s conclusion:** We found significant differences in age at onset and multiple primary cancers between ESCC patients with or without a positive family history of the cancer. Younger onset age possibly stands for genetic and environmental interaction, but multiple primary cancers represent only genetic predisposition.
Notes: NOS rating: 5/8 stars

- Confusing separation into EAC and GEJAC group, although previously stated that distinction between both groups is difficult outside surgical setting (?) - therefore combination of both group by authors. Resulting unclear validity of results concerning separated and combined groups
- Unclear validity of BMI results due to confounding variable classifications as dichotomous and ordinal
- No reporting on why cohort number is once stated as 1,088,530 and once as 1,088,242

Author's conclusion: Overweight during adolescence was found to be substantially associated with the subsequent development of EAC and GEJAC. In addition, although potential confounding by Helicobacter pylori infection status or lifestyle factors was not fully accounted for in the analyses, lower SES as well as immigration from higher-risk countries are important determinants of NCGC.

Outcome Measures/results


Evidence level: 2b
Study type: Cohort Study

Funding sources: N.r.  Conflict of Interests: The authors declare no conflicts of interest.  Randomization: N.r.  Blinding: N.r.  Dropout rates: N.r.  Total no. patients: N.r.  Recruiting Phase: Canadian adults aged 25+ years in 2010  Inclusion criteria: Canadian adults aged 25+ years in 2010  Exclusion criteria: N.r.  Interventions: BMI (Overweight: 25.00 - 29.99 kg/m^2; Obese: 30.00+ kg/m^2)  Comparison: N.r.

Notes: NOS-rating: 2/8 stars

BMI data is partly based on self-report (bias), partly on adjusted data on a subsample of respondents who agreed to have their height and weight measured in addition to providing self-reports. Data was pooled later on.

No report of duration of overweight/obesity - impact on cancer risk

Different sources of cancer case data were merged later on (Canadian Cancer Registry for whole Canada and Statistics Canada's website especially for Quebec) Cancer case counts for Quebec needed to be adjusted for a few cancers not directly available through Statistics Canada's website.

No assumption of no cancer risk for BMI below 25.00 kg/m^2 without evidence. Results only applicable on BMI above 25.00 kg/m^2

Author's conclusion: An estimated 5.7% (1 in 18) of all new cancer cases diagnosed in Canadian adults in 2010 were attributable to high BMI after correcting for bias in self-reported height and weight.
### Schlüsselfrage:

**AG 1 Risikofaktoren:** Wird das Ösophaguskarzinomrisiko (SCC AC) durch einen der folgenden Faktoren beeinflusst?

### Bewertungsformulare:

**NEUCASTLE - OTTAWA Checklist 3: Case Control**

<table>
<thead>
<tr>
<th>Evidence level: 3b</th>
<th>Study type: Case-control study</th>
<th>Patient characteristics</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Funding sources: The Medical Research Council provided funding for this study under a project license. The funding source had no input regarding the design, conduct, or interpretation of this study.</td>
<td>Total no. patients: 1126 cases, 4192 controls</td>
<td>Interventions: - Statin prescription - Statin duration (≥ 1 t &lt; 4 years; ≥ 4 to &lt; 6 years; ≥ 6 years)</td>
<td></td>
</tr>
<tr>
<td>Conflict of Interests: The authors disclose no conflicts.</td>
<td>Patient characteristics: EAC: 581 patients with ESCC: 1242 controls</td>
<td>Comparison: - No Statin prescription - Statin duration</td>
<td></td>
</tr>
<tr>
<td>Randomization: N.r.</td>
<td>Inclusion criteria: cases: patients with EAC, EGJA, ESCC controls: patients without a history of any cancer, according to sex, year of birth, general practice (socioeconomic status)</td>
<td>Notes: NOS-rating: 6/8 stars</td>
<td></td>
</tr>
<tr>
<td>Dropout rates: N.r.</td>
<td>Exclusion criteria: cases: participants with less than 10 months of statin use in the year before diagnosis</td>
<td>- There were too few prescriptions of individual statins to allow meaningful analysis</td>
<td></td>
</tr>
</tbody>
</table>

**Author's conclusion:** In a nested case-control analysis of a UK population-based cohort, statin use was inversely associated with histologic subtypes of esophageal cancer. Randomized controlled trials are warranted to determine whether statins have chemo-preventive effects in high-risk groups.

### Outcome Measures/results

<table>
<thead>
<tr>
<th>Primary Adjusted Odds Ratios (95% CI)</th>
<th>Secondary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Results: EAC:</td>
<td>- Regular statin prescription was inversely associated with EAC (OR = 0.58; 95% CI: 0.390.87; p = 0.009) and there was evidence of both a dose-response (p for trend = .036) and duration-response (p for trend = .005) relationship.</td>
</tr>
<tr>
<td>EGJA:</td>
<td>- Regular statin prescription was not significantly associated with EGJA (OR = 0.60; 95% CI: 0.331.11; p = .102) (Table 2), however, there was evidence of a doseresponse (p for trend = .040) and durationresponse (p for trend = .052) with borderline significance. Only high-dosage regular statin prescriptions were significantly inversely associated with EGJA (OR = 0.29; 95% CI: 0.090.92; p = .036).</td>
</tr>
<tr>
<td>ESCC:</td>
<td>- Regular statin prescription was non-significantly inversely associated with risk of ESCC (OR = 0.61; 95% CI: 0.351.06; p = .081) with borderline evidence of a doseresponse (p for trend = .057) relationship, and no significant durationresponse (p for trend = .249). Statin use for between 1 and 4 years was significantly inversely associated with ESCC (OR = 0.51 95% CI: 0.270.98; p = .045).</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Evidence level: 3b</th>
<th>Study type: Case-control study</th>
<th>Patient characteristics</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Funding sources: This study was financially supported by Extramural grant of Indian Council of Medical Research (ICMR), New Delhi</td>
<td>Total no. patients: 2367 (703 ESCC cases and 1664 controls without ESCC)</td>
<td>Interventions: - Family History of Cancer (FHC; FDRs= Parents, siblings and children; Second-degree relatives= cousins, uncles, aunts, stepsiblings)</td>
<td></td>
</tr>
<tr>
<td>Conflict of Interests: The authors declare no conflict of interest</td>
<td>SDRs: cousins, uncles, aunts, stepsiblings</td>
<td>Comparison: No FHC, FDRs, SCRs</td>
<td></td>
</tr>
<tr>
<td>Randomization: Not relevant</td>
<td>Inclusion criteria: cases:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blinding: Not relevant</td>
<td>- histopathologically confirmed ESCC - age above 18 years - no personal history of cancer controls: - hospital-based - matched for sex, age (± 5 years), place of residence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dropout rates: Not relevant</td>
<td>Exclusion criteria: controls: disease with relation to tobacco or alcohol use or affection of dietary habits of the patient (e.g. diabetes)</td>
<td>Notes: NOS-rating: 5/8 stars</td>
<td></td>
</tr>
<tr>
<td>Outcome Measures/results</td>
<td>Evidence level</td>
<td>Methodical Notes</td>
<td>Patient characteristics</td>
</tr>
<tr>
<td>--------------------------</td>
<td>---------------</td>
<td>------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td><strong>Primary</strong> ESCC risk (Adjusted Odds Ratio)</td>
<td>3b</td>
<td>Funding sources: National Natural Science &amp; Technology Pillar Program, Key Scientific and Technological Projects of Shandong Province</td>
<td>Total no. patients: 619 esophageal cancer cases (648 cases of ESCC, 63 cases of esophageal adenocarcinoma, 7 cases of other types of esophageal cancer)</td>
</tr>
<tr>
<td><strong>Secondary</strong> gene polymorphisms (Adjusted Odds Ratio)</td>
<td>3b</td>
<td>Conflict of Interests: The authors declare no competing financial interests.</td>
<td></td>
</tr>
</tbody>
</table>

Notes: NOS-rating: 5/8 stars

- no mentioning of exclusion criteria of cases, untransparent description of case recruitment
- review of section performed only by one study pathologist (risk of bias)

Author's conclusion: Our results indicate that familial aggregation of ESCC in endemic area is notable. The shared genetic susceptibility and environmental exposures, or possibly their interaction, might contribute to this phenomenon which urges future studies to explore the underlying mechanisms.

Outcome | Primary | Risk of ESCC (adjusted Odds Ratio) | Results: -excess risks of ESCC increased monotonically with the...
Increasing number of first-degree relatives reportedly afflicted with esophageal cancer

-individuals whose both parents were diagnosed with esophageal cancer had an 8-fold excess risk of ESCC, compared with those without any parents affected by esophageal cancer (adjusted OR=7.96, 95% CI: 1.74–36.32)

-increasing number of affected siblings did not seem to further increase the relative risks

-excess ESCC risks were associated with a positive family history of any cancer (Adjusted OR=1.43, 95% CI: 1.13–1.81) or digestive tract cancer (adjusted OR=1.55, 95% CI: 1.23–1.96)


Evidence level Methodological Notes Patient characteristics Interventions

Evidence level: 3b Study type: Nested case-control study Funding sources: The Upper GI Blues', CSDL Medical Research UK Conflict of Interests: The authors declare that there is no conflict of interest. Randomization: N.r. Blinding: N.r. Dropout rates: N.r. Total no. patients: 3749 Patient characteristics: BO subjects were identified from The Health Improvement Network (THIN) database. THIN database contains computerized and anonymized longitudinal records from 326 UK general practice (GP) surgeries, covering 5 million patients that are regionally and demographically representative of the UK population. Inclusion criteria: BO subjects (data record period: 1988-2004) with a minimum of 1 year of follow up, and when applicable, a minimum of 1 year between diagnosis of BO and OC cases: Subjects developing OC (oesophageal cancer) controls: Subjects who did not develop OC Exclusion criteria: Cases proven to be squamous cell carcinoma Interventions: age, gender, smoking, body mass index, medication (aspirin/nonsteroidal anti-inflammatory drugs/proton pump inhibitors, lower oesophageal sphincter relaxing and asthma drugs).

Notes: NOS-rating: 6/8 stars

-It cannot be guaranteed that medication is dispensed or taken by the patient. In some cases (e.g. b-agonist inhalers), multiple devices may be obtained but not used.

-over-the-counter medication and drugs prescribed at other institutions will not be recorded.

Author's conclusion: Progression to OAC from BO is more common among men and with increasing age. There is some evidence of smoking being associated with progression to OAC but this association was not significant on multivariate analysis. LOS-relaxing drugs do not appear to be associated with OAC development once drugs for asthma are excluded. The association of inhaled steroids with OAC development strongly suggests that it is the pathophysiology of asthma/chronic asthma or the severity of gastro oesophageal reflux necessary to cause asthma, rather the drugs themselves that are associated with progression to OAC.

Outcome Measures/results

Primary -Hazard ratios of risk of developing oesophageal adenocarcinoma from Barrett's oesophagus Secondary -

Results: Male gender was associated with progression to OAC (HR 3.06, 95% CI 1.50–6.24, p = 0.002), with 84% of those developing OAC compared with 63% of those remaining with BO.

-Increasing age (HR for each year: 1.03, 95% CI 1.01–1.05, p = 0.005) was associated with developing OAC, with a median age of 67 years (Interquartile range IQR 59–73 years) among those developing OC, compared with a median age of 63 years (IQR 52–72 years) among those who did not progress.

-Having smoked doubled the risk for progression to OAC on univariate analysis (HR 2.36, 95% CI 1.13–4.93, p = 0.023), but there was no significant association when corrected for age and gender (HR 1.99, 95% CI 0.94–4.19, p = 0.07).

-There was no association between increasing BMI and progression to OC on univariate and multivariate analyses.

-No association was seen when analysed by categorizing BMI 25 kg/m², overweight (BMI 25.1–30 kg/m²), and obese (BMI >30 kg/m²)

-No association was seen between developing OAC and the following drug classes: aspirin, NSAIDs, COX-2 inhibitors, and statins. There was also no association with iron preparations, anticholinergics, ACE-I, calcium-channel antagonists, tricyclic antidepressants, benzodiazepines, or nicorandil.

-The use of both inhaled steroids (HR 2.11, 95% CI 1.12–3.97, p = 0.021) and steroid and b-agonist combination inhalers (HR 2.54, 95% CI 1.17–5.51, p = 0.018) was associated with progression to OAC on both univariate and multivariate analysis.

-Increasing number of drugs used for asthma showed an increasing association with progression to OAC (HR 2.91, 95% CI 1.10–7.68, p = 0.031 for the use of all three examined drugs) following correction for age, gender, and smoking status.


Evidence level Methodological Notes Patient characteristics Interventions

Evidence level: 3b Study type: Nested case-control study Funding sources: Institute of Clinical Medicine, Aarhus University Hospital Denmark Conflict of Interests: None Randomization: N.r. Blinding: N.r. Dropout rates: N.r. Total no. patients: 9,883 Patient characteristics: Inclusion criteria: All patients with new diagnosis of BO from 1995 to 2009 in Denmark cases: Patients with HGD or OAC controls: no diagnosis of HGD or OAC before the diagnosis date of the patient, matched according to birth date and date of BO Exclusion criteria: Patients with a diagnosis of HGD or OAC, made before or up to 1 year after the diagnosis of BO Interventions: users of PPI (more than 2 prescriptions)

Notes: NOS-rating: 7/8 stars

-Comparison: never/rare users of PPI (less than 2 prescriptions)
<table>
<thead>
<tr>
<th>Study type</th>
<th>Outcome Measures/results</th>
<th>Study type</th>
<th>Evidence level</th>
<th>Methodological Notes</th>
<th>Patient characteristics</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>3b case-control study</td>
<td>Study type: (smoking in the development of different types of cancer in Brazil)</td>
<td>3b case-control study</td>
<td>Evidence level: 3b</td>
<td>Funding sources: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.</td>
<td>Total no. patients: 231 102</td>
<td>Interventions: gender, smoking</td>
</tr>
<tr>
<td>3b population-based case-control study</td>
<td>Study type: (Use of benzodiazepines or benzodiazepine related drugs and the risk of cancer: a population-based case-control study)</td>
<td>3b population-based case-control study</td>
<td>Evidence level: 3b</td>
<td>Funding sources: Not reported.</td>
<td>Total no. patients: 149 360</td>
<td>Interventions: Ever use and long term use of BZRD (cumulative amount of BZRD equal to/greater than 500 DDD within a period of 5 to 1 year prior to the index date). BZRD: Benzodiazepines or benzodiazepine related drugs.</td>
</tr>
</tbody>
</table>

**Notes:**
- NOS-rating: 5/8 stars
- Author's conclusion: This study confirms a high risk of developing cancer of the hypopharynx, bronchi and lung, larynx, oropharynx and oral cavity, oesophagus and bladder cancer among smokers and establishes the AF attributable to smoking in the development of different types of cancer in Brazil.

**Author's conclusion:**
In conclusion, our findings do not support a carcinogenic effect of BZRD. Most ORs were close to unity, except a few that seemingly can be explained by lifestyle confounding. We also found that the recently reported excess of cancers among BZRD users can be explained entirely by a flawed design. For other reasons than carcinogenesis, however, use of BZRD should generally be avoided, or reserved for short term use in select patient groups.

<table>
<thead>
<tr>
<th>Study type</th>
<th>Outcome Measures/results</th>
<th>Study type</th>
<th>Evidence level</th>
<th>Methodological Notes</th>
<th>Patient characteristics</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>3b hospital-based Case-Control Study</td>
<td>Study type: (Tobacco and alcohol as risk factors for oesophageal cancer in a high incidence area in South Africa. Cancer Epidemiol. 41. 113-21. 2016)</td>
<td>3b hospital-based Case-Control Study</td>
<td>Evidence level: 3b</td>
<td>Funding sources: South African Medical Research Council, The Rockefeller Foundation, Cancer Council NSW and UICC are the main funding sources.</td>
<td>Total no. patients: 670 cases; 1188 controls</td>
<td>Interventions: Tobacco use (smoking status: never vs. ever; Commercial cigarettes: never vs. ever; No. of cigarettes per day: Never vs. 1-4; Hand-rolled cigarettes: Never vs. ever; No. of hand-rolled cigarettes per day: Never vs. 1-3, 4-6, 7+; Pipe: Never vs. ever; No. of pipes per day: Never vs. 1-3, 4-6, 7+; Total Tobacco (grams per day/All smokers): Never vs. 1-7, 7.1-14, 14.5) Alcohol consumption (Alcohol consumption: Never vs. ever; Maize beer consumption per week: Never, ≤ 1 day, 2-4 days, 5-7 days; Quantity of beer consumed per week: )</td>
</tr>
</tbody>
</table>
**Conflict of Interests:** The authors declare that they have no conflict of interest.

**Randomization:** N.r.

**Blinding:** N.r.

**Dropout rates:** N.r.

---

Our study shows that 58% and 48% of oesophageal cancers were attributed to smoking and alcohol consumption respectively, therefore a substantial health benefit could be expected by efforts to reduce the prevalence of smoking and drinking. Recent data suggest that only after at least 10 years of abstaining from drinking does the risk of oesophageal cancer return to being within the risk levels for abstainers and that stopping smoking for 5 years cuts the risk by 50%. After 10 or more years since stopping both habits the relative risk is about one-tenth of that of current smokers and drinkers, but local data on this effect are unavailable.

### Outcome Measures/results

<table>
<thead>
<tr>
<th>Primary</th>
<th>Adjusted Odds Ratio (OR) for risk of developing oesophageal cancer</th>
<th>Results: Tobacco use</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Male smokers:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ever smokers (70%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>had 4-fold increased</td>
</tr>
<tr>
<td></td>
<td></td>
<td>odds compared to</td>
</tr>
<tr>
<td></td>
<td></td>
<td>never smokers (OR = 4.11, 95% CI 2.55–6.65).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Females: ever smokers had approximately 3.5-fold increased odds (OR = 3.45, 95% CI 2.47–4.82) compared to nonsmokers.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Male commercial smokers: 78% indicated smoking commercial cigarettes with ever smokers having almost 40% greater odds of developing OC (OR = 1.39, 95% CI 1.01–1.92).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Males: smoking hand-rolled cigarettes (70%) and pipe smoking (64%): Those reporting having smoked 7 or more hand-rolled cigarettes per day had 4.4-times greater odds of developing OC (OR = 4.40, 95% CI 2.35–8.24), whilst those smoking 7 or more pipes per day had a 7.72 times increased odds compared to non-smokers (95% CI 3.99–14.92).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Amongst the female smokers, 43% indicated having smoked commercial cigarettes. Females having smoked 7 or more hand-rolled cigarettes per day had 3-times greater odds of developing OC (OR = 3.14, 95% CI 1.09–9.07), whilst those smoking 7 or more pipes per day had almost 6-fold increased odds compared to nonsmokers (OR = 5.63, 95% CI 2.05–15.43).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Males and females smoking more than 14 g of tobacco per day had approximately 6-times greater odds of developing OC compared to non-smokers (Male OR = 6.27, 95% CI 3.74–10.52, female OR = 5.60, 95% CI 3.23–9.73).</td>
</tr>
</tbody>
</table>

**Alcohol use:**

- Male ever drinkers had a 3.5-fold increased odds of OC (OR = 3.48, 95% CI 1.99–6.06) and females had 2-fold increased odds (OR = 2.23, 95% CI 1.60–3.11) compared to nondrinkers.
- Males and females consuming maize beer 2–4 days per week had 4-fold increased odds compared to non-drinkers (males OR = 4.04, 95% CI 2.19–7.46; females OR = 4.29, 95% CI 2.49–7.37).
- Risk increased with the quantity of each beverage type consumed with ORs ranging between 4.00 and 5.50 for the highest quantity category, the exception being for females consuming more than 1 litre of wine per week who had 7 times greater odds of developing OC (OR = 7.10, 95% CI 3.39–14.87).
- Total ethanol consumption (representing the sum of the averages of grams of ethanol from each of beer, spirits and wine) was positively associated with OC risk with male drinkers consuming more than 52.8 g per day having almost 5-times the odds of developing OC (OR = 4.72, 95% CI 2.64–8.41) than non-drinkers.
- Male drinkers, 5-fold increased odds was observed for those consuming more than 52.8 g of ethanol per day (OR = 5.24, 95% CI 3.34–8.23).
- Lower estimated ORs were observed for lower alcohol consumption.

**Joint effects:**

- Those using more than 14 g of tobacco/day and consuming more than 371 g ethanol/week had 8.45-fold increased odds of developing oesophageal cancer (95% CI 5.51–12.96) compared to those who are both non-smokers and non-drinkers.

**PAFs:**

- The attributed fraction for both exposures (alcohol and tobacco) combined was 64%
### Evidence level: 3b

<table>
<thead>
<tr>
<th>Study type</th>
<th>Methodical Notes</th>
<th>Patient characteristics</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Series of nested case-control studies</td>
<td>Funding sources: This work was funded by the division of primary care of University of Nottingham. Unified Competing Interest from <a href="http://www.icmje.org/coi_disclosure.pdf">www.icmje.org/coi_disclosure.pdf</a> (available on request from the corresponding author) and declare no support from any additional organisation for the submitted work.</td>
<td>Total no. patients: 5364 cases, 25,101 controls</td>
<td>Interventions: exposure to bisphosphonates (alendronate, etidronate, risedronate)</td>
</tr>
<tr>
<td>Conflict of Interests: All authors have completed the Unified Competing Interest form.</td>
<td>Patient characteristics: Patients aged over or equal 50 with a diagnosis of primary gastrointestinal cancer in 1997-2011, each matched with up to five controls by age, sex, practice and calendar year.</td>
<td>Total: 59,650</td>
<td>Comparison: No exposure to bisphosphonates (alendronate, etidronate, risedronate)</td>
</tr>
<tr>
<td>Randomization: Not relevant</td>
<td>Inclusion criteria: Open cohort for patients aged over or equal 50 years and registered with the practice at some time during the study period (January 1997 to July 2011). -gastrointestinal cancers (oesophageal, gastric, colorectal) -at least two years of data before their index date to ensure the completeness of records.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blinding: Not relevant</td>
<td>Exclusion criteria: -patients aged lower 50 years -cases and controls with prescriptions for bisphosphonates licensed for any malignancies before the index date. -patients with Paget's disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dropout rates: Not relevant</td>
<td>Results: -5135 cases of oesophageal cancer cases were identified from QResearch and CPRD. -Overall bisphosphonate use was not associated with risk of oesophageal cancer in either database. Adjusted odds ratio (95% CI) for QResearch and CPRD were 0.97 (95% CI; 0.79-1.18) and 1.18 (95% CI; 0.97-1.43) for oesophageal cancer. -There were no significant associations for individual types of bisphosphonate</td>
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<td></td>
</tr>
</tbody>
</table>

### Notes:
- NOS-rating: 5/8 stars
  - selection of cases was based on the first record of a cancer while the exact origin site might have been determined only later.
  - no data available on adherence to treatment

**Author's conclusion:** In this series of population based case-control studies in two large primary care databases, exposure to bisphosphonates was not associated with an increased risk of common gastrointestinal cancers.

### Outcome Measures/results

<table>
<thead>
<tr>
<th>Primary</th>
<th>Odds ratios for incident gastrointestinal cancers (colorectal, oesophageal, gastric) and use of bisphosphonates, adjusted for smoking status, ethnicity, comorbidities, and use of other drugs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary</td>
<td>Results: -No significant difference in metformin use in patients with EAC and BE</td>
</tr>
<tr>
<td>Passed:</td>
<td>Age (OR 1.04; 95% CI 1.02-1.07), smoking (OR 2.27; 95% CI 1.28-4.02), diabetes mellitus (OR 2.15; 95% CI 1.27-3.64) were significant risk factors for the development of EAC</td>
</tr>
<tr>
<td>Metformin use did not demonstrate any statistically significant protective effect against development of esophageal adenocarcinoma. Metformin use did not demonstrate any statistically significant protective effect.</td>
<td></td>
</tr>
</tbody>
</table>

### Evidence level: 3b

<table>
<thead>
<tr>
<th>Study type</th>
<th>Methodical Notes</th>
<th>Patient characteristics</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrospective case-control study</td>
<td>Funding sources: The authors have no financial relationships to disclose.</td>
<td>Total no. patients: 583</td>
<td>Interventions: medication (metformin, statin, aspirin, proton pump inhibitor), age, BMI, alcohol use, BMI categories (&lt;25.00, 25-29.99, ≥30), no alcohol use</td>
</tr>
<tr>
<td>Conflict of Interests: The authors have no conflicts of interest to report</td>
<td>Patient characteristics: Veterans (Military veteran's hospital) 115 EAC, 468 BE, 98% men, 96% white</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomization: n.r.</td>
<td>Inclusion criteria: All patients at Military veteran's hospital (U.S.) with diagnoses of BE and EAC between 1992 and 2012</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blinding: n.r.</td>
<td>Exclusion criteria: All patients with histological diagnosis of esophageal squamous cell carcinoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dropout rates: n.r.</td>
<td>Results: -No significant difference in metformin use in patients with EAC and BE</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Notes:
- NOS-rating: 5/8 stars
  - no association analysis was conducted concerning metformin use and risk of EAC
  - no collection of data regarding duration and dosage of metformin use
  - no risk of recall bias due to data collection via chart review

**Author's conclusion:** The three independent variables that predicted progression of Barrett esophagus to esophageal adenocarcinoma in our study were older age, smoking and diabetes mellitus. Statin use showed protective effect against development of esophageal adenocarcinoma. Metformin use did not demonstrate any statistically significant protective effect.

### Outcome Measures/results

<table>
<thead>
<tr>
<th>Primary</th>
<th>Odds Ratios (OR) of risk of developing EAC -</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary</td>
<td>Results: -No significant difference in metformin use in patients with EAC and BE</td>
</tr>
<tr>
<td>Passed:</td>
<td>Age (OR 1.04; 95% CI 1.02-1.07), smoking (OR 2.27; 95% CI 1.28-4.02), diabetes mellitus (OR 2.15; 95% CI 1.27-3.64) were significant risk factors for the development of EAC</td>
</tr>
<tr>
<td>Metformin use was protective against the development of cancer (OR 0.46; 95% CI 0.28-0.75)</td>
<td></td>
</tr>
</tbody>
</table>

### Evidence level: 3b

<table>
<thead>
<tr>
<th>Study type</th>
<th>Methodical Notes</th>
<th>Patient characteristics</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case-control</td>
<td>Funding sources: This study was supported by Extramural Grant of Indian Council of Medical Research (ICMR), New Delhi. Rumaisa Rafiq</td>
<td>Total no. patients: 703 ESCC patients, 1664 controls</td>
<td>Interventions: weekly exposure to secondhand smoking</td>
</tr>
<tr>
<td>Conflict of Interests:</td>
<td>Patient characteristics:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomization:</td>
<td>Inclusion criteria: -cases: ESCC patients from Regional Cancer Centre and Department of Radiation Oncology of Sher-i-Kashmir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blinding:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dropout rates:</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Notes:
- no data available on adherence to treatment

**Author's conclusion:** This study was funded by the Indian Council of Medical Research (ICMR), New Delhi. Rumaisa Rafiq.
was supported by Department of Science and Technology (DST), New Delhi.

Conflicts of Interests: The authors have no conflicts of interest to disclose.

Randomization: N.r.

Blinding: Not reported.

Dropout rates: N.r.

Institute of Medical Sciences (SKIMS) from September 2008 to January 2012.

Controls: SKIMS, Government Medical College Hospital, and 10 district hospitals of Kashmir. Matched for cases regarding sex, age, and district of residence.

Exclusion criteria: -cases: without history of previous cancer

-Controls: Disease for which they had been admitted did not have a strong association with tobacco or alcohol consumption.

Notes: NOS-rating: 5/8 stars

-unclear if interviews were blinded to case/control status

-control group consisted of patients when disease for which they had been admitted did not have a strong association with tobacco/alcohol consumption → ESCC patients not explicitly excluded

-in group of tobacco consumers, patients who chew tobacco were also included (cultural specificity)

Author's conclusion: Our findings indicate increased risk of ESCC due to SHS exposure in dose-dependent manner. Our results may help to increase the awareness about harms of SHS, particularly in developing populations where tobacco use is on rise and ESCC incidence is high. However, more studies with a larger sample size are required before making any conclusion on the association between SHS and ESCC risk.

<table>
<thead>
<tr>
<th>Outcome Measures/results</th>
<th>Primary Odds Ratios (95% CI) for risk of ESCC development</th>
<th>Results:</th>
</tr>
</thead>
</table>
|                          |                                                          | -Secondhand smoking (SHS) in the unadjusted model increased ESCC risk (OR = 1.64; 95% CI, 1.14–2.36); however, the association was attenuated and the 95% CI included unity (OR = 1.23; 95% CI, 0.72–2.11) in the models adjusted for tobacco smoking and chewing and other potential confounding factors. The OR (95% CI) for the association between weekly exposure to secondhand smoke for >14 h and ESCC risk, compared to no exposure, was (OR = 1.91; 95% CI, 0.75–4.89).

-When analysis was limited to never tobacco users (never smokers and never chewers) the OR (95% CI) for the association between SHS and ESCC risk, in adjusted model, was (OR = 1.32; 95% CI, 0.43–4.02) (Table 2). The OR increased with a higher exposure (OR = 2.69; 95% CI, 0.75–20.65) for SHS >14 h a week versus no exposure. |
### Inhaltsverzeichnis der Evidenztabellen

**Schlüsselfrage:**

**AG 2 Diagnostik: Stellenwert endoskopischer Spezialuntersuchungen (z.B. Chromoendoskopie, NBI, Zoom etc.) (Primärdiagnostik)**

<table>
<thead>
<tr>
<th>Citation</th>
<th>Evidence Level</th>
<th>Study Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qumseya, B. J.</td>
<td>2a</td>
<td>Syst REview, Meta Analysis, 14 studies (11 RCTs) (n=843)</td>
</tr>
<tr>
<td>Sharma, P. 2013</td>
<td>1b</td>
<td>RCT - cross over within 3-8 weeks</td>
</tr>
<tr>
<td>Canto, M. I. 2014</td>
<td>1a</td>
<td>RCT</td>
</tr>
<tr>
<td>Gupta, A. 2014</td>
<td>2a</td>
<td>Systematic REview, Meta Analysis, 8 studies, n= 345 patients, n=3080 lesions</td>
</tr>
<tr>
<td>Fugazza, A. 2016</td>
<td>2a</td>
<td>Systematic REview, Meta Analysis, 102 studies (prospective, retrospective clinical studies)n=6943, 16 countries.</td>
</tr>
<tr>
<td>Chung, C. S. 2016</td>
<td>2a</td>
<td>Systematic review and meta-analysis (n= 4918 patients from 16 prospective and randomized trials)</td>
</tr>
<tr>
<td>Coletta, M. 2016</td>
<td>2a</td>
<td>Meta Analysis, 13 prospective studies (n= 1690)</td>
</tr>
</tbody>
</table>
**AG 2 Diagnostik: Stellenwert endoskopischer Spezialuntersuchungen (z.B. Chromoendoskopie, NBI, Zoom etc.) (Primärdiagnostik)**

**Evidenztabellen**

**Schlüsselfrage:**

**AG 2 Diagnostik:** Stellenwert endoskopischer Spezialuntersuchungen (z.B. Chromoendoskopie, NBI, Zoom etc.) (Primärdiagnostik)

**Bewertungsvorlage:**

**OXFORD Appraisal Sheet 1: Systematic Reviews**

<table>
<thead>
<tr>
<th>Evidence level</th>
<th>Study type</th>
<th>Population</th>
<th>Outcomes/Results</th>
<th>Literature References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence level</td>
<td>Study type</td>
<td>Population</td>
<td>Outcomes/Results</td>
<td>Literature References</td>
</tr>
</tbody>
</table>

**Evidence level/Study Types**

**Evidence level:** 2a  
**Study type:** Systematic review and meta-analysis (n=4918 patients from 16 prospective and randomized trials)

**Population:** Patients with esophageal (n=2205) and head and neck (n=1781) cancer. Image-enhanced endoscopy for detection of second primary neoplasm.

**Outcomes/Results**

**Primary:** detection of second primary neoplasm  
**Secondary:** ---

**Intervention:** Patients with esophageal (n=2205) and head and neck (n=1781) cancer. Image-enhanced endoscopy for detection of second primary neoplasm.

**Comparison:** White-light imaging (WLI), narrow band imaging (NBI), and Lugol chromoendoscopy

**Primary:** detection of second primary neoplasm

**Secondary:** ---

**Literature References**


<table>
<thead>
<tr>
<th>Evidence level/Study Types</th>
<th>Population</th>
<th>Outcomes/Results</th>
<th>Literature References</th>
<th>Methodological Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence level: 2a</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Study type: Meta Analysis, 13 prospective studies (n= 1690)</td>
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<tr>
<td>Databases: Ovid MEDLINE, Ovid Embase,Web of Science</td>
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<tr>
<td>Search period: up to March 2014</td>
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</tr>
<tr>
<td>Inclusion Criteria: (1) included adult patients 18 years of age or older, (2) reported data on the diagnostic accuracy of AAC with or without magnification (index test) for the detection of HGD/EC or SIM, (3) used histopathological assessment as the reference standard, (4) described the endoscopic and mucosal patterns of the assessed areas, or (5) performed real-time assessment of lesions or post hoc characterization of digital images or videos</td>
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<tr>
<td>Exclusion Criteria: (1) there was no description of the study design, (2) the study did not assess the diagnostic accuracy of AAC for the detection of HGD/EC or SIM, (3) the study did not use histopathological assessment as the reference standard, (4) the study did not describe the endoscopic and mucosal patterns of the assessed areas, or (5) the study did not perform real-time assessment of lesions or post hoc characterization of digital images or videos</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Intervention: Acetic acid chromoendoscopy for diagnosis</th>
<th>Primary: diagnostic accuracy in HGD/EC</th>
<th>Secondary: Diagnostic accuracy in SIM</th>
<th>Outcomes/Results</th>
<th>Literature References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparison: Histopathology</td>
<td>1. HGD/EC</td>
<td>9 studies, n=1379. Sensitivity 0.92 (95% CI, 0.83-0.97), Specificity 0.96 (95% CI, 0.85-0.99)</td>
<td>Bhandari et al, 2012, Dis Esophagus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. SIM</td>
<td>8 studies, n=516. Sensitivity 0.96 (95% CI, 0.83-0.99), Specificity 0.69 (95% CI, 0.54-0.81)</td>
<td>Ferguson et al, 2006, Am J Gastroenterol</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LR+ 25.0 (95% CI, 5.9-105.3), LR- 0.08 (95% CI, 0.04-0.18)</td>
<td>Fortun et al, 2006, Aliment Pharmacol Ther</td>
<td></td>
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<td></td>
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<td>Guelrud et al, 2001, Gastrointest Endosc</td>
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<td>Hoffman et al, 2006, Gastrointest Endosc</td>
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<td>Hoffman et al, 2014, Gastrointest Endosc</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Longcroft-Wheaton</td>
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</tr>
</tbody>
</table>

**Author's Conclusion:** AAC has

**Funding Sources:** Dr Sami is funded by an Olympus Core National Endoscopy Research Fellowship grant (RB4803), Core charity, United Kingdom.

**COI:** All other authors disclosed no financial relationships relevant to this

<table>
<thead>
<tr>
<th>Evidence level</th>
<th>Study type</th>
<th>Population</th>
<th>Outcomes/Results</th>
<th>Literature References</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>Systematic Review</td>
<td>Meta Analysis, 102 studies (prospective and retrospective clinical studies) n=6943, 16 countries.</td>
<td>Evaluation of the applicability and diagnostic yield of CLE in patients with gastrointestinal and pancreatobiliary diseases.</td>
<td>102 studies</td>
</tr>
<tr>
<td></td>
<td>Database: MEDLINE, EMBASE, Scopus, and Cochrane Oral Health Group Specialized Register</td>
<td>Comparison: histopathological diagnosis</td>
<td>Primary: sensitivity, specificity, accuracy of CLE</td>
<td>Funding Sources: no info</td>
</tr>
</tbody>
</table>

**Evidence level: 2a**
- **Study type:** Systematic Review
- **Meta Analysis:** 102 studies (prospective and retrospective clinical studies) n=6943, 16 countries.
- **Database:** MEDLINE, EMBASE, Scopus, and Cochrane Oral Health Group Specialized Register
- **Search period:** Until January 2015.
- **Inclusion Criteria:** The search was restricted to studies that were performed in humans and that were published in English. Prospective and retrospective clinical studies were both eligible for inclusion, and there were no limits based on trial duration.
- **Exclusion Criteria:** Review articles, case reports, commentaries, editorials, letters, and conference abstracts were not considered. Likewise, ex vivo studies were excluded.

**Intervention:** Evaluate the applicability and diagnostic yield of CLE in patients with gastrointestinal and pancreatobiliary diseases.

**Comparison:** Histopathological diagnosis

**Primary:** Sensitivity, specificity, accuracy of CLE

**Secondary:** None

**Results:** Esophagus
- Surveillance and evaluation of suspicious lesions, Barrett's esophagus
  - "Per lesion" meta-analysis of 7 studies.
  - Pooled sensitivity of 58% (CI95%: 52%–63%; I2: 95.2%), specificity of 90% (CI95%: 89%–91%; I2: 96.9%), Pooled positive likelihood ratio (LR) of 11.57 (CI95%: 5.38–24.89; I2: 93.7%), pooled negative LR of 0.23 (CI95%: 0.08–0.64; I2: 98%). The area under the curve was 0.978.

- "Per patient" meta-analysis based on 4 studies.
  - Pooled sensitivity of 79% (CI95%: 65%–90%; I2: 58.5%), specificity of 90% (CI95%: 85%–94%; I2: 82.9%), Pooled positive LR of 8.04 (CI95%: 2.28–28.3; I2: 63.5%), negative LR of 0.24 (CI95%: 0.08–0.89; I2: 55.4%). The area under the curve was 0.926.

- Stomach and Duodenum
  - Detection of polyps and neoplastic lesions
    - "Per lesion" meta-analysis of 3 of the included studies.
      - Pooled sensitivity of 85% (CI95%: 78%–91%; I2: 52.3%), specificity of 99% (CI95%: 98%–99%; I2: 92.9%), Pooled positive LR of 16.49 (CI95%: 1.48–183.19; I2: 96%), negative LR of 0.16 (CI95%: 0.08–0.35; I2: 57.4%). The area under the curve was 0.929. The estimated diagnostic accuracy of CLE ranged from 85% to 98.8%.

- Gastritis and gastritis metaplasia
  - "Per biopsy" meta-analysis of 6 studies were included.
    - Pooled sensitivity of 94% (CI95%: 92%–96%; I2: 54.8%), specificity of 95% (CI95%: 92%–97%; I2: 55.6%), Pooled positive LR of 17.66 (CI95%: 9.04–34.51; I2: 63.8%), negative LR of 0.07 (CI95%: 0.04–0.12; I2: 99%). The area under the curve was 0.9832.

- Helicobacter Pylori-related gastritis
  - A meta-analysis of two studies
    - Pooled sensitivity of 86% (CI95%: 76%–93%; I2: 0%), specificity of 93% (CI95%: 87%–97%; I2: 2.6%), Pooled positive LR of 11.28 (CI95%: 5.4–23.57; I2: 15.5%), negative LR of 0.16 (CI95%: 0.09–0.27; I2: 0%).

- Assessing celiac disease (intraepithelial lymphocytes and villous atrophy)
  - A meta-analysis performed on 3 studies.
    - Pooled Sensitivity of 84% (CI95%: 72%–92%; I2: 71.3%), specificity of 94% (CI95%: 85%–99%; I2: 66.4%), Pooled positive LR of 9.9 (CI95%: 2.12–46.35; I2: 53.9%), negative LR of 0.15 (CI95%: 0.04–0.52; I2: 45.2%). The area under the curve was 0.969.

- Colon
  - Dysplasia and neoplasia in IBD patients
    - A meta-analysis of 4 studies.
      - "Per lesion" sensitivity of 80% (CI95%: 61%–92%; I2: 84.5%), pooled specificity of 93% (CI95%: 9%–96%; I2: 86.3%), positive LR of 8.76 (CI95%: 1.78–44.23; I2: 71.7%).
Evidence level/Study Types | Population | Outcomes/Results | Literature References | Methodical Notes
--- | --- | --- | --- | ---
COI: There are no conflicts of interest
Study Quality: Oxford RoB table: low risk Heterogeneity: ---
Publication Bias: ----
Notes: ---


Gupta, A. et al. Utility of confocal laser endomicroscopy in identifying high-grade dysplasia and adenocarcinoma in Barrett’s esophagus. A meta-analysis of 7 studies. “per lesion” sensitivity of 83% (CI95%: 79%–87%; I2: 88.8%), pooled specificity of 90% (CI95%: 87%–92%; I2: 94.8%), Pooled positive LR of 6.65 (CI95%: 2.8–15.8; I2: 90.3%), negative LR of 0.17 (CI95%: 0.07–0.43; I2: 92%). The area under the curve was 0.9630.

Colorectal neoplasms and polyps
A meta-analysis of 7 studies.

Secondary: ---
Results: Per-lesion” analysis (7 studies) for the diagnosis of HGD/adenocarcinoma yielded a pooled sensitivity and specificity of 68% (95% CI of 64–73%, I² statistic of 96.1%) and 88% (95% CI of 87–89%, I² statistic of 95.6%), respectively. The pooled positive and negative likelihood ratios were 6.56 (95% CI of 3.61–11.90, I² statistic of 89%) and 0.24 (95% CI of 0.09–0.63, I² statistic of 98%), respectively.

Similar numbers were calculated on the basis of ‘per-patient’ basis (4 studies), which showed a pooled sensitivity and specificity of 86% (95% CI of 74–94%, I² statistic of 54%) and 83% (95% CI of 77–88%, I² statistic of 90.9%), respectively. The pooled positive and negative likelihood ratios were 5.61 (95% CI of 2.00–15.69, I² statistic of 80.5%) and 0.21 (95% CI of 0.08–0.59, I² statistic of 55.8%), respectively.

Author’s Conclusion: Our systematic review and meta-analyses suggest that CLE with targeted biopsies has good diagnostic performance in detecting HGD/adenocarcinoma in Barrett’s esophagus. The pooled positive and negative likelihood ratios were 5.61 (95% CI of 2.00–15.69, I² statistic of 80.5%) and 0.21 (95% CI of 0.08–0.59, I² statistic of 55.8%), respectively.

Author’s Conclusion: In gastrointestinal and pancreatobiliary diseases, endoscopy-associated new technologies should offer the possibility to make clear diagnosis when routine procedures make it difficult to be cost-effective with clear impact on the choice of endoscopy versus surgical therapies for macroscopic lesions and achieve early detection of malignancies in those individuals with very high risk of cancer development. CLE is one of these new technologies able to address the challenge. The overall sensitivity, specificity, accuracy, and predictive values of CLE are favorable and were often found to be superior in comparison with standard endoscopy plus histopathology. However, the widespread use of CLE remains limited by its low availability, high costs, and need for trained personnel. Moreover, there is a need for further clinical trials, including medicoeconomic evaluations, to assess the applicability and implementation of CLE in routine clinical practice, as currently very few such studies exist.

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<tr>
<th>Evidence level/Study Types</th>
<th>Population</th>
<th>Outcomes/Results</th>
<th>Literature References</th>
<th>Methodical Notes</th>
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<tr>
<td>Evidence level/Study Type: 2a</td>
<td>Study type: Systematic Review, Meta-Analysis, 14 studies (11 RCTs) (n=843)</td>
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<td>Databases: Medline and Embase</td>
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<td>Search period: The last date of search was 10/1/2012. Inclusion Criteria: (i) prospective clinical studies and randomized controlled trials; (ii) studies that were published in peer-reviewed journals; (iii) studies that had the assessment of dysplasia and/or non-invasive EAC as one of their outcomes; (iv) studies that included both WLE with random biopsy and CE (or VC) with targeted biopsies; (v) studies with extractable information regarding the diagnostic yield of WLE vs. CE (or VC). Exclusion Criteria: (i) no random biopsies were performed or if the diagnostic yield was not extractable from the study design; (ii) diagnostic yield assessment was done on a per-lesion basis with no results on a per-patient basis; (iii) if the outcome reported was intestinal metaplasia, and not dysplasia or neoplasia.</td>
<td>Intervention: White light endoscopy (WLE), random biopsies. Comparison: Advanced imaging technologies (i.e. Chromoendoscopy CE, virtual chromoendoscopy VC). Primary: Our metamer (estimate of interest was the paired-risk difference (RD), defined as the difference in yield of detection of dysplasia or cancer using advanced imaging vs WLE. Secondary: none. Results: Advanced imaging techniques increased the diagnostic yield for detection of dysplasia or cancer by 34% (95% CI, 20%-56%; P &lt; .0001) in a subgroup analysis showed that virtual chromoendoscopy significantly increased diagnostic yield of detected dysplasia or cancer by 34% (95% CI, 20%-56%; P &lt; .0001) in a subgroup analysis.</td>
<td>Sharma, M, Coriat P, Leblanc S, et al. World J Gastroenterol. 2012; Curvers WL, Herrera LA, Wallace MB, et al. Gastroenterology. 2010; Curvers WL, van Vlietseren FG, Baak LC, et al. Gastrointest Endosc. 2011; Wolfsen HC, Crook JE, Krishna M, et al. Gastroenterology. 2008; Horwath JD, Maydonovitch CL, Ramos F, et al. Am J Gastroenterol. 2008; Curvers WL, Singh R, Song LM, et al. Gut. 2008; Fortun PJ, Anagnostopoulos GK, Kaye P, et al. 2006; Ragunath K, Krasner N, Raman VS, et al. Endoscopy. 2003; Niepsuj K, Niepsuj G, Cebula W, et al. Gastrointest Endosc. 2003; Wo JM, Ray MB, Mayfield-Stokes S, et al. C Gastrointest Endosc. 2001; Canto MI, Setrakian S, Willis J, et al. Gastrointest Endosc. 2000; Kara MA, Peters FP, Rosmolen WD, et al. Endoscopy. 2005; Gossner L, Pech O, May A, et al. Funding Sources: Dr. White’s effort was supported in part by a NIDDK Career Development Award (K01 DK078154-04) and the Houston VA HSR&amp;D Center of Excellence (HFP90-020). Dr. Sharma receives funding from Grant support from Olympus, Cook and Takeda. COI: Drs. Qumseya, Wang, Uzomba, Badie, and Parasa have no conflicts to report. Study Quality: QUADAS Score (1-4), between 11-14. Heterogeneity: I2 was found to be 58%. Publication Bias: A potentially small study or publication bias was assessed using the funnel plot and classic fail-safe test. Notes:</td>
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<td>Sources:</td>
<td>Funding Sources: Dr. White’s effort was supported in part by a NIDDK Career Development Award (K01 DK078154-04) and the Houston VA HSR&amp;D Center of Excellence (HFP90-020). Dr. Sharma receives funding from Grant support from Olympus, Cook and Takeda. COI: Drs. Qumseya, Wang, Uzomba, Badie, and Parasa have no conflicts to report. Study Quality: QUADAS Score (1-4), between 11-14. Heterogeneity: I2 was found to be 58%. Publication Bias: A potentially small study or publication bias was assessed using the funnel plot and classic fail-safe test. Notes:</td>
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## Evidenztabellen

**Schlüsselfrage:**

**AG 2** *Diagnostik: Stellenwert endoskopischer Spezialuntersuchungen (z.B. Chromoendoskopie, NBI, Zoom etc.) (Primärdiagnostik)*

**Bewertungsvorlage:**

OXFORD Appraisal Sheet 2: RCT


<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention</th>
<th>Outcomes/Results</th>
<th>Methodical Notes</th>
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<tr>
<td></td>
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<td>Funding Sources: This study was funded through an ASGE research award and an investigator initiated grant from Olympus America. COI: PS has received previous grants/research support from Olympus America Inc, BARRX Medical Inc and Takeda Pharmaceutical Company Ltd. RHH serves as a consultant for Olympus America. PF serves as a consultant for Boston Scientific and Torax Medical. He has received grant/research support from Olympus Medical Systems and royalties from Elsevier. AR has received previous grant/research support from Olympus America. JJB has received previous grant/research support from BARRX Medical, Cook Medical, Olympus and Astra Zeneca. All other authors have no conflicts of interest to declare. Randomization: Patients were randomised in a 1:1 ratio using a computergenerated list of random numbers and administered by study coordinators in sealed opaque envelopes that were opened after patient enrolment and immediately before the first study procedure. Blinding: The performing endoscopists kept blinded to the patient's previous endoscopy and biopsy results Dropout Rate/ITT-Analysis: per protocol no info about drop outs Notes: registered at clinicaltrials.gov (NCT00576498), correct sample size calculation</td>
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<td></td>
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<td>Funding Sources:</td>
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**Evidence level:** 1b

**Study type:** RCT - cross over within 3-8 weeks

**Number of Patient:** 123

**Recruiting Phase:** October 2005 to April 2009

**Inclusion Criteria:** erosive oesophagitis or grossly visible nodules or lesions (>5 mm) within the BO segment suggestive of invasive OAC or contraindications to oesophageal biopsies such as anticoagulation or varices

**Exclusion Criteria:** age over the age of 18

**Study type:** RCT - cross over within 3-8 weeks

**Number of Patient:** 8

**Recruiting Phase:** October 2010 to December 2011

**Inclusion Criteria:** adults undergoing outpatient endoscopy for either routine surveillance of Barrett’s oesophagus (BE) (surveillance group) or suspected or biopsy-proven unlocalized BE-associated HGD and/or early intramuscosal ECA (neoplasia group) referred for confirmation

**Exclusion Criteria:**...
of diagnosis and/or endoscopic therapy

**Exclusion Criteria:** patients with BE ha 1cm and > 10 cm, known ECA, advanced BE lesions 2 cm or more in size, Paris classification of 0-Ip (polypoid), 0-Ib (protruding sessile), 0-IIa (flat elevated), or 0-IIb (flat), any Paris 0-IIc (superficial shallow depressed) or 0-III (excavated) lesion, esophageal strictures or altered anatomy preventing passage of the endomicroscope, allergy to fluorescein or history of any severe anaphylactic reaction, active gastrointestinal bleeding, coagulopathy or chronic anticoagulation, pregnancy, contraindications to endoscopy due to medical instability.

surveillance group (p < 0.0001) comparing HDWLE and HDWLE + eCLE. With comparable sampling of neoplastic BE (41 in HDWLE+eCLE versus 40 in HDWLE-alone) and fewer biopsies of non-neoplastic BE, there was a higher diagnostic yield for neoplasia obtained using HDWLE+eCLE+TB approach (yield 40/119 or 34%) compared to HDWLE+RB (yield 41/580 or 7%, p < 0.0001). The difference in diagnostic yield was seen mainly in the neoplasia group (45% with eCLE versus 9% for HDWLE alone, p=0.004). The diagnostic yield was higher in the surveillance group (12% versus 5%) but this did not reach statistical significance.

the addition of eCLE to HDWLE led to a 2.7-fold higher diagnostic yield for neoplasia (6/98 or 22% vs. 21/94 or 6%, p=0.002). This difference between HDWLE+eCLE+TB and HDWLE+RB was found primarily in patients with neoplasia (12/24 or 75% vs. 5/23 or 22%, p=.0004).

**Per patient analysis**

Performance Characteristics per biopsy basis

The sensitivity of the HDWLE+eCLE+TB for the in vivo detection of BE neoplasia was higher than HDWLE+RB (86% versus 10%, respectively, p < 0.0001) with comparable overall accuracy (92% versus 93%, p=0.45), despite lower specificity.

per patient analysis

the addition of eCLE imaging to HDWLE increased the sensitivity of neoplasia detection from 40% to 95% (p < 0.0001) and increased the NPV from 90% to 98% (p=0.005), with comparable accuracy.

**Clinical Impact**

Of the 94 patients in the HDWLE+eCLE group, 32 (34%) had a correct change in dysplasia grade after eCLE when compared to initial HDWLE endoscopic findings.

**Author's Conclusion:** Real time eCLE and targeted biopsy after HDWLE can improve the diagnostic yield and accuracy for neoplasia and significantly impact in vivo decision-making by altering the diagnosis and guiding therapy.

In summary, the addition of in vivo imaging with eCLE to HDWLE is associated with improved targeting of neoplasia, decrease in unnecessary mucosal biopsies, and significant change in diagnosis and management plan in BE patients. The approach of real time CLE diagnosis and imaging-guided therapy represents a potential paradigm shift in BE surveillance. Research studies are needed to address training in CLE, comparative effectiveness studies of advanced endoscopic imaging techniques, the role of imaging-guided therapy, and advances in CLE devices and contrast agents.
Inhaltsverzeichnis der Evidenztabellen

Schlüsselfrage:

AG 2 Erweiterte Diagnostik: Stellenwert des endoskopischen Ultraschalls EUS

<table>
<thead>
<tr>
<th>Citation</th>
<th>Evidence Level</th>
<th>Study Type</th>
</tr>
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<tbody>
<tr>
<td>Russell, I. T. 2013</td>
<td>1b</td>
<td>RCT</td>
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<tr>
<td>Findlay, J. M. 2015</td>
<td>1b</td>
<td>Cohort</td>
</tr>
<tr>
<td>van Rossum, P. S. 2016</td>
<td>2a-</td>
<td>Systematic Review, Meta Analysis, 23 studies, N=1281 patients.</td>
</tr>
<tr>
<td>Luo, L. N. 2016</td>
<td>2a</td>
<td>Meta Analysis, 44 studies (n=2280)</td>
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### Evidence level/Study Types

<table>
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<tr>
<th>Intervention</th>
<th>Evidence level</th>
<th>Study type</th>
<th>Population</th>
<th>Outcomes/Results</th>
<th>Literature References</th>
<th>Methodical Notes</th>
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<tbody>
<tr>
<td>Endoscopic Ultrasound</td>
<td>2a</td>
<td>Meta Analysis, 44 studies (n=2280)</td>
<td>Pathological staging</td>
<td>Primary: The overall T-staging diagnostic accuracy of EUS was 79% (95%CI: 77 to 80), and for the overall N-staging the diagnostic accuracy of EUS was 71% (95%CI: 69 to 73).</td>
<td>Luo, L. N. et al. Endoscopic Ultrasound for Preoperative Esophageal Squamous Cell Carcinoma: a Meta-Analysis. PLoS One. 11 e0158373. 2016</td>
<td></td>
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<tr>
<td>Comparison</td>
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<td>The pooled sensitivity and specificity of T1 were 77% (95%CI: 73 to 80) and 95% (95%CI: 94 to 96). Among the T1 patients, EUS had a pooled sensitivity in differentiating T1a and T1b of 84% (95%CI: 80 to 88) and 83% (95%CI: 80 to 86), and a specificity of 91% (95%CI: 88 to 94) and 89% (95%CI: 86 to 92).</td>
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<td>For the T2 stage, EUS had a pooled sensitivity of 66% (95%CI: 61 to 70) and a specificity of 88% (95%CI: 86 to 89).</td>
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<td>For T3 staging cancer, EUS had a pooled sensitivity of 87% (95%CI: 85 to 89) and a pooled specificity of 87% (95%CI: 84 to 89).</td>
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<td>To stage T4, EUS had a pooled sensitivity of 84% (95%CI: 79 to 89) and a specificity of 96% (95%CI: 95 to 97).</td>
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<td></td>
<td>The diagnostic accuracies of EUS and CT in T-staging were 77% (95%CI: 73 to 81) and 59% (95%CI: 54 to 64).</td>
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<td>The diagnostic accuracies of EUS and CT in N-staging were 71% (95%CI: 69 to 73) and 73% (95%CI: 70 to 76).</td>
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### Funding Sources:
This work was supported by the Science and Technology Plan Projects of Guangdong Province, P.R. China (No: 2012B061700076 and 2014A020212146); and Sun Yat-Sen University Cancer Center Clinical Research 308 Program and Plan Project of Guangdong Esophageal Cancer Research Institute. COI: The authors have declared that no competing interests exist.

### Study Quality:
prospective designs (43%) and retrospective designs (57%). The included studies had a median quality score.

### Heterogeneity:
I² between 22% and 91%.

### Publication Bias:
--

### Notes:

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<tr>
<th>Evidence level/Study Types</th>
<th>Population</th>
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<th>Literature References</th>
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<tr>
<td>Study type:</td>
<td>Databases: PubMed/Medline, Embase, Cochrane library</td>
<td><strong>Results:</strong> Pooled estimates for sensitivity of endoscopic biopsy after nCRT were 34.5% (95% confidence interval [CI], 26.0%-44.1%) and for specificity 91.0% (95% CI, 85.6%-94.5%). Pooled estimates for sensitivity of EUS after nCRT were 96.4% (95% CI, 91.7%-98.5%) and for specificity were 10.9% (95% CI, 3.5%-29.0%) for detecting ypT¹, and 62.0% (95% CI, 41.8%-70.5%) for detecting ypN¹, respectively. Subgroup analysis Sensitivity of endoscopic biopsy after nCRT was significantly higher for studies mainly including patients with squamous cell carcinoma (n = 5) compared with studies mainly including patients with adenocarcinoma (n = 5) (49.3% vs 23.6%, respectively; P = .001) with similar specificities (90.6% vs 88.2%, respectively; P = .633).</td>
<td>Ajiarn JA, Corea AM, Hofstetter WL, et al. Ann Oncol 2012; Yang Q, Cleary KR, Yao JC, et al. Dis Esophagus 2004; Miyata H, Yamasaki M, Takiguchi S, et al. Ann Surg 2011; Molena D, Sun HH, Badr AS, et al. Dis Esophagus 2014; Sarkaria IS, Rizk NP, Bains MS, et al. Ann Surg 2009; Schneider PM, Metzger R, Schaefer H, et al. Ann Surg 2008; Kalha I, Kaw M, Fukami N, et al. Cancer 2004; Griffin JM, Reed CE, Denlinger F.</td>
<td>Funding Sources: ---</td>
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</table>
moderate accuracy for detecting residual lymph node involvement. Based on these findings, these endoscopic modalities cannot be used to withhold surgical treatment in test-negative patients after nCRT.

Heterogeneity: --  
Publication Bias: --  
Notes: Clinical trial registration number: CRD42015016527.

Inclusion Criteria:
1. Patients with biopsy-proven oesophageal cancer, had not started treatment, were free of metastatic disease, were fit for surgery (even if not planned) and had disease, were fit for surgery.
2. Patients who were medically fit for surgery.
3. Patients with any suspicion of peritoneal metastases.
4. Patients with localised tumours and no contraindications were eligible for randomisation to EUS.

Exclusion Criteria:
Evidence of metastases or plans for palliative treatment or known to be medically unfit for surgery.

In the resulting intervention group (or ‘EUS group’), the final choice of treatment followed the EUS scan. In the resulting control group (or ‘non-EUS group’), the choice of treatment depended on the results of the completed initial staging investigations, revisited if necessary.

Comparison: no EUS.

Results:
1. Survival censored at between 12 months (for those last recruited) and 54 months.
2. Participant-reported quality of life using three questionnaires: European Quality of Life – 5 Dimensions (EQ-5D) (generic), Functional Assessment of Cancer Therapy – General (FACT-G) scale (cancer related) and FACT Additional Concerns (FACT-AC) scale (gastro-oesophageal cancer specific).
3. Process of care:
   - Changes in management plans agreed by MDTs
   - Complete resection rate, and adverse events related to EUS.

Secondary:
1. Survival reported.
2. Process of care:
   - Evidence of metastases.
   - Complete resection rate, and adverse events related to EUS.

Author’s Conclusion:
Endoscopic ultrasound significantly improves (quality-adjusted) survival, has the potential to reduce health-care resource use (not statistically significant) and is probably cost-effective (with 96% probability). We recommend research into the best time to evaluate new technologies.

**Evidenztabellen**

**Schlüsselfrage:**

AG 2 Erweiterte Diagnostik: Stellenwert des endoskopischen Ultraschalls EUS

**Bewertungsvorlage:**

NEWCASTLE - OTTAWA Checklist 4: Cohort

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<thead>
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<th>Study type:</th>
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**Conflict of Interests:** The authors declare no conflict of interest.

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<th>Randomization:</th>
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<th>Blinding:</th>
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<th>Dropout rates:</th>
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**Total no. patients:** 953

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<th>Patient characteristics</th>
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**Interventions:** Patients without unequivocal metastases on CT were - routinely staged sequentially using [18F]fluorodeoxyglucose (FDG) PET–CT, EUS and laparoscopy, with oesophagogastroduodenoscopy (OGD) for GOJ tumours and distal oesophageal tumours extending below the diaphragm.

- Neoadjuvant chemotherapy was considered for disease beyond T1 N0.

- ER was used from 2008 for possible T1a tumours.

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<th>Comparison:</th>
<th>Data development vs validation</th>
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**Notes:**

Author's conclusion: Although EUS provided additional information on T and N category, its risk outweighed potential benefit in patients with T2–T4a disease on CT. Laparoscopy seemed justified for distal oesophageal tumours of T2 or greater.

**Outcome Measures/results**

**Primary** Calculate the net benefits and risks of EUS, PET–CT and laparoscopy, their primary utilities (probability of altering management) and probability thresholds (Pt; at which test benefit equals risk), using decision theory in a development data set.

**Secondary** - Determine whether clinical, radiological and histopathological factors could be identified that were related to these endpoints, in order to generate predictive models to identify patient subgroups for selective staging.

- Refine existing staging algorithms on the basis of optimal pragmatism, maximal efficiency and minimal patient risk, evaluated using a validation data set.

**Results:** A total of 953 consecutive patients were staged following CT by [18F]FDG PET–CT (918), EUS (798) and laparoscopy (458). Of these, 829 comprised the development data set (800, 698 and 397 respectively) and 124 the validation set (118, 100 and 81).

**PET-CT**

[18F]FDG PET–CT altered management in 23.0 per cent: confirming metastases (7.1 per cent), identifying unsuspected metastases (13.0 per cent) and additional pathology (2.1 per cent), and staging synchronous cancers (0.8 per cent).

Predicting unsuspected metastases Analysis was restricted to the 700 patients with CT M0 examinations.

No factors could be used to identify patients with a probability below the Pt (0.083 per cent), that is patients in whom the risk of demonstrating metastases was sufficiently low not to justify the risk of PET–CT. Although there was zero incidence in EUS T1 disease, the 95 % CI was broad (0.6–12 per cent), suggesting that, contrary to common clinical practice, PET–CT may have utility in tumours staged by EUS as T1.

**Endoscopic ultrasonography**

In 501 patients (71.8 per cent) without possible T1 or T4b disease on CT, EUS altered management in just two (0.4 per cent). In the 81 patients with impassable tumours, EUS altered management in three (4 per cent), confirming T4b with miniprobe EUS. Excluding the 17 patients who, after EUS, underwent ER without surgical resection (in whom pN status could not be assessed), EUS was 83 per cent sensitive and 84 per cent specific for pT1N0 (PPV 83 per cent; NPV 84 per cent).

The Pt for EUS T4b disease was 2.02 per cent (based on T4 disease overall).

**Staging laparoscopy**

Some 397 patients underwent laparoscopy, and metastases were demonstrated in 28 (7.1 per cent). Metastases were demonstrated in two (4 per cent) of 54 distal oesophageal tumours not involving the GOJ endoscopically.

No factor could identify patients below the Pt (0.38 per cent).

**Refinement of existing algorithm**

As a result of the findings that the incidence of T1N0 disease on EUS among patients staged as T2–T4a by CT was minimal, and insufficient to justify the EUS test risk, it is proposed that EUS should be reserved only for patients with possible T1 or T4b disease on CT.
Validation of new endoscopic ultrasonography algorithm

Some 91 patients in the validation set underwent PET–CT and EUS. No patient was staged by EUS as having T1N0 disease among the 60 with avid nodes. Twelve had possible T4b disease on CT; seven underwent EUS refuting T4b and EUS was omitted in five.

Modelling

The optimal model for identifying T1N0 disease by EUS before PET–CT was a decision tree; this reserved EUS for those with possible T1 disease on CT, and was identical to the pragmatic CT-guided algorithm.

After PET–CT, the optimal model was a modified decision tree; this reserved EUS for patients with possible T1 disease on CT without FDG-avid nodes, or CT T2–T4a disease with SUVmax below 6·38 and length less than 3·4 cm on PET–CT.

The optimal model for identifying T4b disease by EUS was a decision tree identical to the proposed algorithm; this reserved EUS for patients with possible T4b disease on CT (100 per cent sensitivity).

Suggested staging algorithm

Based on these findings, the following staging algorithm is proposed when considering patients for resection. Following CT, EUS (with or without FNA or staging ER) should be reserved for patients with either: Tx/possible T1 disease on CT, passable at OGD; or possible T4b disease without metastases on PET–CT. For all other patients EUS can be omitted, thereby reducing risk, delay and expenditure.
Schlüsselfrage:

AG 2 Erweiterte Diagnostik: Stellenwert der PET–CT

<table>
<thead>
<tr>
<th>Citation</th>
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<tbody>
<tr>
<td>Goense, L. 2015</td>
<td>2a</td>
<td>Systematic Review, Meta Analysis, 8 studies with n=486 patients</td>
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<tr>
<td>Findlay, J. M. 2015</td>
<td>1b</td>
<td>Cohort</td>
</tr>
</tbody>
</table>
### Evidenztabellen

**Schlüsselfrage:**
AG 2 Erweiterte Diagnostik: Stellenwert der PET-CT

**Bewertungsvorlage:**
OXFORD Appraisal Sheet 1: Systematic Reviews

<table>
<thead>
<tr>
<th>Evidence level/Study Types</th>
<th>Population</th>
<th>Outcomes/Results</th>
<th>Literature References</th>
<th>Methodical Notes</th>
</tr>
</thead>
</table>

**Intervention:** Assess the diagnostic performance of 18F-FDG PET and integrated 18F-FDG PET/CT for diagnosing recurrent esophageal cancer after initial treatment with curative intent.

**Comparison:** histopathologic biopsy or clinical follow-up

**Primary:** Presence of recurrent esophageal cancer as determined by histopathologic biopsy or clinical follow-up.

**Secondary:** ---

**Results:** Pooled estimates of sensitivity and specificity for 18F-FDG PET and PET/CT in diagnosing recurrent esophageal cancer were 96% (95% confidence interval, 93%–97%) and 78% (95% confidence interval, 66%–86%), respectively. Subgroup analysis revealed no statistically significant difference in diagnostic accuracy according to type of PET scanner (standalone PET vs. integrated PET/CT) or indication of scanning (routine follow-up vs. on indication).

**Author's Conclusion:** 18F-FDG PET and PET/CT are reliable imaging modalities with a high sensitivity and moderate specificity for detecting recurrent esophageal cancer after treatment with curative intent. The use of 18F-FDG PET or PET/CT particularly allows for a minimal false-negative rate. However, histopathologic confirmation of 18F-FDG PET–or PET/CT-suspected lesions remains required, because a considerable false-positive rate is noticed.

**COI:** No potential conflict of interest relevant to this article was reported.

**Study Quality:** The quality of the included studies assessed by the QUADAS-2 tool was considered reasonable; there were few concerns with regard to the risk of bias and applicability. The risk of bias concerning patient selection was low in 7 of the included studies.

**Heterogeneity:** ---

**Publication Bias:** ---
Evidenztabellen

Schlüsselfrage:  
AG 2 Erweiterte Diagnostik: Stellenwert der PET-CT

Bewertungsvorlage:  
NEWCASTLE - OTTAWA Checklist 4: Cohort


<table>
<thead>
<tr>
<th>Evidence level</th>
<th>Methodical Notes</th>
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<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Interventions</th>
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<tbody>
<tr>
<td>Total no. patients</td>
<td></td>
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<tr>
<td>953</td>
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<tr>
<th>Interventions</th>
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<tbody>
<tr>
<td>Patients without unequivocal metastases on CT were routinely staged sequentially using [18F]fluorodeoxyglucose (FDG) PET–CT, EUS and laparoscopy, with oesophagogastroduodenoscopy (OGD) for GOJ tumours and distal oesophageal tumours extending below the diaphragm. - Neoadjuvant chemotherapy was considered for disease beyond T1 N0. - ER was used from 2008 for possible T1a tumours.</td>
</tr>
</tbody>
</table>


**Notes:**  
Author's conclusion: Although EUS provided additional information on T and N category, it's risk outweighed potential benefit in patients with T2–T4a disease on CT. Laparoscopy seemed justified for distal oesophageal tumours of T2 or greater.

**Outcome Measures/results**  
Primary Calculate the net benefits and risks of EUS, PET–CT and laparoscopy, their primary utilities (probability of altering management) and probability thresholds (Pt; at which test benefit equals risk), using decision theory in a development data set.  
Secondary - Determine whether clinical, radiological and histopathological factors could be identified that were related to these endpoints, in order to generate predictive models to identify patient subgroups for selective staging. - Refine existing staging algorithms on the basis of optimal pragmatism, maximal efficiency and minimal patient risk, evaluated using a validation data set.

**Results:** A total of 953 consecutive patients were staged following CT by [18F]FDG-PET–CT (918), EUS (798) and laparoscopy (458). Of these, 829 comprised the development data set (800, 698 and 397 respectively) and 124 the validation set (118, 100 and 81).

**PET-CT**  
[18F]FDG-PET–CT altered management in 23.0 per cent: confirming metastases (7.1 per cent), identifying unsuspected metastases (13.0 per cent) and additional pathology (2.1 per cent), and staging synchronous cancers (0.8 per cent).  
Predicting unsuspected metastases Analysis was restricted to the 700 patients with CT M0 examinations. No factors could be used to identify patients with a probability below the Pt (0-083 per cent), that is patients in whom the risk of demonstrating metastases was sufficiently low not to justify the risk of PET–CT. Although there was zero incidence in EUS T1 disease, the 95 % CI was broad (0-083-12 per cent), suggesting that, contrary to common clinical practice, PET–CT may have utility in tumours staged by EUS as T1.

**Endoscopic ultrasonography**  
In 501 patients (71.8 per cent) without possible T1 or T4b disease on CT, EUS altered management in just two (0.4 per cent). In the 81 patients with impassable tumours, EUS altered management in three (4 per cent), confirming T4b with miniprobe EUS. Excluding the 17 patients who, after EUS, underwent ER without surgical resection (in whom pN status could not be assessed), EUS was 83 per cent sensitive and 84 per cent specific for pT1N0 (PPV 83 per cent; NPV 84 per cent).

The Pt for EUS T4b disease was 2-02 per cent (based on T4 disease overall).

**Staging laparoscopy**  
Some 397 patients underwent laparoscopy, and metastases were demonstrated in 28 (7.1 per cent). Metastases were demonstrated in two (4 per cent) of 54 distal oesophageal tumours not involving the GOJ endoscopically. No factor could identify patients below the Pt (0.38 per cent).

**Refinement of existing algorithm**  
As a result of the findings that the incidence of T1N0 disease on EUS among patients staged as T2–T4a by CT was minimal, and insufficient to justify the EUS test risk, it is proposed that EUS should be reserved only for patients with possible T1 or T4b disease on CT.
Validation of new endoscopic ultrasonography algorithm

Some 91 patients in the validation set underwent PET–CT and EUS. No patient was staged by EUS as having T1N0 disease among the 60 with avid nodes. Twelve had possible T4b disease on CT; seven underwent EUS refuting T4b and EUS was omitted in five.

Modelling

The optimal model for identifying T1N0 disease by EUS before PET–CT was a decision tree; this reserved EUS for those with possible T1 disease on CT, and was identical to the pragmatic CT-guided algorithm.

After PET–CT, the optimal model was a modified decision tree; this reserved EUS for patients with possible T1 disease on CT without FDG-avid nodes, or CT T2–T4a disease with $\text{SUV}_{\text{max}}$ below 6·38 and length less than 3·4 cm on PET–CT.

The optimal model for identifying T4b disease by EUS was a decision tree identical to the proposed algorithm; this reserved EUS for patients with possible T4b disease on CT (100 per cent sensitivity).

Suggested staging algorithm

Based on these findings, the following staging algorithm is proposed when considering patients for resection. Following CT, EUS (with or without FNA or staging ER) should be reserved for patients with either: Tx/possible T1 disease on CT, passable at OGD; or possible T4b disease without metastases on PET–CT. For all other patients EUS can be omitted, thereby reducing risk, delay and expenditure.
Schlüsselfrage:

**AG 2 Pathologie: Korrelation Tumorregressionsgrad (TRG)**

<table>
<thead>
<tr>
<th>Citation</th>
<th>Evidence Level</th>
<th>Study Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Davies, A. R. 2014</td>
<td>2b</td>
<td>Prospective cohort study</td>
</tr>
<tr>
<td>Robb, Wb 2015</td>
<td>1b</td>
<td>RCT post hoc analysis</td>
</tr>
<tr>
<td>Smyth, E. C. 2016</td>
<td>1b</td>
<td>RCT, MAGIC-Trial, Sub-Study</td>
</tr>
<tr>
<td>Shapiro, J. 2017</td>
<td>1b</td>
<td>Post hoc analysis RCT</td>
</tr>
</tbody>
</table>
Evidenztabellen

Schlüsselfrage:
AG 2 Pathologie: Korrelation Tumorregressionsgrad (TRG)

Bewertungsvorlage:
OXFORD Appraisal Sheet 2: RCT


Population
Evidence level: 1b
Study type: RCT post hoc analysis
Number of Patient: 195
Recruiting Phase: 2000 until June 2009
Inclusion Criteria:
younger than 75 years - suitable for curative surgical resection with clinical stage I and II
- World Health Organization (WHO) performance status 0 or 1, - World Health Organization (WHO) treatment within 6 months of diagnosis
- curative surgical resection for EC. This has implications for the current quality criteria for downstaging but also predicts fewer LNs being identified after surgical resection for EC.

Exclusion Criteria:
---

Intervention: Neoadjuvant Chemoradiation nCRT, 5 weeks.
Comparison: Surgery alone.
Primary: Effects of nCRT on the pN status, lymph nodes resected NLNr, and lymph nodes invaded NLNi in the resected specimen
Secondary: ----
Results: RCT:
After a median follow-up of 93.6 months, the overall survival was not significantly different between the groups [hazards ratio (HR) group nCRT vs group S, 0.99; 95% confidence interval (CI): 0.69–1.40, P = 0.94]. This result, in conjunction with an in-hospital postoperative mortality that was significantly higher in the nCRT group than surgery alone (11.1% vs 3.4%, P = 0.049), meant that the trial was halted on the basis of futility and led to the conclusion that nCRT does not provide a survival benefit in stage I and II EC.

Post hoc analysis:
- nCRT resulted in tumoral downstaging (pT0, 40.7% vs 1.1%, P < 0.001), LN downstaging (pN0, 69.1% vs 47.2%, P = 0.016), and reduction in the median NLNr [16.0 (range, 0–47.0) vs 22.0 (range, 3.0–58.0), P = 0.001] and NLNi [0 (range, 0–25) vs 1.0 (range, 0–25), P = 0.001]. A good histological response (TRG1/2) in the resected esophageal specimen correlated with reduced median NLNi [0 (range, 0–10) vs 1.0 (range, 0–4), P = 0.007]. After adjustment by treatment, NLNi [hazards ratio (HR) (1–3 vs 0) 3.5, 95% confidence interval (CI): 2.3–5.5, and HR (> 3 vs 0) 3.5, 95% CI: 2.0–6.2, P < 0.001] correlated with prognosis, whereas NLNr [HR ( < 15 vs ≥ 15) 0.95, 95% CI: 0.9–2.0, P = 0.131] did not. In Poisson regression analysis, nCRT was an independent predictive variable for reduced NLNr [exp(coefficient) 0.80, 95% CI: 0.66–0.96, P = 0.018].

Author’s Conclusion:
nCRT is not only responsible for disease downstaging, but also predicts fewer LNs being identified after surgical resection for EC. This has implications for the current quality criteria for surgical resection.


Population
Evidence level: 1b
Study type: RCT, MAGIC- Trial, Sub-Study
Number of Patient: n = 330
Recruiting Phase: 1994-2002
Inclusion Criteria:
- adenocarcinoma of the stomach, gastroesophageal junction, and lower esophagus.

Exclusion Criteria:
---

Intervention: RCT: use of perioperative chemotherapy for patients with resectable adenocarcinoma of the stomach, gastroesophageal junction, and lower esophagus.

Comparison: Surgery alone.
Primary: whether pathologic response and lymph node status after neoadjuvant chemotherapy are prognostic in patients treated in the MAGIC trial.
Secondary: ----
Results: In chemotheraphy-treated patients with a TRG of 1 or 2, median OS was not reached, whereas for patients with a TRG of 3, 4, or 5, median OS was 20.47 months. On univariate analysis, high TRG and lymph node metastases were negatively related to survival (Mandard TRG 3, 4, or 5: hazard ratio [HR], 1.94; 95% CI, 1.11 to 3.39; P = .0209; lymph node metastases: HR, 3.63; 95%CI, 1.88 to 7.0; P < .001). On multivariate analysis, only lymph node status was independently predictive of OS (HR, 3.36; 95% CI, 1.70 to 6.63; P < .001).

Author’s Conclusion:
Lymph node metastases and not pathologic response to chemotherapy was the only independent predictor of survival after chemotherapy plus resection in the MAGIC trial. Prospective evaluation of whether omitting postoperative chemotherapy and/or switching to a noncross-resistant regimen in patients with lymph node-positive disease whose tumor did not respond to preoperative epirubicin, cisplatin, and fluorouracil may be appropriate.

Funding Sources:
- COI: ---
- Randomization: ----
- Blinding: ---
- Dropout Rate/ITT- Analysis: ---
- Notes: Recorded on the ClinicalTrials.gov Web site under the identifying number NCT00047112.

Original RCT:

Notes:
---

Funding Sources:
- Supported by Cancer Research UK (CEA A18052), European Union FP7 (CIG 334281), and the National Institute for Health Research (NIHR) Biomedical Research Centre (BRC) at The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research (grants A62, A100, A101) to N.V.
- A.W., and N.V. acknowledge funding from the NIHR ICR/RMH BRC.
- COI: disclosure information provided by authors
- Randomization: Two independent
pathologists using the Mandard tumor regression grading system (TRG).

**Dropout Rate/ITT-Analysis:** ---

**RCT:** ITT Notes: the results do not differentiate the individual tumor entities

No description of the original RCT.


Schlüsselbegriffe: AG 2 Pathologie: Korrelation Tumorregressionsgrad (TRG)

Evidenztabellen

AG 2 Pathologie: Korrelation Tumorregressionsgrad (TRG)

Zurück

Studientyp: Prospektive cohort study

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<th>Evidence level</th>
<th>Methodical Notes</th>
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<td>2b</td>
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</table>

Note: Criteria for inclusion or exclusion are inadequately described.

Author's conclusion: "This study indicates that tumor stage after neo-adjuvant chemotherapy determines survival in patients with adenocarcinoma of the esophagus and esophagogastric junction. The importance of tumor downstaging in terms of survival, complete surgical resection, and recurrence pattern has significant clinical implications."

Outcome Measures/results

Primary: Tumor staging: Each patient was allocated a tumor stage (cTNM) before commencement of neoadjuvant chemotherapy as decided by the multidisciplinary team. After neoadjuvant chemotherapy, patients were restaged using CT but not routinely using endoscopy, EUS, or FDG-PET. All patients underwent definitive resection; final tumor histology available for comparison (ypTNM), and analyzed by a member of a team of dedicated upper-GI histopathologists. This pathologic stage was determined using the 7th edition of the American Joint Committee on Cancer TNM staging system. Downstaging was defined as a reduction in T stage or N stage of pathologic staging (ypTNM) compared with clinical staging (cTNM). Pathologic tumor regression used a categorical scale between 1 and 5 according to Mandard.

Secondary -

Results: Downstaging Effect of Chemotherapy

Primary - neo-adjuvant chemotherapy group: 175 patients (44%) benefitted from a downstaging effect. This group of responders, compared with non-responders, had improved rates of clear surgical resection margins (R0: 74% vs 40%, respectively; P < .001) and lower rates of isolated local recurrence (6% v 13%) p = .03.

The responders also experienced lower rates of systemic metastatic recurrence compared with non-responders, both alone (19 v 29%, p < .027) and in combination with locoregional recurrence (30% v 48%, p < .001). The majority of down-staged patients had evidence of pathologic response to neoadjuvant chemotherapy (Mandard score 1-4 in 144 of 162 patients, 89%). This group of down-staged patients had significantly improved Mandard scores compared with those who were not down-staged (p < .001).

Evidenztabellen


Evidence level: 1b

Study type: Post hoc analysis RCT

Funding sources: ----

Conflict of Interests: ----

Randomization: ----

Blinding: The interobserver agreement was determined between 3 independently scoring upper-GI pathologists

Inclusion criteria: Potentially curable esophageal or junctional cancer, who were treated with neoadjuvant chemoradiotherapy (nCRT) plus surgery according to the CROSS regimen.

Interventions: from the nCRT plus surgery group: resection specimens (primary tumor and all resected lymph nodes)

Comparison: ----
Both squamous cell carcinoma and adenocarcinoma tumor types were included. **Exclusion criteria:** Patients who did not receive at least 80% of the planned dose of chemoradiotherapy, who received a different nCRT regimen or in whom surgical resection could not be completed.

**Notes:**
Original RCT not described:

**Author’s conclusion:** PrepT-stage and prepN-stage can be estimated reproducibly. Prognostic strength of prepT-stage is comparable with clinical T-stage, whereas prepN-stage is better than cN-stage. PrepNp patients who become ypN0 after nCRT have a worse survival compared with prepN0 patients. Pretreatment pathological staging should be considered useful as a new staging parameter for esophageal cancer and could also be of interest for other tumor types.

**Outcome Measures/results**

**Primary** - determine the interobserver reproducibility of this new pretreatment pathological staging system,
- compare this pretreatment pathological staging system with the pretreatment clinical staging system,
- determine the value of this new pretreatment pathological staging system for posttreatment prognostication.

**Secondary** ----

**Results:** Overall concordance for prepT-stage and prepN-stage was 0.69 and 0.84, respectively. Prognostic strength of prepT-stage was similar to clinical T-stage and worse compared with ypT-stage (DAIC 1.3 versus 2.0 and 8.9, respectively). In contrast, prognostic strength of prepN-stage was better than cN-stage and similar to ypN-stage (DAIC 17.9 versus 6.2 and 17.2, respectively). PrepNp patients who become ypN0 after nCRT have a worse survival compared with prepN0 patients, with a five year overall survival of 51% versus 68%, P < 0.019, respectively.
Schlüsselfrage:

**AG 3 Chirurgie: Art des operativen Zugangs**

<table>
<thead>
<tr>
<th>Citation</th>
<th>Evidence Level</th>
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<td>Kurokawa, Y. 2015</td>
<td>1b</td>
<td>Randomized trial</td>
</tr>
<tr>
<td>Maas, K. W. 2015</td>
<td>1b</td>
<td>Randomized clinical trial multicentric.</td>
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<tr>
<td>Straatman, J. 2017</td>
<td>1b</td>
<td>Randomized clinical trial</td>
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</tbody>
</table>
Kurokawa, Y. et al. Ten-year follow-up results of a randomized clinical trial comparing left thoracoabdominal and abdominal transhiatal approaches to total gastrectomy for adenocarcinoma of the oesophagogastric junction or gastric cardia. Br J Surg. 102. 341-8. 2015

<table>
<thead>
<tr>
<th>Evidence level: 1b Study type: Randomized trial</th>
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<tbody>
<tr>
<td>Number of Patient: 167 (82, 85 per arm)</td>
</tr>
<tr>
<td>Recruitung Phase: Between July 1995 and December 2003</td>
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<tr>
<td>27 hospitals in Japan</td>
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**Inclusion Criteria:**
- histologically confirmed ACC of the gastric body or cardia with oesophageal invasion of 3 cm or less, cT2 – 4 category
- age 75 years or less
- no distant metastasis
- no lymph nodes larger than 1 cm in the hepatoduodenal ligament or para-aortic field
- a forced expiratory volume in 1 s of at least 50 per cent
- arterial oxygen tension of at least 9.3 kPa while breathing ambient air

**Exclusion Criteria:**
none described

**Intervention:** Transhiatal surgery (TH); total gastrectomy with D2 lymphadenectomy including splenectomy. Additional dissection of the lymph nodes along the left inferior phrenic vessels and the para-aortic nodes lateral to the aorta and above the left renal vein was performed in patients with curable disease. This included patients with positive findings on peritoneal lavage cytology, but without overt peritoneal metastasis. All procedures were undertaken via laparotomy, and the lower mediastinum was accessed transhiatally. Mediastinal resection included the lower oesophagus and perioesophageal lymph nodes only.

**Comparison:** Left thoraco-abdominal surgery (LTA) An oblique incision over the left thorax and abdomen was made for the LTA approach, followed by the same procedure in the abdominal cavity as for the TH operation. In the thoracic cavity, a thorough mediastinal node dissection below the left inferior pulmonary vein was undertaken with appropriate oesophagectomy.

**Outcomes/Results**

**Primary:** Overall survival (OS).
Over 10 year follow up period.

**Secondary:** Disease-free survival (DFS), Morbidity and Mortality, Postoperative symptoms and postoperative respiratory function

**Results:**
- Median follow-up for all censored patients was 10.6 (range 5.1 – 17.1) years. There had been 52 and 63 deaths in the TH and LTA group respectively, with 42 and 50 patients respectively dying from cancer.

**Author’s Conclusion:** “LTA resections should be avoided in the treatment of adenocarcinoma of the OGJ or gastric cardia.”


<table>
<thead>
<tr>
<th>Evidence level: 1b Study type: Randomized clinical trial multicentric.</th>
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<tr>
<td>Number of Patient: 115 (56,59 per arm)</td>
</tr>
<tr>
<td>Recruitung Phase: Between June 1</td>
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</table>

**Intervention:** Patients in both groups received identical pre and postoperative treatment. For most patients, neoadjuvant treatment consisted of weekly administrations of 50 mg/m2 paclitaxel plus carboplatin and concurrent radiotherapy (54.1, 4 Gy in 23 fractions for 5 days per week). After 6–8 weeks, neoadjuvant treatment was followed by surgery by open or minimally invasive.

**Primary:** Postoperative pulmonary infection defined as clinical manifestation of pneumonia or bronchopneumonia confirmed by thoracic radiographs or CT scan and a positive sputum culture, within the first 2 weeks of surgery and during the whole stay in hospital.

**Secondary:** Short term endpoints: Postoperative complications; (e.g., anastomotic
2009 and March 31, 2011 at five centers in the Netherlands, 1 in Spain, 1 in Italy.

Inclusion Criteria:
- resectable esophageal cancer (cT1–3, N0–1, M0)
- histologically proven AC, SCC, or undifferentiated carcinoma of the intrathoracic esophagus and GEJ
- Patients were aged 18–75 years
- WHO performance status of two or less.

Exclusion Criteria:
- patients with cervical esophageal cancer or another malignancy

esophagectomy. Both procedures included a two-field esophageal resection with 3–4 cm wide gastric tube formation followed by a cervical or intrathoracic anastomosis. Open esophagectomy (OE): involved a right posterolateral thoracotomy in the lateral decubitus position with double tracheal intubation and lung block, midline laparotomy, and cervical or intrathoracic anastomosis. MIE was performed through a right thoracotomy in the prone position with a single-lumen tracheal intubation, upper abdominal laparoscopy, and cervical incision. For patients undergoing MIE with an intrathoracic anastomosis, a bronchus blocker was placed in the right bronchus to help with one-lung ventilation during anastomosis.

Results: Secondary: QoL after 1 year. Significantly better scores after 1-year follow-up for the MIE group as compared to the OE group. These differences are present in three domains: physical activity [SF36: 50 (6; 48–53) vs. 45 (3; 42–48) p = 0.003]; global health [C30: 79 (10; 76–83) vs. 67 (21; 60–75) p = 0.004]; and pain [QoL C30: 8 (9; 6–10) vs. 6 (6; 5–8) p = 0.001]. Late complications: After 1 year, 26 patients (44 %) in the MIE and 22 patients (39 %) in the OE group were diagnosed and treated for symptomatic anastomotic stenosis.

Recurrence: 32 patients died during the first year, 18(32%) in the OE group and 14(23%) in the MIE group (p = 0.314). Death was related principally to distant metastases (19 patients), without significant differences between the two groups (p = 0.167). Local recurrence was observed in three patients in the OE group (p = 0.072). overall and disease-free survival:
- No significant differences between the two groups.

Author's Conclusion: “In conclusion, this first randomized trial shows that MIE for esophageal cancer is associated with a better mid-term 1-year quality of life compared to open esophagectomy.”

Notes: Male surplus in both groups. No description of potential COI or funding sources. Primary outcome not reported, likely due to initial study that was previously published.


Population
Evidence level: 1b
Study type: Randomized clinical trial.
Number of Patient: 115 (56, 59 per arm).
Recruitment Phase:
Between June 2009 and March 2011. 5 European centers.
Inclusion Criteria:
- Patients between 18 and 75 years.
- resectable esophageal cancer (cT1–3, N0–1, M0) of intrathoracic esophagus or GEJ
- indication for neoadjuvant therapy
- ECOG performance

Intervention: Both groups: All patients received neoadjuvant treatment, mostly chemoradiotherapy according to the CROSS scheme, before resection. Both procedures included a two-field esophageal resection with a 3 to 4 cm wide gastric tube formation followed by a cervical or intrathoracic anastomosis. For patients undergoing MIS with an intrathoracic anastomosis, a bronchus blocker was placed in the right bronchus to help with one-lung ventilation during anastomosis.

Comparison: MIS: was performed through a right thoracotomy in the prone position with a single-lumen tracheal intubation, upper abdominal laparoscopy, and cervical incision. To maintain partial collapse of the right lung during thoracoscopy, the thoracic activity was insufflated with carbon dioxide at 8 mm Hg.

Outcomes/Results
Primary: Respiratory infections were defined as clinical manifestation of pneumonia or bronchopneumonia confirmed by thoracic radiographs or CT scan (assessed by independent radiologists) and a positive sputum culture, within the first 2 weeks of surgery and during the whole stay in hospital.
Secondary: surgery, peripерoperative, and postoperative-related events; such as duration of the procedure, blood loss, and conversion rate. postoperative morbidity; including reoperations and intensive care unit admission. Morbidity was registered during admission, and in the first 14 days postoperatively. long-term survival analysis.

Results: Mean age 62±8.4 years per group. Patients received nCRT according CROSS scheme (92.2%) or chemotherapy alone (7.8%).

Primary: Respiratory infections: At 2 weeks postoperatively, 5(9%) in the MIS had a pulmonary infection, versus 16(29%) in the open group (P= 0.05). Similar leakages, vocal cord paralysis confirmed by SF 36 Health Survey (version 2) and EORTC QoL questionnaires C30 and OES18 module.

Mid-term endpoints: QoL at 1 year: assessed by SF 36 and EORTC C30 and OES18 module.

Morbidity was registered during perioperative, and postoperative-stay in hospital.

Dropout Rate/ITT-Analysis:
- “Data were analysed according to the intention-to-treat principle.” Similar distribution of dropouts (less than 20% total).

Notes: Male surplus in both groups. No description of potential COI or funding sources. Primary outcome not reported, likely due to initial study that was previously published.

COI: No description.
Randomization: e used a computer-generated randomisation sequence to randomly assign patients, in a 1:1 ratio, to undergo either open or minimally invasive esophagectomy. Randomisation was stratified by study.

Blinding: No blinding was performed.

Dropout Rate/ITT-Analysis:
- “Data were analysed according to the intention-to-treat principle.” Similar distribution of dropouts (less than 20% total).

Notes: Male surplus in both groups. No description of potential COI or funding sources. Primary outcome not reported, likely due to initial study that was previously published.

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Dropout Rate/ITT-Analysis:
- “Data were analysed according to the intention-to-treat principle.” Similar distribution of dropouts (less than 20% total).

Notes: Male surplus in both groups. No description of potential COI or funding sources. Primary outcome not reported, likely due to initial study that was previously published.
status of 0, 1 or 2
- Participating surgeons performed, and had experience with, both open and minimally invasive procedures, with a minimum of 10 MIE performed before start of the trial
- Only institutions that performed more than 30 esophagectomies per year

Exclusion Criteria:
none described.

results were seen for total in-hospital pulmonary infection rates, being 7 (12%) in the minimally invasive group versus 19 (34%) in the open group (P=0.005).

Secondary: Complications: No differences were seen in complications due to the operative technique P=0.302. Survival: 3 years follow-up: No differences were observed for overall survival and disease-free survival in patients who underwent MIS compared with open esophagectomy.

Author’s Conclusion: “In conclusion, the TIME trial showed less pulmonary complications and a better QoL in the short-term follow-up for MIE. For the long-term follow up, it showed an equally safe outcome regarding survival and disease-free survival.”

participating centers, where he observed at least 2 MIE by thoracoscopy in prone position per surgeon, in order to assure quality and standardized treatment.” could potentially have a large impact on the results or introduce selection bias.
Schlüsselfrage:

AG 3 Chirurgie: Ausmaß der Lymphadenektomie

<table>
<thead>
<tr>
<th>Citation</th>
<th>Evidence Level</th>
<th>Study Type</th>
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<tr>
<td>Li, B. 2015</td>
<td>1b</td>
<td>Randomized clinical trial</td>
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</table>
### Evidence Summary

**Study Title:** A comparison of Ivor-Lewis vs Sweet esophagectomy for esophageal squamous cell carcinoma: a randomized clinical trial.

**JAMA Surg. 150. 292-8. 2015**

**Population:**

<table>
<thead>
<tr>
<th>Evidence level: 1b</th>
<th>Study type: Randomized clinical trial</th>
<th>Number of Patient: 300</th>
</tr>
</thead>
</table>

**Recruitment Phase:**

- **DESIGN,SETTING,ANDPARTICIPANTS**
  - ARandomizedclinicaltrialwas conducted from May 2010 to July 2012 at Fudan University Shanghai Cancer Center, Shanghai, China.

**Inclusion Criteria:**

- Patients with resectable disease (cT1-T3, N0-N1, and M0)
- No evidence of distant metastases
- Histologically confirmed SCC or high-grade dysplasia in the middle and lower thirds of the thoracic esophagus

**Exclusion Criteria:**

- Age older than 75 years
- Presence of enlarged lymph nodes in the upper mediastinum (>5 mm)
- History of other malignant disease
- Previous gastric or esophageal surgery
- Neoadjuvant chemotherapy or radiotherapy
- Severe major organ dysfunction
- Karnofsky Index score less than 80

**Intervention:**

<table>
<thead>
<tr>
<th>Intervention:</th>
<th>Sweet procedure: patients were placed in a right lateral decubitus position at an angle of 80°. A thoracic incision was performed through the sixth or seventh intercostal space. The diaphragm was incised to access and expose the abdominal cavity. The esophagus was mobilized and a gastric tube, about 4 cm in width, was placed along the greater curvature. The tumor was then resected with at least 5 cm of proximal clearance, and a frozen-section histological analysis of the proximal margin performed. Finally, an end-to-side esophagogastric anastomosis was fashioned with a circular staple at the sub- or supra-aortic level. Anastomosis with manual suture on the left side of the neck was performed in selected cases. A feeding tube was inserted in the jejunum and nasogastric tube position in the gastric tube.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparison:</td>
<td>Ivor-Lewis procedure: patients were placed initially supine. Through an upper midline abdominal incision, gastric tubulization was completed and feeding jejunostomy performed. Then, the patient was positioned in the left lateral decubitus, and a right thoracotomy with a muscle-sparing incision was made in the fourth intercostal space. After ligating and dissecting the azygos vein, the esophagus was resected. Then, the gastric tube was delivered into the thorax and a circular stapled end-to-side esophagogastric anastomosis was fashioned in the upper mediastinum. A nasogastric tube was also positioned in the gastric tube to prevent vomiting and acute gastric tube distension. It should be noted that thoracic duct ligation was routinely conducted in the Ivor-Lewis procedure but not in the Sweet procedure.</td>
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</tbody>
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**Outcomes/Results:**

<table>
<thead>
<tr>
<th>Primary:</th>
<th>Operative morbidity</th>
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<tr>
<td>Secondary:</td>
<td>Oncologic efficacy: number of lymph nodes resected and positive lymph nodes. Postoperative mortality: defined as death from any cause. Postoperative complications: anastomotic leak, respiratory complications (pneumonia or bronchopneumonia); cardiovascular complications (persistent arrhythmia); chylothorax; wound infections; other complications (delayed gastric emptying, pleural effusion, recurrent nerve injury).</td>
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</tbody>
</table>

**Secondary:**

- Postoperative mortality: Did not differ significantly between the 2 cohorts (3 of 150 [2.0%] in the Sweet vs 1 of 150 [0.7%] in the Ivor-Lewis groups; P=0.25).
- Postoperative complications: The incidences of anastomotic leakage, chylothorax, and pulmonary infections were numerically, but not significantly, higher in the Sweet group. Oncologic efficacy: Resection without macroscopical residual (RO/R1) was achieved in 149 of 150 patients (99.3%). A significantly higher number of lymph nodes was retrieved in the Ivor-Lewis group (median, 22; range, 8-56) compared with the Sweet group (median, 18; range, 3-51; P < .001). Dissection area: The Ivor-Lewis procedure showed superiorly in the dissection of lymph nodes both in the upper mediastinum and areas around the common hepatic and celiac arteries, whereas the number of lymph nodes retrieved in the middle/lower esophagus and perigastric regions was similar between the 2 groups. Consequently, more patients in the upper mediastinum had positive lymph nodes following the Ivor-Lewis procedure (18 of 150 [12.0%]) than the Sweet procedure (5 of 150 [3.3%]) (P=0.005). |

**Author’s Conclusion:** "Our data provide evidence for the superiority of the Ivor-Lewis esophagectomy over the Sweet procedure with regard to short-term outcomes such as lymph node retrieval and overall morbidity for patients with squamous cell cancer in the middle and lower third of the thoracic esophagus."
Schlüsselfrage: 

**AG 3 Multimodale Therapie: Verbessert eine adjuvante Radio- oder Radiochemotherapie das Überleben?**

<table>
<thead>
<tr>
<th>Citation</th>
<th>Evidence Level</th>
<th>Study Type</th>
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<tbody>
<tr>
<td>Ma, D. Y. 2014</td>
<td>1b-</td>
<td>Randomized controlled trial.</td>
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**Schlüsselfrage:**
AG 3 Multimodale Therapie: Verbessert eine adjuvante Radio- oder Radiochemotherapie das Überleben?

**Bewertungsvorlage:**
OXFORD Appraisal Sheet 2: RCT

<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention</th>
<th>Outcomes/Results</th>
<th>Methodological Notes</th>
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**Evidence level:** 1b-
**Study type:** Randomized controlled trial.
**Number of Patient:** 98 (49 per group)
**Recruiting Phase:** Between January 2002 and June 2003, from the First Hospital affiliated with North Sichuan Medical College, P.R. China
**Inclusion Criteria:** Patients with histopathologically confirmed advanced locoregional ESCC. Post operative normal liver, kidney, and bone marrow functions were demonstrated by blood tests. Good tolerance for radiotherapy or chemotherapy according to the World Health Organization performance status of 0 or 1.
**Exclusion Criteria:** “Patients who underwent neoadjuvant or adjuvant radiotherapy and/or chemotherapy were excluded from our study. In addition, those with supravacular lymph node involvement, only anastomotic stoma recurrence, or hematogenous metastases.”

**Intervention:** -Initial radical esophagectomy and lymph node dissection for ESCC with a R0 margin
-Assessment of locoregional mediastinal recurrence (confirmed by the presence of a growing irregular mass by chest CT or MRI.)

**Intervention:** group A: three-dimensional conformal radiotherapy: “The prescribed dosage for 95% PTV was calculated using 4–6 fields of the coplanar or noncoplanar 3-DCRT plan, which was determined to be 62–70 Gy/31–35 fractions. for 1 week, divided into two phases” details see paper

**Comparison:** Comparison: Group B: Concurrent chemotherapy intravenously administered cisplatin at a dose of 30 mg per m² of body-surface area weekly.

**Primary:** Overall survival [%] calculated as the time interval from initiation of treatment to death and was analyzed using the Kaplan–Meier method.

**Secondary:** Severe morbidity [%] of grade 2 or higher.

**Results:** Primary: overall survival For survivors, the median follow-up was 60 months (range, 8–63). The ITT analyses showed a median overall survival of 19 months in group A versus 35 months in group B (P=0.051 log-rank test; HR, 0.76; 95% CI, 28–34). No difference in the overall survival rate at five years between both groups (P = 0.051), the overall survival rates at 1 year and 3 years in group B were significantly better than those in group A (P = 0.032, P = 0.038).

**Mortality:** 5 (10.2%); vs 13 (26.5%) in group B, A died from distant metastases of ESCC (¥2 = 4.356, P = 0.036).

**Secondary: Morbidities and adverse effects:**
No life-threatening toxic effects were observed in either group. The adverse effects in the hematological and gastrointestinal systems in group B were obviously more common than in group A. However, there was no significant difference between the incidence of late adverse effects between both groups.

**Author’s Conclusion:** “In summary, the combined modality of 3-DCRT and chemotherapy was well tolerated compared to radiation alone and yielded superior overall survival rates in patients with postoperative recurrence of mediastinal lymph node metastases of ESCC.”

**Funding Sources:** This work was supported by Medjaden.

**COI:** The authors declare that they have no competing interests.

**Randomization:** Assignment by using “a random number table”.

**Blinding:** no blinding is mentioned, but at least partial blinding could have been achieved.

**Dropout Rate/ITT-Analysis:** The intention-to-treat analyses, no mentioning of dropouts

**Notes:** -No blinding or concealment of allocation was performed. This might not impact the primary endpoint (survival), but it is still a risk of bias and could have partially been achieved
-Only 31% female participants
-Potentially unequal treatment between groups: “In parallel with concurrent radiochemotherapy, the thymic peptide alpha1 was injected i.h. at a dose of 1.6 mg per day for 3 weeks in order to retain systemic immune function.”
Schlüsselfrage:

AG 3 Multimodale Therapie: Verbessert eine präoperative (bzw. prä- und) postoperative (fortgesetzte) Chemotherapie das Überleben?

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<tr>
<td>Zhao, Y 2014 1b</td>
<td></td>
<td>Randomized controlled trial.</td>
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**Schlüsselfrage:**
AG 3 **Multimodale Therapie:** Verbessert eine präoperative (bzw. prä- und) postoperative (fortgesetzte) Chemotherapie das Überleben?

**Bewertungsvorlage:**
OXFORD Appraisal Sheet 2: RCT


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<tr>
<td>Study type: Randomized controlled trial.</td>
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<tr>
<td>Number of Patient: 346 (175, 171 per arm).</td>
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<tr>
<td>Recruiting Phase: Between January 2005 and April 2007, in two Chinese hospitals (First Affiliated Hospital and the Second Affiliated Hospital of Xi’an Jiaotong University).</td>
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<td>Inclusion Criteria: -no evidences of previous chemotherapy or radiotherapy, Patients aged 18 years and older; WHO performance status 0 or 1 were eligible if they had histopathologically proven squamous cell carcinoma of esophagus that was considered as suitable for curative resection. The disease had to be confined to primary and regional nodes, although celiac nodal involvement (M1a) was permitted for primary tumor localized in the distal esophagus or gastroesophageal junction. Patients had to be operative candidates without excessive clinical risks and had no evidences of distant disease or involvement of tracheobronchial tree or other structures that would preclude a complete resection. Laboratory parameters included adequate bone marrow reserve consisting of a white blood cell count of more than 3500 cells/ml, platelet count of more than 100,000 cells/ml, normal liver function with total bilirubin of less than 1.5mg/100ml, and creatinine clearance of more than 60ml/min.</td>
<td>Each arm received two pre-operative cycle of chemotherapy followed by surgery. The intervention arm (arm A) received two additional cycles of PCF post surgery. Each 3-week cycle consisted of PCF: paclitaxel (100 mg per square meter of body surface area) by a 3-hour intravenous infusion on day 1, cisplatin (60 mg per square meter of body surface area) intravenously with hydration on day 1 and 5- uorouracil (700mg per square meter of body surface area) daily through day 1 to 5 by continuous intravenous infusion with a double-lumen Hickman catheter.</td>
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Comparison: Patients received two pre-operative cycles of PCF before surgery (arm B). | 

Primary: Relapse-free survival was calculated from randomization to the first event (i.e., local recurrence, distant recurrence, or death from any cause). Secondary: Overall survival: was calculated from randomization to death from any causes. Results: The median follow-up was 60 and 61 months in arm A and arm B. Before deaths, local recurrence was confirmed in 25 patients (14.2%) in arm A and 35 patients (20.5%) in arm B, and distant metastasis was confirmed in 41 patients (23.4%) in arm A and 62 patients (36.3%) in arm B. The median relapse-free survival and overall survival were 23 and 29 months in arm A versus 15 and 22 months in arm B. Comparing with arm B, arm A had the significantly higher possibility of relapse-free survival (hazard ratio for relapse, 0.62; 95% confidence interval [CI], 0.49–0.73; p < 0.001, Fig. 2A) and of overall survival (hazard ratio for death, 0.59; 95% CI, 0.59–0.95; p < 0.001, Fig. 2B). Five-year relapse-free survival rate was 35.0% (95% CI, 26.1–47.2) in arm A compared with 19.1% (95% CI, 15.3–28.7) in arm B. Five-year survival rate was 38.0% (95% CI, 29.5–43.0) in arm A compared with 22.0% (95% CI, 16.6–29.4) in arm B. | 

Author's Conclusion: "In conclusion, our results showed that perioperative chemotherapy with the regimen of PCF improved 5-year relapse-free and overall survival in patients with resectable squamous cell carcinoma of esophagus compared with preoperative che-motherapy alone. Therefore, this treatment should be considered as an option for patients with resectable squamous cell carcinoma of esophagus." |

Notes:
- COI: The authors declare no con ict of interest.
- Randomization: Randomization not specified.
- Blinding: non blinded study.
- Dropout Rate/ITT-Analysis: Intention-to-treat analysis. 3 out of 175 and 2 out of 171 patients were excluded in group A and B.
- Sources:
  - Funding: This work was supported by National Natural Science Foundation of China (No. 81301847) and the Fundamental Research Funds for the Central Universities.
  -Authors declare no con ict of interest.
Schlüsselfrage:

**AG 3 Multimodale Therapie: Verbessert eine präoperative Radiochemotherapie das Überleben?**

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<tr>
<td>Ajani, J. A. 2013</td>
<td>1b</td>
<td>Phase II Randomized controlled trial</td>
</tr>
<tr>
<td>Mariette, C. 2014</td>
<td>1b</td>
<td>Phase III randomized controlled trial, multicentric study (30 centers in France)</td>
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<tr>
<td>Klevebro, F. 2015</td>
<td>1b</td>
<td>Randomized controlled trial</td>
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<tr>
<td>Shapiro, J. 2015</td>
<td>1b</td>
<td>Randomized controlled trial</td>
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<tr>
<td>Rajabi Mashhadi, M. 2015</td>
<td>1b-</td>
<td>Randomized controlled trial</td>
</tr>
<tr>
<td>Nederlof, N. 2016</td>
<td>1b</td>
<td>Randomized controlled trial</td>
</tr>
<tr>
<td>Klevebro, F. 2016</td>
<td>1b</td>
<td>Randomized clinical trial</td>
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<tr>
<td>Stahl, M. 2017</td>
<td>1b</td>
<td>Unblinded, prospective and randomised phase III study.</td>
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### Bewertungsvorlage: OXFORD Appraisal Sheet 2: RCT

**Schlüsselfrage:**
AG 3 **Multimodale Therapie:** Verbessert eine präoperative Radiochemotherapie das Überleben?

**Evidenztabellen**


<table>
<thead>
<tr>
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</tr>
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<tbody>
<tr>
<td><strong>Evidence level:</strong> 1b</td>
<td><strong>Intervention:</strong> Neoadjuvant chemotherapy (nCT); Treatment had to be started within 2 weeks of randomization. Three cycles of cisplatin, 100 mg/m² day 1, and fluorouracil 750 mg/m²/24 h, days 1–5, were given. Each cycle lasted 21 days. The same chemotherapy regimen was administered in each treatment arm.</td>
<td><strong>Primary:</strong> Histological complete response. <strong>Secondary:</strong> Overall survival; number of lymph-node metastases; R0-resection rate; progression-free survival; site of recurrence.</td>
<td><strong>Funding Sources:</strong> This work was financially supported by the Swedish Society of Medicine, the Swedish Cancer Society, the Cancer Research Foundations of Radiumhemmet, and the Stockholm County Council, grant number not applicable. The sponsors had no involvement in the study design, data collection, or interpretation of the results.</td>
</tr>
<tr>
<td><strong>Study type:</strong> Randomized clinical trial</td>
<td><strong>Surgery:</strong> In both arms, Patients were scheduled to undergo resection 4–6 weeks after having completed neoadjuvant treatment. The protocol required two-field lymphadenectomy, and the recommended procedure was oesophagectomy with intrathoracic anastomosis through a laparotomy and a right-sided thoracotomy (Ivor Lewis procedure). A three-stage resection, with a right-sided thoracotomy, laparotomy, and cervical incision (McKeown procedure), was recommended for tumours in the middle and upper thirds of the oesophagus. Other procedures were accepted in cases where the individual surgeon considered it appropriate.</td>
<td><strong>Results:</strong> Primary: Histological complete response was achieved in 7 (9%) of the patients in the nCT arm versus 22 (28%) in the nCRT arm (P = 0.002). <strong>Secondary:</strong> Three-year overall survival: 49% in the nCT arm, and 47% in the nCRT arm (P = 0.77).</td>
<td><strong>COI:</strong> The authors have declared no conflicts of interest.</td>
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<tr>
<td><strong>Number of Patient:</strong> 181 (90 and 91 per group)</td>
<td><strong>Comparison:</strong> Neoadjuvant Radiotherapy (nCRT) In patients randomized to receive chemoradiotherapy, 40 Gy was given (2 Gy once daily in 20 fractions, 5 days a week) with a photon beam linear accelerator concomitant with chemotherapy cycles 2 and 3. A 3D dose planning system was used.</td>
<td><strong>Survival:</strong> R0 resection rate</td>
<td><strong>Randomization:</strong> No description of the randomization sequence or protocol.</td>
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<tr>
<td><strong>Recruiting Phase:</strong> The neoadjuvant chemotherapy versus chemoradiotherapy in resectable cancer of the oesophagus and gastric cardia (NeoRes) trial was performed in Norway and Sweden during the period 2006–2013.</td>
<td></td>
<td><strong>Blinding:</strong> The pathologist reviewing the surgical specimen was blinded to the randomization outcome of each individual patient.</td>
<td><strong>Notes:</strong> Randomization sequence not described; male surplus in both groups; primary outcome: histological complete response is not described</td>
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<thead>
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<tr>
<td><strong>Evidence level:</strong> 1b</td>
<td><strong>Intervention:</strong> Chemothearpy: The nCT treatment cycle was 21 days (treatment during weeks 1, 4, and 7). Cisplatin in a dose of 100 mg/m² (day 1) was given intravenously, in combination with 5-fluorouracil in the amount of 750 mg/m²/24 h (days 1e5). In patients with borderline renal function or severe renal impairment, cisplatin was replaced by oxaliplatin (130 mg/m²) in adenocarcinoma patients or with carboplatin (AUC 5) in squamous carcinoma patients. <strong>Surgery:</strong> Patients were scheduled to undergo resection 4e6 weeks after having completed neoadjuvant treatment. Protoc</td>
<td><strong>Primary:</strong> Incidence of perioperative complications: directly caused by surgery or nonsurgical complications. Severity of perioperative complications.</td>
<td><strong>Funding Sources:</strong> The Swedish Society of Medicine has financially supported the conduct of the study.</td>
</tr>
<tr>
<td><strong>Study type:</strong> Randomized controlled trial</td>
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<tr>
<td><strong>Number of Patient:</strong> 181 (91, 90 per arm)</td>
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<tr>
<td><strong>Recruiting Phase:</strong> Between 2006 and 2013, we have performed a</td>
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</table>

**Notes:** Inclusion Criteria: Patients with histologically confirmed SCC or AC of the oesophagus or GOJ (including Siewert types I and II) who were eligible for curative treatment with surgical resection were enrolled. Clinical tumour stage: T1–3, any N (with the exception of T1N0) were included, cervical cancers were required to be resectable without laryngectomy.

**Exclusion Criteria:** none described.
randomized controlled trial, the \textit{Neoadjuvant Chemoradiotherapy versus Surgery alone in Resectable Cancer of the Esophagus and Gastric Cardia Trial (NeoRes)}.

\textbf{Inclusion Criteria:} All patients with histologically confirmed, non-distant metastatic SCC or AC of the esophagus or GOJ, considered to tolerate esophagectomy, were eligible for inclusion. Tumours located anywhere in the oesophagus or Siewert types I and II junctional tumours were included, although cervical cancers were excluded.

Study participants were allowed to be no more than 75 years of age, considered fit for oesophagectomy, and have a WHO performance status of 0 or 1. All patients were also required to be suitable for chemotherapy and concomitant radiotherapy in terms of adequate renal and haematological functions. Using TNM-6, patients with T1e3, any N (with the exception of T1N0) without evidence of distant metastatic disease, were eligible for inclusion.

\textbf{Exclusion Criteria:} Manifestations of major heart disease within the last year or within the last five years contained the CTV and additional proximal, metastatic SCC or AC of the esophagus or GOJ.

In addition to the same patients (98, 97 per arm). Centers in France).

\textbf{Recruiting Phase:} From June 2000 to June 2009.

\textbf{Inclusion Criteria:} Patients age < 75 years,

\textbf{Case Control:} After having completed neoadjuvant treatment. All participating centres performed esophagectomies regularly, and the protocol required two-field lymphadenectomy. The recommended procedure was transthoracic oesophagectomy with intrathoracic anastomosis through a right-sided thoracotomy (Ivor-Lewis) for distal oesophageal and junctional cancers. Three-stage resection with neck anastomosis (McKeown) was recommended for tumours in the mid oesophagus and the upper third of the oesophagus.

\textbf{Comparison: Chemoradiotherapy:} In addition to the same chemotherapy as in the nCT group, patients in the nCRT group also received external beam radiation to a total dose of 40 Gy, delivered in 2 Gy fractions five days per week, starting day one (week 4) of the second chemotherapy cycle and ending at the completion of the third chemotherapy cycle (week 7). All dose planning was performed with a CT-based three-dimensional planning system with inhomogeneity correction. Dose level to heart, lung, and spinal cord was minimized using the multiple-field technique. During the radiation therapy, patients were assessed for adverse events at least once every week.

\textbf{Study participants were assessed for adverse events at least once every week.}

\textbf{Exclusion Criteria:} Manifestations of major heart disease within the last year or within the last five years contained the CTV and additional proximal, metastatic SCC or AC of the esophagus or GOJ.

\textbf{Recruiting Phase:} From June 2000 to June 2009.

\textbf{Inclusion Criteria:} Patients age < 75 years,
judged suitable for curative resection, with untreated stage I or II (T1 or T2, N0 or N1 and T3N0, M0) thoracic esophageal adenocarcinoma or squamous cell carcinoma, as assessed by computed tomography (CT) scan and endoscopic ultrasound (EUS), were included. All patients were required to be capable of receiving either treatment, with WHO performance status of 0 or 1.

Exclusion Criteria: Reasons for patient exclusion included weight loss > 10% at baseline and respiratory, liver, or cardiac insufficiency. Patients with a previously treated malignancy, evidence of supraclavicular or celiac nodes, a multifocal tumor, a tumor with a proximal margin < 19 cm from the tracheal bifurcation, or with anastomosis was mandatory when the proximal margin was above the carina. All patients received chemotherapy after finishing NCRT, including physical re-evaluation 2 to 4 weeks after surgery alone will be treated asap after in-hospital postop mortality

Primary: 30 days postoperative complications:

Definition according to the National Cancer Institute's Common Terminology Criteria for Adverse events, v. 4.0. Severity of complications: Grading of complications using the Common Terminology Criteria for Adverse events, v. 4.0.

Secondary: Subgroup analysis of complications:

- Anastomotic leakage
- Pulmonary complications
- Cardiac complications
- Thromboembolic events
- Chyle leakage
- Wound infections

Results: Primary: Complications: Grade 3 or 4 complications were seen in 43% of patients in NCRT versus 49% of patients after surgery alone (p = 0.049). The overall rate of DFS did not differ between groups (HR for group CRT versus group S, 0.99; 95% CI, 0.69 to 1.40; P = 0.84).

Secondary: DFS: In the overall population, recurrent disease was observed in 71 patients (36.4% in group CRT vs 44.3% in group S; P = 0.02). Locoregional recurrence was diagnosed in 43 patients (22.1% in group CRT vs 28.9% in group S; P = 0.02), whereas distant recurrence was diagnosed in 50 patients (26.6% in group CRT vs 28.9% in group S; P = 0.31).

Median DFS was 27.8 months (95% CI, 15.0 to 42.9) and 26.7 months (95% CI, 22.9 to 41.1), and 5-year DFS was 35.6% (95% CI, 25.9% to 45.4%) and 27.7% (95% CI, 19.8% to 34.7%), respectively. In groups CRT and S, DFS did not differ between patients (HR for group CRT vs group S, 0.92; 95% CI, 0.66 to 1.30; P = 0.648).

Postoperative morbidity and mortality similar between groups (55.6% vs 52.8%; P = 0.72); R0 resection was significantly higher in the CRT group (11.1% vs 3.4%; P = 0.049).

Author’s Conclusion: “Compared with surgery alone, NCRT with cisplatin plus fluorouracil does not improve R0 resection rates or survival but enhances perioperative mortality in patients with stage I or II EC.”


Population

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<tr>
<th>Intervention</th>
<th>Methodical Notes</th>
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<tr>
<td>Chemotherapy regimen</td>
<td>Paclitaxel 50 mg/m² and Carboplatin AUC = 6 will be given by intravenous infusion on days 1, 8, 15, 22 and 29. All patients receiving NCRT, and 24 hours after finishing NCRT, will be given an initial dose of carboplatin of 750 mg/m² for 24 hours. After the completion of NCRT in group CRT, and within 4 weeks of random assignment in group S. A total dose of 41.4 Gy will be delivered by intravenous infusion on days 1, 8, 15, 22 and 29. All patients receiving chemotherapy will receive half an hour before the first cycle of chemotherapy. The patient will receive 23 fractions of 1.8 Gy, 5 fractions per week, starting the first day of the first cycle of chemotherapy. All patients will be radiated by external beam radiation, using 3-D conformal radiation technique. The patient will be positioned in supine position.</td>
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esophageal junction, a transthoracic approach with a two-field lymph node dissection or a transhiatal approach can be performed depending on both patient characteristics and local expertise. For distal tumors involving the gastro-esophageal junction a transhiatal esophageal resection is preferred. 0.37). There was no statistically significant difference for grade II–V complications. Severity of complications: There was no statistically significant difference in the CCI between both groups. Median CCI in the combined treatment group was 26.22 (IQR 17.28–42.43) compared with 25.74 (IQR 8.66–43.01) in the surgery alone group (p = 0.58).

Secondary: Subgroup analysis of complications In subgroup analyses of the specific complications, CCI for patients who developed an anastomotic leak was not statistically different between groups: 8.66 [8.66–33.73] vs. 8.66 [8.66–33.73] (p = 0.78). The same was true for the other subgroups with patients who developed pulmonary or cardiac complications, thromboembolic event, chyle leakage, or wound infection.

Author's Conclusion: "Neoadjuvant chemoradiotherapy according to CROSS did not have a negative impact on postoperative complication severity expressed by CCI compared with patients who underwent surgery alone for potentially curable esophageal or junctional cancer."
The primary end-point was in three groups: 0% was described.

Exclusion Criteria: Past or current history of malignancy other than the oesophageal malignancy, previous chemotherapy and/or radiotherapy, and weight loss of more than 10% of the original bodyweight.

Inclusion Criteria: Patients up to 70 years old, histologically proven (type I to III Siewert's classification) untreated locally advanced malignancy of the oesophagogastric junction; locally advanced oesophageal malignancy other than the oesophagus or adenocarcinoma of the oesophagus or adenocarcinoma subtypes. Neoadjuvant chemoradiotherapy according to CROSS followed by surgical resection should be viewed as a standard of care for patients with resectable locally advanced oesophageal or junctional cancer.

Author's Conclusion: "In conclusion, chemoradiotherapy according to the CROSS regimen improves long-term overall and progression-free survival in patients with oesophageal and junctional cancer. This improvement is statistically significant and clinically relevant for both squamous cell carcinoma and adenocarcinoma subtypes. Neoadjuvant chemoradiotherapy according to CROSS followed by surgical resection should be viewed as a standard of care for patients with resectable locally advanced oesophageal or junctional cancer."

Funding Sources: This research was supported by grants from Ortho Biotech (Janssen) and from Baxter for funding companies had no role in the study design, data analysis, data interpretation or writing of the report.

There were no tests for differences in group demographics. The chemoradiotherapy regimen in group B consists of the induction chemotherapy regimen in group A plus additional radio and chemotherapy. The differences in observed effect might not be solely related to the addition of radiotherapy. Male surplus in both arms.


**Evidence level:** 1b
**Study type:** Unblinded, prospective and randomised phase III study.

**Number of Patient:** 126, (59, 60 per arm) from 19 German centres.

**Recruiting Phase:** Between November 2000 and December 2005.

**Inclusion Criteria:** Patients up to 70 years old, histologically proven (type I to III Siewert's classification) untreated locally advanced malignancy of the oesophagogastric junction; locally advanced oesophageal malignancy other than the oesophagus or adenocarcinoma of the oesophagus or adenocarcinoma subtypes. Neoadjuvant chemoradiotherapy according to CROSS followed by surgical resection should be viewed as a standard of care for patients with resectable locally advanced oesophageal or junctional cancer.

**Intervention:** Arm A: Patients received 12 applications of peroperative chemoradiotherapy with weekly 5-fluorouracil (2000 mg/m², 24 h infusion)/folinic acid (500 mg/m², 2 h infusion) and biweekly cisplatin (50 mg/m², 1 h infusion), within 14 weeks, followed by another 3-weekly applications.

**Comparison:** Arm B: Patients received the same 14-weeks peroperative chemotherapy for induction, followed by a 3-week course of combined CRT with cisplatin (50 mg/m², 1 h infusion, days 2 and 8) and etoposide (80 mg/m², 1 h infusion, days 3e5). A total dose of 30 Gy was applied, using 15 fractions of 2 Gy within 3 weeks.

**Primary:** Overall survival: The primary end-point of the study was overall survival at 3 years which was calculated from the date of randomisation to the date of death or to the last day of follow-up.

**Secondary:** Progression-free survival was defined as the interval from randomisation to disease progression at any site or to death from any cause.

**Notes:** No blinding was performed; male surplus in both study arms, time between immediate surgery and surgery after chemoradiotherapy (29 days regimen + 4-6 weeks) might influence comparability.

**Funding Sources:** This research was supported by grants from Ortho Biotech (Janssen) and from Baxter for supporting the conducting and monitoring the study. The funding companies had no role in the study design, data analysis, data interpreta- tion or the writing of the report.

**COI:** None declared.

**Randomization:** "Randomisation was done centrally at the Institute for Medical Informatics, Biometry and Epidemiology, University of Duisburg-Essen, Germany."

**Blinding:** No blinding was performed.

**Response Rate/ITT-Analysis:** Data analysis was done according to the intention-to-treat principle.

**Notes:** No tests for differences in group demographics are displayed. The chemoradiotherapy regimen in group B consists of the induction chemotherapy regimen in group A plus additional radio and chemotherapy. The differences in observed effect might not be solely related to the addition of radiotherapy. Male surplus in both arms.


**Evidence level:** 1b
**Study type:** Phase II Randomized controlled trial

**Number of Patient:** 126 (63 per group)

**Intervention:** Arm A: consisted of preoperative chemoradiation: Patients received 50.4 Gy of proton photon (intensity modulated) radiation in 28 fractions.

**Response rate (pathCR):** In three groups: 0% of tumor cells (pathCR), 1%-50%, 51%-100% tumor cells.

**Primary: Primary:** Pathological complete response rate (pathCR)

**Secondary:** Secondary: Disease free survival

**Notes:** No blinding was performed.

**Funding Sources:** The trial was partly supported by Sanofi Oncology, NJ and partly funded by the Sultan.
Concurrently, patients received fluorouracil (250 mg/m²/daily as 24-hour infusion from Monday to Friday for 5 weeks) and oxaliplatin (40 mg/m² intravenously once a week for five doses).

Author's Conclusion: In conclusion, our data demonstrate that the use of induction chemotherapy before chemoradiation may not meaningfully increase the rate of pathCR, almost certainly does not increase 30-day surgical mortality, does not prolong OS, does not increase the rate of surgical complications, and is associated with no significant increase in grade 3 or 4 toxic effects. Based on the results of this first randomized study addressing this strategy, we cannot recommend the use of induction chemotherapy in trimodality-eligible patients undergoing therapy.

Results: Primary: PathCR: 7 (11% of 63 randomized) in Arm A achieved a pathCR, compared with 14 (22% of 63 randomized) in Arm B (P = 0.094, Fisher’s exact test).

Secondary: Overall survival: The median actuarial OS for all patients (54 deaths) was 45.62 months (95% CI 27.63–NA), with median OS 45.62 months (95% CI 25.56–NA) in Arm A and 43.68 months (95% CI 27.63–NA) in Arm B (P = 0.69).

Comparison: Arm B induction chemotherapy followed by full protocol of Arm A Induction chemotherapy: up to 8 weeks, with each 4-week cycle consisting of oxaliplatin 100 mg/m² on days 1 and 15 and fluorouracil 2200 mg/m² over 48 h as infusion starting on days 1 and 15. This particular regimen was a modification of a colon regimen and agreed upon by the Sponsor. A maximum of two cycles (four doses) were administered.

Intervention: Chemoradiotherapy: Group A patients received chemoradiotherapy and cisplatin followed by 50 Gy radiation and then undergoing surgery 3–4 weeks later (see comparison). The proximal field of radiation therapy was 5–7 cm to the tumor and the distal field was adjacent to L1.

Comparison: Surgery: Group B included 50 patients undergoing surgery only. Patients underwent undertake transhiatal esophagectomy, and the stomach was used as a conduit.

Results: Primary: Post-operative complications: Anastomotic site leakage; Pulmonary complications (atelectasis, pneumonia, emphysema, and pulmonary insufficiency); Chylothorax; Cardiovascular; Secondary: 30-day Mortality; perioperative blood loss, time of surgery number of lymph nodes resected.

Results: Primary: Complications:

- Anastomosis site leakage was detected in none of the patients in the group receiving NACR plus surgery and one patient in the surgery-only group, although the difference was not statistically significant (P>0.05).
- Pulmonary complications were observed in four patients in each of the groups, with no significant difference between the two groups (P>0.99).
- Chylothorax was observed in two cases in Group A and one case in Group B (P>0.99).
- Cardiovascular: In Group A, five patients developed post-operative accidents (myocardial infarction [MI] in three patients and arrhythmia requiring...
treatment in two patients). In Group B, six patients showed complications (three cases of MI and three cases of arrhythmia). Two patients from Group A and three patients from Group B developed deep vein thrombosis (DVT) and underwent appropriate treatment.

**Secondary:** Mortality In the first 30 days after surgery, mortalities occurred in 4 patients in the nCRT group (two MI complications and 2 pulmonary embolism) and in 3 patients in the surgery group (2 MI and 1 pulmonary embolism).

Significant differences (p<0.05) between the two groups were identified in terms of time of surgery (185±20 and 175±25 in group A and B), perioperative blood loss (405cc±25 and 390cc±15 in group A and B), and number of lymph nodes resected (5±2 and 7±2 in group A and B).

**Author's Conclusion:** "There was no significant difference between the groups receiving or not receiving NACR in terms of early side effects of transhiatal esophagectomy for esophageal SCC. Only the emergence of chylothorax in the group receiving NACR was higher. Therefore, the use of NACR does not cause an increase in early post-operative complications."
Schlüsselfrage:

AG 3 Multimodale Therapie: Stellenwert und Indikation der definitiven Radiochemotherapie

<table>
<thead>
<tr>
<th>Citation</th>
<th>Evidence Level</th>
<th>Study Type</th>
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<tr>
<td>Teoh, A. Y. 20131b-</td>
<td>1b-</td>
<td>prospective multicentered randomized controlled study</td>
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#### Population
- **Inclusion Criteria:**
  - Patients <75 years with resectable mid-or lower thoracic esophageal SCC.
  - Staging workup included esophagoscopy, bronchoscopy for mid thoracic tumor, EUS, CT of thorax and abdomen with contrast of normal organs. Target volume length defined as macroscopic clearance of the esophageal tumor.

#### Intervention:
- **Primary:** 2-year overall survival.
- **Secondary:** 5-year overall survival, disease-free survival.

#### Outcomes/Results
- **Results:**
  - The median follow-up time was 93 months (95% CI 83.65–102.36).
  - **Primary:**
    - 2-year overall survival: The difference was, however, insignificant (P = 0.147).
    - 5-year disease-free survival showed a trend to significance favoring CRT, with surgery being 25% (95% CI 15.9–42.9) in the surgery group and 50% (95% CI 32.5–64.7) in the CRT group. The difference was, however, insignificant (P = 0.068).
  - **Secondary:**
    - Overall 5-year survival: Being 25% (95% CI 12.06–37.54) and CRT being 47.2% (95% CI 32.5–64.7, P = 0.068).

- **Recurrence:**
  - The mean (SD) time to recurrence was 481.88 (424.39) days in the surgery group and 525.74 (790.83) days in the CRT group (P = 0.219). The patterns of recurrences in both groups were similar. About 31.8% of the patients in the CRT group suffered from mediastinal and abdominal lymph nodes. The difference was, however, insignificant (P = 0.147). The patterns of recurrences in both groups were similar. About 31.8% of the patients in the CRT group suffered from mediastinal and abdominal lymph nodes. The difference was, however, insignificant (P = 0.147).

- **Notes:**
  - In conclusion, definitive CRT for squamous esophageal carcinoma resulted in comparable long-term survival to surgery. Further large-scale studies would be required to confirm the results of the current study and to further investigate the role of CRT in node-positive patients.

#### Funding Sources:
- This work was supported by the Research Grant Council of Hong Kong Special Administrative Region, China.

#### COI:
- The authors have declared no conflicts of interest.

#### Randomization:
- Sequence not described, no centralized randomization.

#### Blinding:
- Non blinded study.

#### Dropout Rate/ITT-Analysis:
- "Statistical analyses were carried out according to the intention-to-treat principle."

#### Notes:
- No description of randomization sequence
- Randomization was not centralized
- No information on age or gender in the characteristics
- Tests for group differences are not mentioned.
Schlüsselfrage:

AG 4 Palliative Therapie: Indikation, Nutzen und Schaden der palliativen Chemotherapie

<table>
<thead>
<tr>
<th>Citation</th>
<th>Evidence Level</th>
<th>Study Type</th>
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<tbody>
<tr>
<td>Hall, P. S. 2017</td>
<td>1b-</td>
<td>Randomised phase II trial</td>
</tr>
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</table>

### Population
- **Inclusion Criteria:**
  - Patients aged 75 years (range 50–87).
  - For the primary outcome evaluation, analysis was performed.
  - Both regimens were administered as a 1:1 ratio using a central telephone randomisation service. Stratified permuted block randomisation was used with the stratification factors age (p75 vs 475 years) and the presence of distant metastases (yes vs no).

### Intervention
- **Primary:**
  - EOX regimen was identical to EOX.
  - OX is the preferred regimen.

### Results
- **Overall:**
  - Median overall survival was 7.1 months. Median OS was 8.1, 9.5 and 3.6 months for patients receiving EOX, OX and X, respectively.

### Secondary:
- **PFS:** Overall, median PFS was 4.4 months. Median PFS was 5.4, 5.6 and 3.0 months for patients receiving EOX, OX and X.

### Blooming
- **No blindling performed.**

### Dropout
- **Rate/ITT Analysis:**
  - No description of dropouts, no mention of analysis principle or ITT.

### Notes
- **With similar treatment regimens at least partial blinding could have been performed; allocation is also not masked.** No tests for group differences are described. No mention of dropouts, analysis principle or ITT. Lack of description and reporting reduce the confidence in the primary outcome (recruitment rate achievable).
for further study. Overall treatment utility shows promise as a comparator between treatment regimens for feasibility and randomised trials in the elderly and/or frail GO cancer population.