User Group Clinical Guideline Services

Leitlinienprogramm Onkologie

1913 DGVS Deutsche Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten

Evidenztabellen für die Version 3 der S3-Leitlinie Diagnostik und Therapie der Plattenepithelkarzinome und Adenokarzinome des Ösophagus

Inhaltsverzeichnis

04 Erweiterte Diagnostik - Endoskopischer Ultraschall

Inhalt: *3 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
de Gouw, Djjm 2019	1	Systematic review and meta-analysis
Eyck, B. M. 2019	1	Systematic Review and Meta-analysis
Qumseya, B. J. 2018	1	Systematic review and meta-analysis.

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

de Gouw, Djjm et al. Detecting Pathological Complete Response in Esophageal Cancer after Neoadjuvant Therapy Based on Imaging Techniques: A Diagnostic Systematic Review and Meta-Analysis. J Thorac Oncol. 14. 1156-1171. 2019

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: Systematic review and meta-analysis Databases: Medline, Embase, and Cochrane Library Search period: 01.2000 - 12.2017 Inclusion Criteria: Studies were considered eligible when imaging results	Population: 57 studies involving 3660 esophageal cancer patients were included. Imaging techniques used to diagnose ypCR: CT 8, PET-CT 35, EUS 15, MRI 3 studies). In general, studies had a retrospective design and included an uninterrupted series of patients. Intervention: imaging techniques (MRI, CT, PET-CT, EUS)	Primary: The primary outcome was the accuracy of predicting ypCR after neoadjuvant therapy compared with the final histopathological results after resection. Secondary: Primary Tumor Response, Diagnostic Accuracy: Regional Lymph Node Response, Subgroup and Sensitivity Analyses.	56 studies, see article.

of restaging were reported after neoadjuvant therapy and before surgery in patients with esophageal cancer.
Only studies in which patients were treated with curative intent, consisting of neoadjuvant chemotherapy and/or radiotherapy followed by esophageal resection
and lymph node dissection, were included. Studies addressing a combination of diagnostic modalities (imaging and nonimaging) were included only if separate data on the imaging test was available.

Exclusion Criteria: Studies without comparison with histopathological or imaging tests that were performed during neoadjuvant treatment were excluded. Other reviews, case reports, conference abstracts, and studies with fewer than 10 patients were excluded. Publications before the year 2000 were excluded to ensure that the review would represent contemporary imaging techniques.

Funding Sources: not described.

COI: The authors declare no conflicts.

Comparison: Histopathology

Results: **Diagnostic Accuracy: complete response** The pooledsensitivities of CT, PET-CT, EUS, and MRI for detecting ypCR were 0.35, 0.62, 0.01 and 0.80, respectively, whereas the pooled specificities were 0.83, 0.73, 0.99,and 0.83, respectively. The positive predictive value indetecting ypCR was 0.47 for CT, 0.41 for PET-CT, notapplicable for EUS, and 0.61 for MRI.

Author's Conclusion: Current imaging modalities such as CT, PET-CT, and EUS seem to be insufficiently accurate to identify complete responders. More accurate diagnostic tests are needed to improve restaging accuracy for patients with esophageal cancer.

Methodical Notes

Study Quality: The methodological quality of each study was assessed by the Cochrane Quality Assessment of Diagnostic Accuracy Studies, version 2, model.

Heterogeneity: not investigated.

Publication Bias: not investigated.

Notes:
Evidence level 1: Systematic review and meta-analysis.
Publication bias and heterogeneity not investigated.

Eyck, B. M. et al. Accuracy of Detecting Residual Disease After Neoadjuvant Chemoradiotherapy for Esophageal Cancer: A Systematic Review and Meta-analysis. Ann Surg. . . 2019

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: Systematic Review and Meta-analysis Databases: Embase, Medline, Cochrane, and Web-of-Science Search period: Inception until 02/2018 Inclusion Criteria: (1) the study population consisted of patients with adenocarcinoma or squamous cell carcinoma of the esophagus or esophago-gastric junction;	Population: Esophageal cancer patients after neoadjuvant chemoradiotherapy. 65 articles comprising one or more index tests of interest were included for qualitative analysis. Endoscopic biopsies by 13 articles, EUS by 16 articles, and PET(-CT) by 40 articles. 21 studies were excluded from quantitative synthesis because a pathological response criterion other than pCR was used or because <4 studies were included that evaluated the same index test or the same combination of index tests. 44 studies were included for	Primary: Accuracy of detecting residual disease after neoadjuvant chemoradiotherapy for esophageal cancer. Secondary: Results: Pooled sensitivities and specificities were 33% and 95% for endoscopic biopsies, 96% and 8% for qualitative EUS, 74% and 52% for qualitative PET, 69% and 72% for PETSUVmax, and 73% and 63% for PET-%DSUVmax. For detecting residual nodal	44 Studies were included. See article for list.

(2) endoscopic biopsy, EUS, and/or 18F FDG PET(-CT) were investigated; (3) the index tests evaluated detection of residual disease after nCRT at the primary tumor site or in regional lymph nodes; (4) histopathological examination of the surgical resection specimen was used as reference standard; and (5) the study contained sufficient data for construction of a 2 X 2 contingency table.

Exclusion Criteria: Studies written in other languages than English, conference abstracts, letters to the editor, editorials, reviews, and studies including<10 patients were excluded. Also, studies reporting on cervical esophageal cancer only were excluded because the current standard of care with curative intent for these tumors is definitive chemoradiotherapy.

quantitative synthesis, comprising 6 index test modalities.

Intervention: Endoscopic biopsies, EUS, and 18F-FDG PET(-CT).

Comparison:

disease, 11 studies evaluated qualitative EUS with a pooled sensitivity and specificity of 68% and 57%, respectively. In subgroup analyses, sensitivity of PET-%DSUVmax and EUS for nodal disease was higher in squamous cell carcinoma than adenocarcinoma.

Author's Conclusion: Current literature suggests insufficient accuracy of endoscopic biopsies, EUS, and 18F-FDG PET(-CT) as single modalities for detecting residual disease after nCRT for esophageal cancer.

Methodical Notes

Funding Sources: No means of funding were received for this contribution.

COI: The authors declare no conflicts of interest.

Study Quality: The quality of the included studies was independently appraised by 2 authors according to the revised Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool.
"According to the QUADAS-2 tool, most studies were of low quality. The majority was retrospectively designed and had insufficient statistical

power."

Heterogeneity: The existence of between-study heterogeneity was primarily assessed through visually inspecting forest plots for the degree of overlapping confidence
intervals. The extent of heterogeneity was assessed by visual inspection of 95% prediction regions in SROC plots, where high heterogeneity was depicted by larger 95% prediction regions than 95% confidence regions.

Publication Bias: Not investigated.

Notes:
Evidence level 1: Systematic review and meta-analysis.
Publication bias not investigated.

Qumseya, B. J. et al. High rate of over-staging of Barrett's neoplasia with endoscopic ultrasound: Systemic review and meta-analysis. Dig Liver Dis. 50. 438-445. 2018

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: Systematic review and meta-analysis. Databases: Medline, Embase, Web of Science, and Cochrane Central Search period: Inception - 09/2016 Inclusion Criteria: (i) randomized controlled trials, prospective clinical studies, retrospective cohort studies; (ii) studies	Population: patients with BE with suspected dysplasia, early neoplasia, or nodules. Intervention: BE staging by Endoscopic ultrasound EUS Comparison: Histology staging of BE	Primary: Rate of over-staging, at the tumor level, of patient using EUS. " This was defined as the rate of staging a patient with T1b or deeper invasion when he/she had disease limited to the mucosa (T1a, HGD, LGD, or non-dysplastic BE). We referred to this rate as the false positive rate (FPR):" Secondary: False negative rate, and the false detection rate (FDR). FDR Results: **Population:** Of 1872 studies (9 retrospective 2 prospective studies), 11 met our inclusion criteria	Thota 2016 Bartel 2016 Fernandez-Sordo 2012 Pouw 2011 Thomas 2010 Prasad 2007 Pech 2006 Mino-Kenudson 2005

published in peer-reviewed journals; (iii) included patients with BE with suspected dysplasia, early neoplasia, or nodules referred for EUS; and (iv) diagnosis was confirmed by esophagectomy or EMR Exclusion Criteria: (i) patients had confirmed advanced disease at the time of referral who were included in the analyses and could not be differentiated from the rest of the patients; (ii) pathological confirmation was not available; or (iii) EUS was done for indications other than Barrett's esophagus.	n=895 patients. Most studies looked at patients with BE with high-grade dysplasia (HGD) and/or EAC although some included Barrett's esophagus with low-grade dyspepsia (LGD), as well. Of the 11 studies, 7 were in from various US centers while the others were from European centers. The prevalence of advanced disease in the baseline populations varies from 5% to 45% **Results: Primary: FPR** Based on random effects models, the pooled FPR for advanced disease was 9.1% ([6.5–12.5%], $p < 0.001$). Tests of heterogeneity showed no significant heterogeneity for this outcome. Secondary: FNR The pooled false negative rate was 9.2% [95%CI: 4.7–17.3%], $p < 0.01$. Overall, the pooled accuracy of EUS results in BE neoplasia patients was low at 74.6% [58.7–85.8%], $p = 0.004$. Author's Conclusion: "The use of EUS in BE patients with dysplasia and early neoplasia results in a large proportion of patients falsely over-staged and under-staged."	Larghi 2005 Buskens 2004 Scotiniotis 2001

Methodical Notes

Funding Sources: none stated.

COI: "Dr. Wolfsen receives research funding from Ninepoint Medical. All other authors have no conflicts of interest to disclose."

Study Quality: Quality assessment was done using the QUADAS II tool and showed most studies to be of good quality. None of the studies were find to have high risk of bias.

Heterogeneity: For the primary outcome of FPR, there was no significant heterogeneity."

Publication Bias: Funnel plots and classic fail-safe test were used to assess and quantify publication bias. The results of this analysis suggests a low risk of publication bias."

Notes:
Evidence level 1: Systematic review and meta-analysis.
No methodological complaints.

06 Erweiterte Diagnostik - MRT

Inhalt: *1 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
de Gouw, Djjm 2019	1	Systematic review and meta-analysis

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

de Gouw, Djjm et al. Detecting Pathological Complete Response in Esophageal Cancer after Neoadjuvant Therapy Based on Imaging Techniques: A Diagnostic Systematic Review and Meta-Analysis. J Thorac Oncol. 14. 1156-1171. 2019

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: Systematic review and meta-analysis Databases: Medline, Embase, and Cochrane Library Search period: 01.2000 - 12.2017 Inclusion Criteria: Studies were considered eligible when imaging results	Population: 57 studies involving 3660 esophageal cancer patients were included. Imaging techniques used to diagnose ypCR: CT 8, PET-CT 35, EUS 15, MRI 3 studies). In general, studies had a retrospective design and included an uninterrupted series of patients. Intervention: imaging techniques (MRI, CT, PET-CT, EUS)	Primary: The primary outcome was the accuracy of predicting ypCR after neoadjuvant therapy compared with the final histopathological results after resection. Secondary: Primary Tumor Response, Diagnostic Accuracy: Regional Lymph Node Response, Subgroup and Sensitivity Analyses.	56 studies, see article.

of restaging were reported after neoadjuvant therapy and before surgery in patients with esophageal cancer.

Only studies in which patients were treated with curative intent, consisting of neoadjuvant chemotherapy and/or radiotherapy followed by esophageal resection and lymph node dissection, were included. Studies addressing a combination of diagnostic modalities (imaging and nonimaging) were included only if separate data on the imaging test was available.

Exclusion Criteria: Studies without comparison with histopathological or imaging tests that were performed during neoadjuvant treatment were excluded. Other reviews, case reports, conference abstracts, and studies with fewer than 10 patients were excluded. Publications before the year 2000 were excluded to ensure that the review would represent contemporary imaging techniques.

Comparison: Histopathology

Results: **Diagnostic Accuracy: complete response** The pooledsensitivities of CT, PET-CT, EUS, and MRI for detecting ypCR were 0.35, 0.62, 0.01 and 0.80, respectively, whereas the pooled specificities were 0.83, 0.73, 0.99,and 0.83, respectively. The positive predictive value indetecting ypCR was 0.47 for CT, 0.41 for PET-CT, notapplicable for EUS, and 0.61 for MRI.

Author's Conclusion: Current imaging modalities such as CT, PET-CT, and EUS seem to be insufficiently accurate to identify complete responders. More accurate diagnostic tests are needed to improve restaging accuracy for patients with esophageal cancer.

Methodical Notes

Funding Sources: not described.

COI: The authors declare no conflicts.

Study Quality: The methodological quality of each study was assessed by the Cochrane Quality Assessment of Diagnostic Accuracy Studies, version 2, model.

Heterogeneity: not investigated.

Publication Bias: not investigated.

Notes:
Evidence level 1:Systematic review and meta-analysis
Publication bias and heterogeneity not investigated.

07 Erweiterte Diagnostik - PET-CT

Inhalt: *5 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
de Gouw, Djjm 2019	1	Systematic review and meta-analysis
Eyck, B. M. 2019	1	Systematic Review and Meta-analysis
Hu, J. 2018	1	Systematic review and meta-analysis
Jiang, C. 2018	1	Systematic review and meta-analysis (19 studies)
Kroese, T. E. 2018	1	Systematic review and meta-analysis

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

de Gouw, Djjm et al. Detecting Pathological Complete Response in Esophageal Cancer after Neoadjuvant Therapy Based on Imaging Techniques: A Diagnostic Systematic Review and Meta-Analysis. J Thorac Oncol. 14. 1156-1171. 2019

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: Systematic review and meta-analysis Databases: Medline, Embase, and Cochrane Library Search period: 01.2000 - 12.2017	Population: 57 studies involving 3660 esophageal cancer patients were included. Imaging techniques used to diagnose ypCR: CT 8, PET-CT 35, EUS 15, MRI 3 studies). In general, studies had a retrospective design and included an uninterrupted series of patients.	Primary: The primary outcome was the accuracy of predicting ypCR after neoadjuvant therapy compared with the final histopathological results after resection. Secondary: Primary Tumor Response, Diagnostic Accuracy: Regional Lymph	56 studies, see article.

Inclusion Criteria: Studies were considered eligible when imaging results of restaging were reported after neoadjuvant therapy and before surgery in patients with esophageal cancer.
Only studies in which patients were treated with curative intent, consisting of neoadjuvant chemotherapy and/or radiotherapy followed by esophageal resection
and lymph node dissection, were included. Studies addressing a combination of diagnostic modalities (imaging and nonimaging) were included only if separate data on the imaging test was available.

Exclusion Criteria: Studies without comparison with histopathological or imaging tests that were performed during neoadjuvant treatment were excluded. Other reviews, case reports, conference abstracts, and studies with fewer than 10 patients were excluded. Publications before the year 2000 were excluded to

Intervention: imaging techniques (MRI, CT, PET-CT, EUS)

Comparison: Histopathology

Node
Response, Subgroup and Sensitivity Analyses.

Results: **Diagnostic Accuracy: complete response** The pooledsensitivities of CT, PET-CT, EUS, and MRI for detecting ypCR were 0.35, 0.62, 0.01 and 0.80, respectively, whereas the pooled specificities were 0.83, 0.73, 0.99,and 0.83, respectively. The positive predictive value indetecting ypCR was 0.47 for CT, 0.41 for PET-CT, notapplicable for EUS, and 0.61 for MRI.

Author's Conclusion: Current imaging modalities such as CT, PET-CT, and EUS seem to be insufficiently accurate to identify complete responders. More accurate diagnostic tests are needed to improve restaging accuracy for patients with esophageal cancer.

ensure that the review would represent contemporary imaging techniques.

Methodical Notes

Funding Sources: not described.

COI: The authors declare no conflicts.

Study Quality: The methodological quality of each study was assessed by the Cochrane Quality Assessment of Diagnostic Accuracy Studies, version 2, model.

Heterogeneity: not investigated.

Publication Bias: not investigated.

Notes:
Publication bias and heterogeneity not investigated.

Eyck, B. M. et al. Accuracy of Detecting Residual Disease After Neoadjuvant Chemoradiotherapy for Esophageal Cancer: A Systematic Review and Meta-analysis. Ann Surg. . . 2019

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: Systematic Review and Meta-analysis Databases: Embase, Medline, Cochrane, and Web-of-Science	Population: Esophageal cancer patients after neoadjuvant chemoradiotherapy. 65 articles comprising one or more index tests of interest were included for qualitative analysis. Endoscopic biopsies by 13 articles, EUS by 16 articles, and PET(-CT)	Primary: Accuracy of detecting residual disease after neoadjuvant chemoradiotherapy for esophageal cancer. Secondary:	44 Studies were included. See article for list.

Search period: Inception until 02/2018

Inclusion Criteria: (1) the study population consisted of patients with adenocarcinoma or squamous cell carcinoma of the esophagus or esophago-gastric junction; (2) endoscopic biopsy, EUS, and/or 18F FDG PET(-CT) were investigated; (3) the index tests evaluated detection of residual disease after nCRT at the primary tumor site or in regional lymph nodes; (4) histopathological examination of the surgical resection specimen was used as reference standard; and (5) the study contained sufficient data for construction of a 2 X 2 contingency table.

Exclusion Criteria: Studies written in other languages than English, conference abstracts, letters to the editor, editorials, reviews, and studies including<10 patients were excluded. Also, studies reporting on cervical esophageal cancer only were excluded because the current standard of

by 40 articles. 21 studies were excluded from quantitative synthesis because a pathological response criterion other than pCR was used or because <4 studies were included that evaluated the same index test or the same combination of index tests. 44 studies were included for quantitative synthesis, comprising 6 index test modalities.

Intervention: Endoscopic biopsies, EUS, and 18F-FDG PET(-CT).

Comparison:

Results: Pooled sensitivities and specificities were 33% and 95% for endoscopic biopsies, 96% and 8% for qualitative EUS, 74% and 52% for qualitative PET, 69% and 72% for PETSUVmax, and 73% and 63% for PET-%DSUVmax. For detecting residual nodal disease, 11 studies evaluated qualitative EUS with a pooled sensitivity and specificity of 68% and 57%, respectively. In subgroup analyses, sensitivity of PET-%DSUVmax and EUS for nodal disease was higher in squamous cell carcinoma than adenocarcinoma.

Author's Conclusion: Current literature suggests insufficient accuracy of endoscopic biopsies, EUS, and 18F-FDG PET(-CT) as single modalities for detecting residual disease after nCRT for esophageal cancer.

care with curative intent for these tumors
is definitive chemoradiotherapy.

Methodical Notes

Funding Sources: No means of funding were received for this contribution.

COI: The authors declare no conflicts of interest.

Study Quality: The quality of the included studies was independently appraised by 2 authors according to the revised Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool.
"According to the QUADAS-2 tool, most studies were of low quality. The majority was retrospectively designed and had insufficient statistical power."

Heterogeneity: The existence of between-study heterogeneity was primarily assessed through visually inspecting forest plots for the degree of overlapping confidence
intervals. The extent of heterogeneity was assessed by visual inspection of 95% prediction regions in SROC plots, where high heterogeneity was depicted by larger 95% prediction regions than 95% confidence regions.

Publication Bias: Not investigated.

Notes:
Publication bias not investigated.

Hu, J. et al. Diagnostic value of 18F-fluorodeoxyglucose positron-emission tomography/computed tomography for preoperative lymph node metastasis of esophageal cancer: A meta-analysis. Medicine (Baltimore). 97. e13722. 2018

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

Evidence level: 1 Study type: Systematic review and meta-analysis Databases: MEDLINE / PubMed Search period: 01/2013 - 12/2017.	Inclusion Criteria: Patient pathology confirmed to be EC; lymph node status detected by PET/CT before surgery, for patients treated with neoadjuvant therapy, lymph node status was detected by PET/CT after neoadjuvant therapy and before surgery; use of fluorodeoxyglucose as the PET/CT tracer; histopathological results of lymph node assessment followed gold standards; contained complete information including true positives, false positives, false negatives, and true negatives that could be constructed into a complete 4-squared table; included at least 10 patients. Exclusion Criteria: studies in which the patients who received preoperative neoadjuvant treatment could not be accurately distinguished.	Population: Patients with esophageal cancer Intervention: 18F-fluorodeoxyglucose positron-emission tomography/computed tomography (18FDG PET/CT) Comparison: histopathological workup	Primary: Detection of preoperative lymph node metastases. Sensitivity / Specificity Secondary: - Results: **Study Population:** 14 retrospective studies were included. Pathological types of esophageal squamous cell carcinoma occurred in 13 studies, esophageal adenocarcinomas in 2 studies, and 1 study did not clearly indicate. Twelve studies did not perform preoperative neoadjuvant treatment, while 4 studies did. **Results:** Patients without neoadjuvant treatment had a pooled sensitivity and specificity of 0.57 95% CI(0.45– 0.69) and 0.91 (0.85–0.95), respectively. Patients who received neoadjuvant treatment had a pooled sensitivity and specificity of 0.53 (0.35–0.70) and 0.96 (0.86–0.99), respectively. Author's Conclusion: PET/CT has a high diagnostic specificity but a low diagnostic sensitivity; thus, the diagnosis results cannot accurately reflect the lymph node status. Although accurate N staging is not possible, PET/CT has good test specificity and can be	14 studies, see article.

used to rule out lymph node metastasis and narrow the scope of cleansing.

Methodical Notes

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

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

Study Quality: Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS- 2) was used to evaluate the quality of the studies. All included studies were retrospective. 3 studies achieved 11/11 points, 9 studies responded 10/11 and 2 studies achieve 9/11 points.

Heterogeneity: Heterogeneity among these studies was assessed by Q-tests. Q-test P<.01 indicated heterogeneity high for all outcomes.>
Publication Bias: Publication bias not investigated.

Notes:
Only one database searched, not considered a comprehensive search. Publication bias not investigated. No total number of participants available. Included articles exclusively from China, Korea, Japan, which seems strange. High heterogeneity for the all outcomes.

Jiang, C. et al. Systematic review and meta-analysis of the accuracy of 18F-FDG PET/CT for detection of regional lymph node metastasis in esophageal squamous cell carcinoma. J Thorac Dis. 10. 6066-6076. 2018

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: Systematic review and meta-analysis (19 studies) Databases: PubMed, EMBASE and the	Population: Esophageal squamous cell carcinoma patients before surgery, with suspected regional lymph node metastasis.	Primary: Sensitivity and sensitivity, grouped in into per-patient basis group and per-nodal basis group. Secondary:	19 studies, see article.

Cochrane Library Search period: 01/2006 - 12/2017 Inclusion Criteria: Studies that examined the diagnostic value of 18F-FDG PET/ CT, either in routine clinical practice or in symptomatic patients, in whom regional lymph node metastasis was suspected before surgery using data that could be extracted into a 2×2 contingency table. The reference standard for positive lymph node metastasis in each selected study must be pathology during or after surgery Exclusion Criteria: Non-English language studies were excluded, except those in Chinese. Conference abstracts and letters to journal editors were excluded.	Intervention: 18F-FDG PET/ CT Comparison: Pathology during or after surgery	Results: **Study population:** A total of 19 studies were included. Included studies were grouped according to whether the research unit was the patient or lymph nodes. **Results: Detection of lymph node metastasis on a per-patient basis** 8 articles, total n=506. 18-FDG PET/ CT resulted in a low estimated sensitivity and moderate estimated specificity of 0.65 [95% CI: 0.49–0.78] and 0.81 (95% CI: 0.69–0.89), respectively. I^2-values were 75.26 (95% CI: 57.97–92.55, Cochrane's Q P=0.00) for sensitivity and 76.50 (95% CI: 60.28– 92.72, Cochrane's Q P=0.00) for specificity and indicate substantial heterogeneity. However, no factor was caused the heterogeneity via meta-regression analysis. The positive likelihood ratio (PLR), negative likelihood ratio (NLR) and diagnostic odd ratio (DOR) were 3.4 (95% CI: 2.1–5.4), 0.44 (95% CI: 0.29–0.65) and 8 (95% CI: 4–16), respectively. **Detection of lymph node metastasis on a per-nodal station** 12 articles, 5681 nodal stations analyzed. 18-FDG PET/CT had a low estimated sensitivity and a high estimated specificity of 0.66 (95% CI: 0.51–0.78) and 0.96 (95% CI: 0.92–0.98), respectively. I^2-values were 95.27 (95% CI: 93.61–

96.94, Cochrane's Q P=0.00) for sensitivity and 94.66 (95% CI: 92.71–96.61, Cochrane's Q P=0.00) for specificity, which indicated substantial heterogeneity. Meta-regression showed the type of research (P=0.01) and origin (P=0.00) contributed to the high heterogeneity. The PLR, NLR, and DOR values were 15.2 (95% CI: 8.0–28.8), 0.36 (95% CI: 0.24–0.53), and 43 (95% CI: 19–96), respectively

Author's Conclusion: "Overall, 18F-FDG PET/CT have a moderate to low sensitivity and a high to moderate specificity for detection of regional nodal metastasis in esophageal cancer. Therefore, since the false rate is considerable, extending the extent of lymph node dissection or radiotherapy target volume is necessary after diagnosis of regional nodal metastasis by 18F-FDG PET/CT."

Methodical Notes

Funding Sources: not stated.

COI: The authors have no conflicts of interest to declare.

Study Quality: The Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2, Figure S1) was performed to evaluate the diagnostic accuracy qualities of the 19 eligible articles. 7 studies score 11/11, 7 score 10/11, 3 score 9/11 and 2 scored 8/11.

Heterogeneity: The inconsistency index (I^2) was calculated; I^2 values greater than 50% were considered to indicate substantial heterogeneity.

"I2-values were 75.26 (95% CI: 57.97–92.55, Cochrane's Q P=0.00) for sensitivity and 76.50 (95% CI: 60.28– 92.72, Cochrane's Q P=0.00) for specificity and indicate substantial heterogeneity."

Publication Bias: Deek's funnel plots of diagnostic odds ratio inverse of the square root of the effective sample size were constructed to assess the publication bias of the articles.
The shape of the funnel plots revealed no asymmetry in both subgroups.

Notes:
Inclusion criteria not clearly defined. High heterogeneity was investigated in meta-regression analysis.

Kroese, T. E. et al. Detection of distant interval metastases after neoadjuvant therapy for esophageal cancer with 18F-FDG PET(/CT): a systematic review and meta-analysis. Dis Esophagus. 31. . 2018

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: Systematic review and meta-analysis Databases: Pubmed, Embase, Cochrane. Search period: Inception - 01/2017. Inclusion Criteria: Diagnostic studies reporting on the detection of distant interval metastases with 18F-FDG PET(/CT) in patients with esophageal cancer who received neoadjuvant therapy and both baseline staging and restaging after neoadjuvant therapy with 18F-FDG PET(/CT)	Population: Patients with esophageal cancer who received neoadjuvant therapy Intervention: 18F-FDG PET(/CT) at baseline staging and restaging after neoadjuvant therapy. Comparison: Histological workup of biopsy (not available in all primary studies).	Primary: The proportion of patients who developed true distant interval metastases after neoadjuvant therapy detected by 18F-FDG PET(/CT) restaging among patients whom received both baseline staging and restaging with 18F-FDG PET(/CT) imaging. Secondary: The proportion of patients with false positive distant findings detected by 18F-FDG PET(/CT) restaging among patients who received both baseline staging and restaging with 18F-FDG PET(/CT) imaging. Results: **Population:** 14 included studies, with total n=1110 included patients who	Findlay 2016, Elliott 2014, Stiekama 2014, Piessen 2013, Gillies 2012, Blom 2011, Monjazeb 2010, Bruzzi 2007, Levine 2006, Cerfolio 2005 Kroep 2003, Downey 2003 Flamen 2003

imaging, Studies were included if the total n patients in the study was ≥ 10

Exclusion Criteria: Studies reporting primarily on gastric cancer or gastroesophageal junction cancer ; Studies written in a language other than English, reviews, poster abstracts or with a reference test other than pathology or clinical followup
were excluded. Studies in which no 18F-FDG PET(/CT) was performed during baseline staging— prior to neoadjuvant therapy— were also excluded.

received baseline staging with 18F-FDG PET(/CT) imaging, 1001 patients (90%) underwent restaging with 18F-FDG PET(/CT) imaging.
Results: Primary: The pooled proportion of patients in whom true distant interval metastases were detected by 18F-FDG PET(/CT) restaging was 8% (95% CI: 5–13%).
Secondary: The pooled proportion of patients in whom false positive distant findings were detected by 18F-FDG PET(/CT) restaging was 5% (95% CI: 3–9%).

Author's Conclusion: "In conclusion, 18F-FDG PET(/CT) restaging after neoadjuvant therapy for esophageal cancer detects true distant interval metastases in 8% of patients. Therefore, 18F-FDG PET(/CT) restaging can considerably impact on treatment decision-making. However, false positive distant findings occur in 5% of patients at restaging with 18F-FDG PET(/CT), underlining the need for pathological confirmation of suspected lesions."

Methodical Notes

Funding Sources: "This research did not receive any specific grant from funding agencies in het public, commercial, or non-profit sectors."

COI: The authors have nothing to disclose and the authors declare that they have no conflict of interest.

Study Quality: "Two authors independently critically appraised the included studies for risk of bias and applicability concerns on 4 domains using the revised Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool."
"Studies were generally of moderate quality."

Heterogeneity: "The I2 test was used to test for the presence of statistical heterogeneity across studies beyond chance. Statically significant heterogeneity was defined as I2 > 50%. "Statistical heterogeneity ofthe primary outcome measure across studies was considered high (I^2 = 72%)."

Publication Bias: not investigated.

Notes:
Publication bias not investigated. High heterogeneity of I^2 72% for the main analysis, likely partly due to inconsistencies regarding staging method, type of neoadjuvant therpy and application of reference standard.

08 Pathologie

Inhalt: *1 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Noordman, B. J. 2018	2	Prospective multicentre, diagnostic cohort study

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

Noordman, B. J. et al. Detection of residual disease after neoadjuvant chemoradiotherapy for oesophageal cancer (preSANO): a prospective multicentre, diagnostic cohort study. Lancet Oncol. 19. 965-974. 2018

Evidence level/Study Types	Population	Outcomes/Results
Evidence level: 2 Study type: Prospective multicentre, diagnostic cohort study	Number of patients / samples: 207 with neoadjuvant CRT and clinical response evaluations (84 regular biopsy, 123 bite-on-bite biopsy) as well as PET-CT and endoscopic ultrasonography. Reference standard: Biopsy (84 regular biopsy, 123 bite-on-bite biopsies) Validation: Endoscopic ultrasonography, PET-CT Blinding: Yes, all endoscopy reports and endoscopic ultrasonography images were reviewed by an experienced upper-gastrointestinal gastroenterologist, who was blinded to patho logical response results in	Results: 8 of 26 TRG3 or TRG4 tumours (31% [95% CI 17–50]) were missed by endoscopy with regular biopsies and fine-needle aspiration. 4 of 41 TRG3 or TRG4 tumours (10% [95% CI 4–23]) were missed with bite-on-bite biopsies and fine-needle aspiration. Endoscopic ultrasonography with maximum tumour thickness measurement missed TRG3 or TRG4 residual tumours in 11 of 39 patients (28% [95% CI 17–44]). PET–CT missed six of 41 TRG3 or TRG4 tumours (15% [95% CI 7–28]). PET–CT detected interval distant histologically proven metastases in 18 (9%) of 190 patients (one squamous cell carcinoma, 17 adenocarcinomas). Author conclusions: After neoadjuvant chemoradiotherapy for oesophageal cancer, clinical response evaluation with

the resected specimen after surgery.
All scans were reviewed by an experienced PET–CT radiologist (RV), who was blinded to pathological response results.

Inclusion of clinical information: Yes

Dealing with ambiguous clinical findings: -

endoscopic ultrasonography, bite-on-bite biopsies, and fine-needle aspiration of suspicious lymph nodes was adequate for detection of locoregional residual disease, with PET–CT for detection of interval metastases. Active surveillance with this combination of diagnostic modalities is now being assessed in a phase 3 randomised controlled trial.

Methodical Notes

Funding Sources: Funding Dutch Cancer Society. The study funder had no role in study design; data collection, analysis, interpretation, or writing of the report. JJBvL had access to all study data and had final responsibility for the decision to submit for publication.

COI: EWS has received royalties from Springer for a book on prediction models. JJBvL has received research grants from the Dutch Cancer Society, Coolsingel Stichting, and the Erasmus MC/MRace Fund. All other authors declare no competing interests.

Notes: Evidence level 2: Individual cross sectional study with consistently applie reference standard and blinding.
The variation regarding the biopsy modality is a potential source of bias.

09 Endoskopische Therapie - Indikation

Inhalt: *3 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
de Matos, M. V. 2019	2	Systematic review and meta-analysis (7 studies)
Pandey, G. 2018	1	Systematic review and meta-analysis (8 studies)
Yang, D. 2018	1	Systematic review and meta-analysis. (11 studies)

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

de Matos, M. V. et al. Treatment of high-grade dysplasia and intramucosal carcinoma using radiofrequency ablation or endoscopic mucosal resection + radiofrequency ablation: Meta-analysis and systematic review. World J Gastrointest Endosc. 11. 239-248. 2019

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 2 Study type: Systematic review and meta-analysis (7 studies) Databases: MEDLINE, Scopus, and LILACS, Search period: not described. Inclusion Criteria: Studies involving adult patients of any age with BE with	Population: Patients with BE and HGD or intramucosal carcinoma. Intervention: Endoscopic mucosal resection EMR + radiofrequency ablation RFA Comparison: radiofrequency ablation RFA alone	Primary: Effectiveness in treatment of dysplasia. Secondary: Complications: stenosis, bleeding, and thoracic pain Results: **Study population:** 7 studies, Observational retrospective, n=1950 (742 abllation with ESR, 1208 in the RFA alone group. Results: The use of EMR + RFA was significantly more effective in the treatment of HGD [RD 0.35 (0.15, 0.56)] than was the use of RFA alone. The	Li 2015, Strauss 2014, Haidry 2013, Kim 2012, Caillol 2012, Okoro 2012, Pouw 2008.

HGD or intramucosal carcinoma, comparing RFA and EMR + RFA, regardless of randomization status.

Exclusion Criteria: not described.

evaluated complications (stenosis, bleeding, and thoracic pain) were not significantly different between the two groups.

Author's Conclusion: "Endoscopic resection in combination with RFA is a safe and effective method in the treatment of HGD and intramucosal carcinoma, with higher rates of remission and no significant differences in complication rates when compared to the use of RFA alone."

Methodical Notes

Funding Sources: not stated.

COI: The authors have no conflicts of interest.

Study Quality: Newcastle Ottawa scale was used. Studies with a score of ≥ 6 were included. Studies that presented losses of > 20% were excluded. 2 studies scored 8/9, 3 scored 7/9 and 2 6/9.

Heterogeneity: High heterogeneity $I^2$95% in the main analysis of the effectiveness outcome.

Publication Bias: Adressed, but no investigated.

Notes:
Evidence level 1: Systematic review and meta-analysis. Downgrade to evidence level 2.

Search description is missing publication period / date of search. Lacking description of inclusion criteria and outcomes. High heterogeneity of I^2=95% in the main analysis (effectiveness). Publication bias is mentioned, but no investigated or discussed.

Pandey, G. et al. Systematic review and meta-analysis of the effectiveness of radiofrequency ablation in low grade dysplastic Barrett's esophagus. Endoscopy. 50. 953-960. 2018

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: Systematic review and meta-analysis (8 studies) Databases: MEDLINE, EMBASE, and Web of Science Search period: 01/1990 - 05/2017 Inclusion Criteria: Randomized controlled trial or observational study, Adults diagnosed with low grade dysplasia, Patients receiving RFA compared with control group not receiving RFA, Outcome measure: progression to high grade dysplasia or esophageal adenocarcinoma or complete eradication Exclusion Criteria: Reviews, commentaries, case reports, Age < 18	Population: Adults diagnosed with low grade dysplasia Intervention: Radiofrequency ablation RFA Comparison: no radiofrequency ablation	Primary: complete eradication of intestinal metaplasia IM (CE-IM) and dysplasia (CE-D), meaning the absence of IM or dysplasia of any grade. Secondary: rates of progression to HGD or cancer, recurrence of dysplasia post-eradication, and adverse events Results: **Study characteristics:** 8 articles were included: 2 RCTs, six observational cohort studies (3 prospective). age 65 [range 18– 84]) with low grade dysplastic BE. The total number of patients treated with RFA was 404. 3 studies compared RFA to surveillance endoscopy. Complete eradication of IM or dysplasia was assessed in 7 studies. Progression to HGD or cancer was recorded in 4 studies and recurrence after eradication in five studies. The length of the BE segment ranged from 0.5 to 13 cm. Diagnosis of LGD was confirmed by two	Phoa 2014, Shaheen 2009, Guthikonda 2016, Haidry 2013, Komanduri 2017, Orman 2013, Small 2015, Sharma 2009.

years, Studies with high grade dysplasia and adenocarcinoma but no low grade dysplasia, Articles with full text unavailable	pathologists in all of the studies. The median follow-up was 26 months (range 12 – 44 months). **Results: Primary** Complete eradication of intestinal metaplasia 6/8 studies addressed CE-IM in the results. The overall pooled rate of CE-IM after RFA was 88.17% (95%CI 88.13%– 88.20 %; P < 0.001) I^2 = 100 % Complete eradication of dysplasia 6 studies reported CE-D in the results. Pooled results of all the studies concluded that 96.69% of patients receiving RFA achieved CE-D (95%CI 96.67%– 96.71 %; P < 0.001) I^2 = 100 %. When compared with surveillance, patients who underwent RFA were more likely to achieve CE-D (P < 0.001). **Secondary:** When compared with surveillance, RFA resulted in significantly lower rates of progression to HGD or cancer (odds ratio [OR] 0.07, 95 %CI 0.02 – 0.22). The pooled recurrence rates of IM and dysplasia were 5.6% (95%CI 5.57 – 5.63; P < 0.001) and 9.66% (95%CI 9.61 – 9.71; P < 0.001), respectively. Author's Conclusion: In conclusion, RFA safely eradicates IM and dysplasia and reduces the

rates of progression from LGD to HGD or cancer in the short term. Long-term RFA outcomes however remain unknown and further research including detailed follow-up is warranted.

Methodical Notes

Funding Sources: not described.

COI: No competing interests.

Study Quality: The quality was assessed, by the Cochrane risk of bias tool, the CASP and Newcastle – Ottawa scale.
"The studies were ranked 1 to 4 in terms of quality. 2 RCT achieved the highest score 1, one study scored 2, 4 scored 3 points and one received the lowest rating of 4.

Heterogeneity: Heterogeneity was quantified using the I^2 value and associated test for heterogeneity which was reported for each analysis. Where heterogeneity was apparent the DerSimonian and Laird random-effects method was used to pool estimates with inverse-variance weights.

Publication Bias: Funnel plots for each analysis are investigated, available in the supplementary material, but the results are not discussed in the article.

Notes:
High heterogeneity I^2=100% in both primary outcomes was not adequately discussed in the article. Publication bias investigated mentioned, but not discussed in the article.

Yang, D. et al. Endoscopic submucosal dissection for early Barrett's neoplasia: a meta-analysis. Gastrointest Endosc. 87. 1383-1393. 2018

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

Evidence level: 1 Study type: Systematic review and meta-analysis. (11 studies) Databases: MEDLINE/ PubMed, EMBASE, and Ovid Search period: Inception - 03/2017. Inclusion Criteria: Inclusion criteria were (1) retrospective or prospective, case-control, or cohort studies and clinical trials (including randomized controlled trials) and (2) studies reporting clinical outcomes of ESD in the treatment of BE. Exclusion Criteria: (1) animal studies; (2) case reports; (3) ESD for EAC not arising from BE; (4) EMR or hybrid endoscopic resection techniques used; (5) fewer than 5 patients included; (6) commentaries, reviews, or surveys; and (7) publications in a language other than English.	Population: Patients with visible early Barett esophagus (BE) neoplasia (defined as either dysplastic BE (low- or high-grade dysplasia) or EAC based on preprocedural staging (ie, cross-sectional imaging, EUS, histopathology) Intervention: Endoscopic submucosal resection (ESR) Comparison: no comparison.	Primary: Efficacy and adverse events. Efficacy was determined based on the en bloc and R0 (complete) resection rates. En bloc resection was defined as excision of the targeted lesion in a single specimen. R0 resection was defined as negative lateral and deep margins for BE dysplasia and/or EAC in the ESD specimen. Secondary: Curative resection rate and recurrence Results: **Study population:** 11 studies (501 patients, 524 lesions) were included. Mean lesion size was 27 mm (95% CI, 20.9-33.1). **Results:** Pooled estimate for en bloc resection was 92.9% (95% CI, 90.3%-95.2%). The pooled R0 (complete) and curative resection rates were 74.5% (95% CI, 66.3%-81.9%) and 64.9% (95% CI, 55.7%-73.6%), respectively. There was no association between R0 or curative resection rates and study setting (Asia vs West), length of BE, lesion characteristics, procedural time, or length of follow-up. The pooled estimates for perforation and	Neuhaus 2012, Hoteya 2013, Nagami 2014, Kagemoto 2014, Probst 2015, Chevaux 2015, Hobel 2015, Barret 2015, Terheggen 2016, Yang 2016

bleeding were 1.5% (95% CI, .4%-3.0%) and 1.7% (95% CI, .6%-3.4%), respectively. Esophageal stricture rate was 11.6% (95% CI, .9%-29.6%). Incidence of recurrence after curative resection was .17% (95% CI, 0%-.3%) at a mean follow-up 22.9 months (95% CI, 17.5-28.3).

Author's Conclusion: "ESD for early BE neoplasia is effective and associated with a high en bloc resection rate. The procedure is safe with a low incidence of bleeding or perforation. Although esophageal stricture formation remains the most commonly reported late adverse event, this can be managed successfully with endoscopic intervention. Careful lesion characterization and selection may play a crucial role in ensuring complete and curative resection."

Methodical Notes

Funding Sources: All authors disclosed no financial relationships relevant to this publication.

COI: not described.

Study Quality: The methodologic quality of the observational studies was assessed by 3 investigators using the Newcastle-Ottawa scale. The

average quality score was 5.2. The risk of bias was considered to be moderate in all 10 studies (quality score <10).

Heterogeneity: "Significant heterogeneity was defined as I2 > 40% and P < .0572.3) resection rates."
"There was significant heterogeneity found in both R0 (Cochran Q test P < .001, I^2 = 70.5) and curative (Cochran Q test P < .001, I^2 =

Publication Bias: "Based on the Egger regression test and symmetric distribution, there was no obvious publication bias detected for these outcome measures."

Notes:
No conflicts of interest statements. High heterogeneity in the main analysis, but adressed and investigated in a meta-regressiona analyis.

10 Endoskopische Therapie - Vorgehen

Inhalt: *1 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Yang, D. 2018	1	Systematic review and meta-analysis. (11 studies)

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

Yang, D. et al. Endoscopic submucosal dissection for early Barrett's neoplasia: a meta-analysis. Gastrointest Endosc. 87. 1383-1393. 2018

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: Systematic review and meta-analysis. (11 studies) Databases: MEDLINE/ PubMed, EMBASE, and Ovid Search period: Inception - 03/2017. Inclusion Criteria: Inclusion criteria were (1) retrospective or prospective, case-control, or cohort studies and clinical trials (including randomized controlled trials) and (2)	Population: Patients with visible early Barett esophagus (BE) neoplasia (defined as either dysplastic BE (low- or high-grade dysplasia) or EAC based on preprocedural staging (ie, cross-sectional imaging, EUS, histopathology) Intervention: Endoscopic submucosal resection (ESR) Comparison: no comparison.	Primary: Efficacy and adverse events. Efficacy was determined based on the en bloc and R0 (complete) resection rates. En bloc resection was defined as excision of the targeted lesion in a single specimen. R0 resection was defined as negative lateral and deep margins for BE dysplasia and/or EAC in the ESD specimen. Secondary: Curative resection rate and recurrence Results: **Study population:** 11 studies (501 patients, 524 lesions) were included.	Neuhaus 2012, Hoteya 2013, Nagami 2014, Kagemoto 2014, Probst 2015, Chevaux 2015, Hobel 2015, Barret 2015, Terheggen 2016, Yang 2016

studies reporting clinical outcomes of ESD in the treatment of BE.

Exclusion Criteria: (1) animal studies; (2) case reports; (3) ESD for EAC not arising from BE; (4) EMR or hybrid endoscopic resection techniques used; (5) fewer than 5 patients included; (6) commentaries, reviews, or surveys; and (7) publications in a language other than English.

Mean lesion size was 27 mm (95% CI, 20.9-33.1).
Results: Pooled estimate for en bloc resection was 92.9% (95% CI, 90.3%-95.2%). The pooled R0 (complete) and curative resection rates were 74.5% (95% CI, 66.3%-81.9%) and 64.9% (95% CI, 55.7%-73.6%), respectively. There was no association between R0 or curative resection rates and study setting (Asia vs West), length of BE, lesion characteristics, procedural time, or length of follow-up. The pooled estimates for perforation and bleeding were 1.5% (95% CI, .4%-3.0%) and 1.7% (95% CI, .6%-3.4%), respectively. Esophageal stricture rate
was 11.6% (95% CI, .9%-29.6%). Incidence of recurrence after curative resection was .17% (95% CI, 0%-.3%) at a mean follow-up 22.9 months (95% CI, 17.5-28.3).

Author's Conclusion: "ESD for early BE neoplasia is effective and associated with a high
en bloc resection rate. The procedure is safe with a low incidence of bleeding or perforation. Although esophageal

stricture formation remains the most commonly reported late adverse event, this can be managed successfully with endoscopic intervention. Careful lesion characterization and selection may play a crucial role in ensuring complete and curative resection."

Methodical Notes

Funding Sources: All authors disclosed no financial relationships relevant to this publication.

COI: not described.

Study Quality: The methodologic quality of the observational studies was assessed by 3 investigators using the Newcastle-Ottawa scale. The average quality score was 5.2. The risk of bias was considered to be moderate in all 10 studies (quality score <10).

Heterogeneity: "Significant heterogeneity was defined as I2 > 40% and P < .0572.3) resection rates."
"There was significant heterogeneity found in both R0 (Cochran Q test P < .001, I^2 = 70.5) and curative (Cochran Q test P < .001, I^2 =

Publication Bias: "Based on the Egger regression test and symmetric distribution, there was no obvious publication bias detected for these outcome measures."

Notes:
No conflicts of interest statements. High heterogeneity in the main analysis, but adressed and investigated in a meta-regressiona analyis.

Schlüsselfrage:

11 Chirurgische Therapie - Art des operativen Zugangs

Inhalt: *10 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Alderson, Derek 2017	2	Open-label, multicentric, phase 3, randomised controlled trial.
Anderegg, M C J 2017	4	Retrospective cohort study.
Deng, J. 2018	1	Systematic review and meta-analysis. (14 studies, 3468 cases)
Gooszen, J A H 2018	3	Propensity score matching cohort study.
Gottlieb-Vedi, E. 2019	1	Systematic review and meta-analysis (55 studies)
Hayata, Keiji 2017	2	A prospective, randomized, controlled trial.
Mariette, C. 2019	2	Randomized, controlled trial, multicenter, open-label
Seesing, Maarten F J 2017	3	Propensity Score Matched Analysis (population-based Cohort)
Straatman, J. 2017	2	Randomized clinical trial.
van der Sluis, Pieter C 2019	2	Randomized controlled trial.

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

Deng, J. et al. Comparison of short-term outcomes between minimally invasive McKeown and Ivor Lewis esophagectomy for esophageal or junctional cancer: a systematic review and meta-analysis. Onco Targets Ther. 11. 6057-6069. 2018

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: Systematic review and	Population: Patients with resectable esophageal or junctional tumors.	Primary: Mortality and anastomotic leak. Secondary: Pulmonary and cardiac complications,	Luketich 2012, Brown 2017, Hao 2014, Nguyen 2008, Chen 2017, Hou

meta-analysis. (14 studies, 3468 cases) Databases: PubMed, Embase, Science Citation Index, The Cochrane Library, ClinicalTrials.gov Search period: Inception -03/2018 Inclusion Criteria: 1) prospective and retrospective studies and 2) studies that compare short-term outcomes of MIME and MILE in patients with resectable esophageal or junctional tumors. Exclusion Criteria: 1) studies that were not compared, 2) overlapped studies, and 3) studies that did not report main results such as mortality and anastomotic leak.	Intervention: minimally invasive McKeown esophagectomy (MIME) Comparison: minimally invasive Ivor Lewis esophagectomy (MILE)	Other complications Results: **Study population:** 3,468 patients from 14 cohort studies underwent totally minimally MILE or MIME were meta-analyzed. No randomized controlled studies or studies adopting hybrid MIE were found. 10 studies reported age; there was no statistical significance between the 2 groups after pooled analysis. 10 studies containing 2,598 cases reported the number of male cases in 2 groups; no apparent difference was detected (OR =1.13, 95% CI =0.93–1.37, P=0.21). AJCC staging (stages 0, I, and II) of patients' esophageal cancer was reported in 7 studies with 1,132 cases; no statistical significance was found between the 2 groups (OR =0.87, 95% CI =0.63–1.22, P=0.42). **Results:** Mortality: 10 studies n=3,034: 30-day/in-hospital mortality risk was 1.8% (28/1,537) in MIME and 1.0% (15/1,497) in MILE. No statistically significant difference existed between the 2 groups (OR =1.76, 95% CI =0.92–3.36, P=0.08), with statistical homogeneity (I2=0%). 3 studies n=499 cases reported 90-day mortality:, and no statistically significant difference was found between the 2 groups (OR =2.22, 95% CI =0.71–6.98, P=0.17). Anastomotic leak 13 studies n=2,457 cases reported the rates of anastomotic leak, where 12.9% (131/1,292) in MIME and 5.7% (63/1,165)in	2017, Zhai 2015, Wu 2014, Lin 2014, Mei 2016, Wei 2016, Rajan 2010, Schmidt 2017, Chang 2018

MILE; MIME was associated with higher incidence of anastomotic leak than MILE (OR =2.55, 95% CI =1.40–4.63, P=0.002) after pooled analysis. High heterogeneity was detected among studies (I2=55.1%).
Secondary outcomes MIME led to more blood loss, longer operating time, and longer hospital stay than MILE. MIME was associated with higher incidence of pulmonary complications (OR =1.96, 95% CI =1.28–3.00), stricture (OR =2.07, 95% CI =1.05–4.07), and vocal cord injury/palsy (OR =5.62, 95% CI =3.46–9.14). the differences of R0 resection rate, number of lymph modes retrieved, blood transfusion rate, length of intensive care unit stay, incidence of cardiac arrhythmia, and Chyle leak between MIME and MILE were not statistically significant.

Author's Conclusion: ".The present meta-analysis suggests that MIME and MILE are comparable with respect to clinical safety. MILE may be a better option when oncologically and clinically suitable, and MIME is still a safe alternative procedure when clinically indicated; however, these findings are at risk for bias, and so randomized controlled trials are needed to validate or correct them."

Methodical Notes

Funding Sources: not described.

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

Study Quality: The quality of the included studies was evaluated by the Newcastle–Ottawa Quality Assessment Scale (NOS) for cohort studies. Quality ranged between 6 and 9 out of 9 possible points.

Heterogeneity: High heterogeneity among studies for anastomotic leakage (I^2=55.1%). A RemL univariate meta-regression according to a country or publication year was performed, and the result indicated that only country (China/non-China) was related to the heterogeneity (P=0.02), which could show 81.17% of between-study variance. A sensitivity analysis, the leave-one-out approach, by removing each study to compare the OR [95% CI] pooled from the remaining 12 studies with the overall OR [95% CI] to evaluate the stability of the result.

Publication Bias: Publication bias was assessed by Egger's test. Significant statistical publication bias was detected with operating time, anastomotic leak, and vocal cord injury/palsy. The trim-and-fill computation was carried out to estimate the effect of publication bias on the result, which indicated the result was consistent and stable.

Notes:
No major methodological downsides.

Gottlieb-Vedi, E. et al. Long-term Survival in Esophageal Cancer After Minimally Invasive Compared to Open Esophagectomy: A Systematic Review and Meta-analysis. Ann Surg. . . 2019

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: Systematic review and meta-analysis (55 studies) Databases: Medline, Embase, Web of Science, and Cochrane Library, plus handsearch of grey literature	Population: Study patients had undergone esophagectomy for esophageal cancer. Intervention: Minimally	Primary: Long term survival: all-cause 5-year Mortaliy Secondary: 3-year mortality, and disease-specific 5-year and 3- year mortality	55 studies, see article for list.

Search period: Inception-05/2018 Inclusion Criteria: 1) Cohort study or RCT. 2) Study patients had undergone esophagectomy for esophageal cancer. 3) Comparing total or hybrid MIE with OE: Total MIE was defined as surgery in which there was no thoracotomy or laparotomy performed. Hybrid MIE is defined as either thoracotomy with laparoscopy; laparotomy with thoracoscopy; or laparotomy with mediastinoscopy. 4) At least 3 years of follow-up for all-cause and disease-specific mortality, presented as hazard ratios (HRs), or Kaplan-Meier curves. Exclusion Criteria: 1) Studies including endoscopic procedures as the primary treatment. 2) Studies not written in the English language.	invasive esophagectomy MIE Comparison: Open esophagectomy OE	Results: **Study characteristics:**55 articles (53 cohort studies, 2 RCTs). Total n=14,592 patients; 7358 (50.4%) underwent MIE and 7234 (49.6%) underwent OE. **Results: Primary:** all-cause 5-year mortality 34 studies; the pooled analysis revealed 18% decreased 5-year mortality after MIE compared with OE (HR 0.82, 95% CI 0.76–0.88).**Secondary:** all-cause 3-year mortality 53 studies; The pooled analysis showed a 15% lower mortality after MIE compared with OE (HR 0.85, 95% CI 0.80–0.92). disease-specific 5-year mortality 13 studies; showed a 17% lower mortality after MIE compared with OE (HR 0.83, 95% CI 0.75–0.91). disease-specific 3-year mortality 22 studies; showed a 16% decrease in mortality in the MIE group compared with the OE group (HR 0.84, 95% CI 0.77–0.92). Author's Conclusion: "The long-term survival after MIE compares well with OE and may even be better. Thus, MIE can be recommended as a standard surgical approach for esophageal cancer."

Methodical Notes

Funding Sources: The study was funded by the Swedish Research Council and Swedish Cancer Society.

COI: The authors declare no conflicts of interest.

Study Quality: The quality of the included studies was assessed using the Newcastle-Ottawa scale for cohort studies and the Cochrane Collaborations Risk of Bias Tool (CCRBT) for randomized clinical trials.
The quality scores of the cohort studies varied between 3 and 9, with a median value of 7 according to the Newcastle-Ottawa scale. The 2 RCTs were evaluated to have low risks of bias, except for performance bias due to the problem of masking surgical treatment, according to the Cochrane Risk of Bias Tool.

Heterogeneity: Main outcome: all-cause 5-year mortality:The statistical heterogeneity of the studies was not important (I^2 = 12%, 95% CI 0%–41%, Chi^2 =0.26).
Secondary outcome: all-cause 3-year mortality: There was a not important level of statistical heterogeneity between studies (I^2 = 26%, 95% CI 0%–46%, Chi^2 = 0.04).

Publication Bias: Main outcome: all-cause 5-year mortality:"The funnel plot was symmetrical both according to visual and statistical testing (Egger test = 0.32), arguing against small-study effects or publication bias.
Secondary outcome: all-cause 3-year mortality: The funnel plot was asymmetrical towards positive HRs (Egger test ¼ 0.04), indicating some level of small-study effects or publication bias.

Notes:
Well conducted systematic review and meta-analysis.

OXFORD (2011) Appraisal Sheet: RCT: *5 Bewertung(en)*

Alderson, Derek et al. Neoadjuvant cisplatin and fluorouracil versus epirubicin, cisplatin, and capecitabine followed by resection in patients with oesophageal adenocarcinoma (UK MRC OE05): an open-label, randomised phase 3 trial. Lancet Oncol. 18. 1249-1260. 2017

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 Study type: Open-label, multicentric, phase 3, randomised controlled trial. Number of Patient: 897 randomized (451, 446 per group). Recruitung Phase: Jan 13, 2005, and Oct 31, 2011, in 72 UK hospitals. Inclusion Criteria: Participants of any age with surgically resectable histologically verified adenocarcinoma of the oesophagus (including Siewert types 1 and 2 gastro-oesophageal junction tumours) stage cT1N1, cT2N1, cT3N0/N1, or cT4N0/N1 where invasion was thought to be confined to diaphragm, crura, or mediastinal pleura and surgically resectable (Union for International Cancer Control [UICC] TNM staging28). Additionally, patients had to meet the following criteria: WHO performance status 0 or 1 and adequate respiratory and cardiac function (forced expiratory volume in 1 sec of >1·5 L and cardiac ejection fraction of ≥50% on echocardiography or multigated acquisition scan) within 4 weeks of randomisation. Within 1 week of randomisation, liver function tests needed to be at most 1·5-times	Intervention: Two cycles of cisplatin and fluorouracil (CF) two 3-weekly cycles of cisplatin [80 mg/m² intravenously on day 1] and fluorouracil [1 g/m² per day intravenously on days 1–4]) before surgery Comparison: Four cycles of epirubicin, cisplatin, and capecitabine (ECX; four 3-weekly cycles of epirubicin [50 mg/m²] and cisplatin [60 mg/m²] intravenously on day 1, and capecitabine [1250 mg/m²] daily throughout the four cycles) before surgery	Primary: Overall survival; was calculated from the date of group assignment to the date of death. Patients either lost to follow-up or still alive at the time of analysis were censored at the date they were last known to be alive. Secondary: Disease-free survival, effects on the primary tumour (as assessed by Mandard TRG), HRQL, and morbidity related to chemotherapy and surgery. Results: **Patient characteristics:** Jan/2005, and Oct/2011, 897 patients were recruited from 72 UK hospitals and randomly allocated to the CF group (n=451) or the ECX group (n=446). The median number of patients per centre was 8 (range 1–73). After chemotherapy, following retrospective review of the baseline CT scan, one patient was found to be ineligible because of adrenal metastases so did not have surgery, but was included in all summaries and analyses. The baseline characteristics of the patients allocated to the CF or ECX groups were similar. The median age was 62 years (IQR 56–67; range 27–81), 810 (90%) of 897 patients were male, 603 (67%) had a WHO performance status of 0, and 576 (64%) had stage T3N1 cancer. Three (4%) of 72 recruiting centres

normal, white blood cell count at least 3×10^9 cells per L, platelet counts at least 100×10^9 platelets per L, and the calculated or measured glomerular filtration rate at least 60 mL/min. Assessment of disease stage required a contrastenhanced multislice CT scan from neck to pelvis and endoscopic ultrasonography within 4 weeks of randomisation. Staging laparoscopy with or without peritoneal cytology and PET scanning were optional according to local practice. The final staging of patients (and Siewert classification) was done on the basis of a multidisciplinary team discussion following endoscopy, endoscopic ultrasonography, CT, and laparoscopy if appropriate.

Exclusion Criteria: Patients were ineligible if investigations indicated blood-borne metastases (radiologically assessed), peritoneal dissemination, local invasion involving the tracheobronchial tree, aorta, pericardium or lung, or abdominal para-aortic lymphadenopathy greater than 1 cm in diameter on CT scan or more than 6 mm in diameter on endoscopic ultrasonography. Patients were also excluded if they had received any previous treatment for oesophageal cancer, had Siewert type 3 cancer, a medical condition that was likely to compromise the proposed trial treatment. Uncontrolled angina pectoris, myocardial

did not take part in the HRQL aspect of the trial for any of their patients, and HRQL assessment data were omitted at baseline for the patients from these centres (37 [4%] of the total 897 patients). Baseline HRQL was also well balanced between the two groups. **Results: Primary:** Overall survival: The observed 3-year overall survival was 39% (95% CI 35–44) in the CF group, and 42% (37–47) in the ECX group (figure 2). Median overall survival was estimated to be 23·4 months (95% CI 20.6–26.3) in the CF group and 26·1 months (22.5–29.7) in the ECX group, with an HR of 0·90 (95% CI 0.77–1.05, p=0·19). **Secondary:** DFS: Median disease-free survival (347 events in the CF group vs 316 events in the ECX group, based on a 6-month landmark analysis) was 11.6 months (95% CI 8.9–13.3) in the CF group and 14.4 months (11.7–16.5) in the ECX group, with an HR of 0.86 (95% CI 0·74–1·00, p=0·051). Other ouctomes see article.

Author's Conclusion: "Four cycles of neoadjuvant ECX compared with two cycles of CF did not increase survival, and cannot be considered standard of care. Our study involved a large number of centres and detailed protocol with comprehensive prospective assessment of health-related quality of life in a patient population confined to people with adenocarcinomas of the

infarction in the 6 months before entry into the trial, heart failure, clinically significant uncontrolled
cardiac arrhythmias, or any patient with a clinically significant abnormal ECG, as well as patients with abnormal left ventricular ejection fraction (LVEF) diagnosed on MUGA scan or echocardiography, including areas of abnormal contractility, were excluded. Patients with positive serology for HIV or hepatitis C, active hepatitis B, or were pregnant were also excluded.

oesophagus and gastro-oesophageal junction (Siewert types 1 and 2). Alternative chemotherapy regimens and neoadjuvant chemoradiation are being investigated to improve outcomes for patients with oesophageal carcinoma."

Methodical Notes

Funding Sources: Extensive list of funding, see article.

COI: Extensive list of potential conflicts of interest, see article.

Randomization: Participants were randomly allocated (1:1) using a computerised minimisation program with a random element and stratified by centre and tumour stage.

Blinding: Open-label study.

Dropout Rate/ITT-Analysis: All safety and primary analyses were done on an intention-to-treat basis. Of the 451 patients in the CF group, eight (2%) stopped chemotherapy because of toxicity and one (<1%) died, whereas in the ECX group, 46 (10%) of 446 patients
stopped because of toxicity, and five (1%) died, one of which was thought to be related to chemotherapy toxicity.

Notes:

Article submitted by hand search.
Evidence level 2: Randomized controlled trial

Hayata, Keiji et al. Circular stapling versus triangulating stapling for the cervical esophagogastric anastomosis after esophagectomy in patients with thoracic esophageal cancer: A prospective, randomized, controlled trial. Surgery. 162. 131-138. 2017

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 Study type: A prospective, randomized, controlled trial. Number of Patient: 100 (49, 51 per group) Recruitung Phase: August 2010 - April 2014 Inclusion Criteria: (1) radical esophagectomy with reconstruction using a gastric conduit passed through the posterior mediastinum or retrosternal route; (2) a cervical anastomosis; (3) 2-field or 3-field lymph node dissection; (4) and provision of written informed consent Exclusion Criteria: Inability to undergo either the CS method or the TS method safely according to intraoperative findings and (2) severe comorbidities, such as interstitial pneumonia, uncontrolled diabetes mellitus, ischemic heart disease, cardiac failure, liver	Intervention: Esophagogastrostomy using the circular stapling (CS) method. Comparison: Esophagogastrostomy using triangulating stapling (TS) method.	Primary: Incidence of anastomotic stricture in the cervical esophagogastric anastomosis within 12 months after the esophagectomy. Secondary: Anastomotic leakage, aspiration pneumonia, reflux esophagitis, and overall post-operative morbidity within the first 12 months postoperatively. Results: **Study population:** 100 patients were randomized to either the CS group (n = 49) or the TS group (n = 51). Two patients in the CS group were excluded, because CS could not be performed, instead TS or hand-sewn anastomosis was performed. No patients in the TS group had their treatment changed to other methods of anastomosis. A total of 98 patients (CS group, n = 47; TS group, n = 51) were analyzed. There were no significant differences between the 2 groups, except for body mass index (P = .018). Total operative time and blood loss were similar for both groups. **Results: Primary:** Anastomotic stricture: The overall anastomotic stricture rate was 17% (17 of 98 patients),

cirrhosis, active hepatitis, and chronic renal failure requiring hemodialysis.

with no significant difference between the 2 groups: 17% (8 of 47 patients) in the CS group vs 19% (9 of 51 patients) in the TS group (P = .935). There were no significant differences between the 2 groups regarding the duration of time from the esophagectomy until the first diagnosis of stricture (CS group: median, 90 days; range, 39–280 days; TS group: median, 70 days; range, 50–130 days) or the frequency of dilatation (CS group: median, 4 times; range, 1–13 times; TS group:median, 3 times; range, 1–5 times). **Secondary:** Anastomotic leakage: The overall incidence of anastomotic leakage was 6 (6%), with no significant difference between the 2 groups (CS group: 5 patients (11%); TS group: 1 patient (2.0%); P = .073). In the CS group, 4 of these 5 patients experienced leakage at the stump of the gastric conduit during upper gastrointestinal endoscopy. Aspiration pneumonia Rates of aspiration pneumonia (CS group: 13%; TS group: 6%), reflux esophagitis (CS group: 13%; TS group: 12%), and Overall morbidity (CS group: 70%; TS group: 69%) were not different between the 2 groups. Three patients in the TS group underwent reoperations due to intrathoracic bleeding, herniation of the transverse colon into the chest via the esophageal hiatus, and disturbances in the passage of ingested foods in the gastric conduit at the esophageal hiatus. No mortality occurred during this trial.

Author's Conclusion: "The triangulating stapling method for cervical anastomosis for thoracic esophageal cancer does not decrease the incidence of anastomotic stricture compared with the circular stapling method within 12 postoperative months but may affect the rate of anastomotic leakage."

Methodical Notes

Funding Sources: No funding was sought for the study.

COI: The authors declare no conflict of interest.

Randomization: Patients were randomized in a 1:1 ratio to the CS group or the TS group when the gastric conduit was pulled up to the neck after the thoracic and abdominal
procedures. Randomization was stratified according to the route of reconstruction (retrosternal or posterior mediastinal route), neoadjuvant chemoradiotherapy, or neither. A clinical researcher performed the randomization using a computer-generated, random block of 4 in a central registry for studies at WMUH.

Blinding: Partial blinding." Although surgeons were unable to be blinded during the operation, the physicians caring for the patients postoperatively as well as the patients. Records detailing the operative procedure were stored during the blinding periods and were not available to any staff members until the completion of this study unless complications of the operation occurred."

Dropout Rate/ITT-Analysis: "2 Dropouts occured in one group and changed to the other group "Two patients
in the CS group were excluded, because one had a narrow cervical esophagus that prevented the anvil head of the 25-mm CS device from being inserted, and one had a gastric conduit of insufficient length for insertion of the CS device. These 2 patients underwent TS anastomosis or hand-sewn anastomosis. No intention to treat analysis was performed."

Notes:
Article submitted by hand search.

Evidence level 2: Randomized controlled trial.
No intention to treat analysis was performed.

Mariette, C. et al. Hybrid Minimally Invasive Esophagectomy for Esophageal Cancer. N Engl J Med. 380. 152-162. 2019

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 Study type: Randomized, controlled trial, multicenter, open-label Number of Patient: 110 Recruitung Phase: 10/2009-04/2012 Inclusion Criteria: Squamous-cell carcinoma or adenocarcinoma of thoracic esophagus with a clinical stage of I, II, or III (tumor stage 1 through 3 [T1, T2, or T3], no nodal involvement [N0] or presence of cancer in lymph nodes [N1] or in distant lymph nodes [≥5 cm from the tumor; N2], and no metastases [M0]) before the receipt of any induction treatment; esophageal cancer in the middle or lower third of the esophagus or junctional (Siewert's type I) tumor; the receipt or nonreceipt of neoadjuvant radiotherapy, chemotherapy, or both; tumors that were considered to be resectable with a curative intention at the time of preoperative evaluation; an age of 18 to 75 years; a World Health Organization performance-	Intervention: Open esophagectomy (open procedure). Comparison: Hybrid minimally invasive esophagectomy (hybrid procedure).	Primary: Intraoperative or postoperative complication of grade II or higher according to the Clavien–Dindo classification (indicating major complication leading to intervention) within 30 days. Secondary: Overall survival after 3 years Results: **Study population:** 207 patients were randomized: 103 patients to the hybrid-procedure group and 104 to the open-procedure group. The demographic and clinical characteristics of the two groups did not differ significantly at BL, except for the American Society of Anesthesiologists risk score (Table 1). The percentage of patients receiving neoadjuvant therapy was similarly high in the two groups (75% vs 72%). **Results:** Complication hybrid minimally invasive esophagectomy was associated with major intraoperative and postoperative morbidity at 30 days that was significantly lower than that with open esophagectomy (36% vs. 64%; P<0.001 by the chi-square test; odds ratio, 0.31; 95% CI, 0.18 to 0.55; P<0.001). Minimally invasive surgery was associated with a 77% lower risk of major intraoperative and postoperative complications within 30

status score of 0, 1, or 2 (on a 5-point scale, with higher numbers indicating greater disability); ability to provide written informed consent; ability to undergo one of the investigated surgical procedures; and ability to attend the follow-up visits.

Exclusion Criteria: Partial pressure of arterial oxygen of less than 60 mm Hg while the patient was breathing ambient air; a partial pressure of arterial carbon dioxide of more than 45 mm Hg; a forced expiratory volume in 1 second of less than 1000 ml; liver cirrhosis; myocardial infarction or progressive coronary artery disease; peripheral arterial occlusive disease of Leriche–Fontaine stage II or higher (in this four-stage system, higher numbers indicate worse symptoms); weight loss exceeding 15% in the 6 months before cancer diagnosis; the presence of another malignant tumor; and receipt of any other simultaneous experimental treatment. The disease-associated exclusion criteria were the following: another histologic subtype of esophageal cancer apart from squamous-cell carcinoma or adeno-carcinoma; tumor located at the pharyngoesophageal junction, the cervical esophagus, the upper third of the esophagus, or the esophagogastric junction
(Siewert type II or III); distant metastases, including peritoneal carcinomatosis or metastasis to the supraclavicular and celiac lymph nodes; recurrent

days than open surgery (adjusted OR, 0.23; 95% CI, 0.12 to 0.44; P<0.001), adjusted for age, sex, American Society of Anesthesiologists risk score, neoadjuvant, therapy use, tumor location, histologic subtype, resection-margin status, pathological tumor and node stages, and trial center).
Secondary: Overall survival after 3 years: overall survival was 67% (95% CI, 57 to 75) in the hybrid-procedure group, as compared with 55% (95% CI, 45 to 64) in the open-procedure group; disease-free survival was 57% (95% CI, 47 to 66) and 48% (95% CI, 38 to 57).

Author's Conclusion: "We found that hybrid minimally invasive esophagectomy resulted in a lower incidence of intraoperative and postoperative major complications, specifically pulmonary complications, than open esophagectomy, without compromising overall and disease-free survival over a period of 3 years."

laryngeal nerve palsy; and tumor involvement of adjacent mediastinal structures.

Methodical Notes

Funding Sources: Supported by the French National Cancer Institute, Programme Hospitalier pour la Recherche Clinique 2008.

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

Randomization: Randomization was performed centrally, with the use of the stratified-field block-randomization method (blocks of four) for each participating center.

Blinding: A randomization list was generated for each center, and numbered envelopes were prepared. The blinded assignment to a trial group was done during surgery, according to serial inclusion.

Dropout Rate/ITT-Analysis: "All the analyses were performed on an intention- to-treat basis; the analyses included all the patients who had undergone randomization, regardless of the surgery performed and eligibility criteria"

Notes:
Evidence level 2: randomized controlled trial.

Straatman, J. et al. Minimally Invasive Versus Open Esophageal Resection: Three-year Follow-up of the Previously Reported Randomized Controlled Trial: the TIME Trial. Ann Surg. . . 2017

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 Study type: Randomized clinical trial. Number of Patient: 115 (56, 59 per arm).	Intervention: Both groups: All patients received neo-adjuvant treatment, mostly chemo-radiotherapy according to the CROSS scheme, before resection. Both procedures included a 2-field esophageal resection with a 3 to 4cm wide gastric tube formation followed by a cervical or intrathoracic anastomosis. For patients undergoing MIS with an	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.

Recruitung 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 intrahoacic esophagus or GEJ
- indication for neoadjuvant therapy
- ECOG performance 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

intrathoracic anastomosis, a bronchus blocker was placed in the right bronchus to help with 1-lung ventilation during anastomosis.

Comparison: Minimally invasive surgery MIS: was performed through a right thoracoscopy in the prone position with 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 8mm Hg

Secondary: surgery, perioperative, 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: **Study population:** Mean age 62±8,4 years per group. Patients received nCRT according CROSS scheme (92.2%) or chemotherapy alone (7.8%).
Results: 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 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

.

Exclusion Criteria: none described.

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."

Methodical Notes

Funding Sources: "The Digestive Surgery Foundation of the Unit of Digestive Surgery of the VU University Medical Centre supported the TIME trial. The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report."

COI: All authors declare that they have no conflict of interest or financial ties to disclose.

Randomization: Randomization was performed centrally via an online module, stratified for participating centers. Patients were randomized in a 1:1 fashion between open and MIS.

Blinding: No blinding was performed, measures are objective.

Dropout Rate/ITT-Analysis: "Data were analyzed according to the intention-to-treat principle." Dropouts per group (6,6; 10%,10%).

Notes:
Evidence level 2: randomized controlled trial

van der Sluis, Pieter C et al. Robot-assisted Minimally Invasive Thoracolaparoscopic Esophagectomy Versus Open Transthoracic Esophagectomy for Resectable Esophageal Cancer: A Randomized Controlled Trial. Ann. Surg. 269. 621-630. 2019

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 Study type: Randomized controlled trial. Number of Patient: 112	Intervention: robot-assisted minimally invasive thoracolaparoscopic esophagectomy (RAMIE)	Primary: percentage of overall surgery-related postoperative complications modified Clavien- Dindo classification (MCDC) surgical complications grade ≥2 Secondary: pulmonary complications (pneumonia, pneumothorax, pulmonary embolus, acute respiratory distress syndrome), cardiac

Recruitung Phase: 01/2012-08/2016 Inclusion Criteria: Supplementary material not available. resectable intrathoracic esophageal cancer Exclusion Criteria: Supplementary material not available.	Comparison: open transthoracic esophagectomy (OTE)	complications (atrial fibrillation, cardiac asthma, myocardial infarction), and postoperative bleeding. Functional Recovery, Pain, and Short-term Quality of Life. Results: **Study population:** 112 patients (allocation ratio 81%) were randomized to undergo either RAMIE or OTE. In the RAMIE group, 1 patient died and 1 patient developed metastases during neoadjuvant treatment. In the OTE group, 1 patient physically deteriorated to WHO-eastern cooperative oncology group (ECOG) 3 after neoadjuvant treatment and refused surgery. Demographic and clinical characteristicswere similar at baseline **Results: Primary:** Overall surgery-related postoperative complications (MCDC grade ≥2) occurred in 32 of 54 patients after RAMIE (59%) and in 44 of 55 patients after OTE (80%) {RAMIE RR 0.74 [95% CI with RAMIE (CI), 0.57– 0.96; P = 0.02]}. **Secondary:** Overall postoperative complications (MCDC grade ≥2) occurred in 34 of 54 (63%) patients after RAMIE and in 44 of 55 (80%) patients after OTE (RR, 0.79; 95% CI 0.62– 1.00; P = 0.049). Pulmonary complications occurred in 17 of 54 patients in the RAMIE group (32%) and in 32 of 55 patients in the OTE group (58%) [RR 0.54 (95% CI, 0.34–0.85; P = 0.005]. Cardiac complications were observed in 17 of 45 patients in the RAMIE group (22%) and in 26 of 55 patients in the OTE group (47%) [RR 0.47 (95% CI 0.27–0.83; P = 0.006)]. Functional recovery at postoperative day 14 was significantly better in the RAMIE group (38/54 patients, 70%) compared to the OTE group (28/55 patients, 51%) [RR 1.48 (95% CI 1.03–2.13; P =0.04)]. Mean postoperative pain (visual analog scale) during the first 14 days was significantly lower after RAMIE compared to OTE (1.86 vs 2.62, P < 0.001. Short-term QoL Both at discharge and 6 weeks post discharge,

short-term QoL was higher after RAMIE compared to OTE [mean difference 13.4 (2.0–24.7, P ¼ 0.02) and 11.1 (1.0–21.1; P = 0.03)]. Physical functionining: Higher in the RAMIE group as compared OTE [13.5 (1.2–25.7, P = 0.03) and 10.7 (0.04–21.4; P = 0.049) at discharge and 6-week postdischarge].

Author's Conclusion: RAMIE resulted in a lower percentage of overall surgery-related and cardio-pulmonary complications with lower postoperative pain, better shortterm QoL, and a better postoperative functional recovery compared to OTE. Oncological outcomes were equal and in concordance with the highest standards nowadays. This randomized controlled trial provides evidence for the use of RAMIE to improve short-term postoperative outcomes in patients with resectable esophageal cancer.

Methodical Notes

Funding Sources: No funding was obtained for this study

COI: not described.

Randomization: Central randomization, method not described.

Blinding: Operator blinding not possible.

Dropout Rate/ITT-Analysis: All analyses were performed according to the intention-to treat (ITT) principle.

Notes:
Inclusion and exclusion criteria are described in supplementary materials, which were not available. Randomization method unclear. No conflict of interest statements.

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

Gooszen, J A H et al. Intrathoracic versus cervical anastomosis and predictors of anastomotic leakage after oesophagectomy for cancer. Br J Surg. 105. 552-560. 2018

Population	Intervention	Outcomes/Results
Evidence level: 3 Study type: Propensity score matching cohort study. Number of Patient: 2086 (intrathoracic anastomosis 928 and a cervical anastomosis (1158) Recruitung Phase: January 2011 and December 2015, all consecutive patients who underwent oesophagectomy for cancer were identified from the Dutch Upper Gastrointestinal Cancer Audit Inclusion Criteria: All patients undergoing oesophagectomy for oesophageal cancer with gastric tube reconstruction between January 2011 and December 2015.	Intervention: intrathoracic anastomosis Comparison: cervical anastomosis	Primary: Anastomotic leakage rates Secondary: Postoperative morbidity and radical resection rates after oesophageal resection Results: **Study population:** Dutch DUCA registry of all patients undergoing surgery with curative intent for oesophageal or gastric cancer in the Netherlands. Total n=2086 (928 intrathoracic anastomosis and 1158 cervical anastomosis patients; predominantly men (77.4 per cent), and the mean(s.d.) age was 64.6(9.0) years. The percentage of patients with an intrathoracic anastomosis increased during the study interval from 20.6 per cent in 2011 to 59.3 per cent in 2015. After propensity matching, 654 patients were included in both groups and all baseline variables including year of surgery were equally distributed **Results: Primary** Anastomotic leakage was less frequent in patients who underwent an intrathoracic anastomosis than in those with a cervical anastomosis: 111 of 654 (17.0 per cent) versus 143 of 654 (21.9 per cent) respectively (P=0.025). Recurrent nerve paresis occurred less often in patients with an intrathoracic anastomosis: 4 of 654 (0.6 per cent) versus 46 of 654 (7.0 per cent) respectively (P <0.001). The median duration of hospital stay was shorter in patients with an intrathoracic anastomosis: 12 (range 3–145)

Exclusion Criteria: -

versus 14 (4–386) days (P <0·001). Surgical reinterventions, duration of ICU stay, in-hospital mortality and number of readmissions were comparable between
the two groups. The associations between location of the anastomosis and outcome parameters were not statistically significant when stratified by type of surgical approach (P for interaction >0·050). Among patients with an anastomotic leak, there was no significant difference between the anastomosis groups in the percentage of patients who had a surgical reintervention (53.2 per cent of patients with an intrathoracic anastomosis versus 44.8 per cent with a cervical anastomosis; p=0·184) or in-hospital mortality (8·1 versus 10·5 per cent respectively; P=0.520). Duration of hospital stay (median 40 (range 9–132) versus 28 (4–132) days; P <0·001) and length of ICU stay (median 8 (1–111) versus 4 (1–155) days; P =0·021) were longer after an intrathoracic compared with a cervical anastomotic leak. Multivariable analysis revealed that ASA fitness grade III or higher, chronic obstructive pulmonary
disease, cardiac arrhythmia, diabetes mellitus and proximal oesophageal tumours were independent predictors of anastomotic leakage.

Author's Conclusion: "Multivariable analysis revealed that ASA fitness grade III or higher, chronic obstructive pulmonary disease, cardiac arrhythmia, diabetes mellitus and proximal oesophageal tumours were independent predictors of anastomotic leakage."

Methodical Notes

Funding Sources: None declared.

COI: The authors declare no conflict of interest.

Randomization: -

Blinding: -

Dropout Rate/ITT-Analysis: -

Notes: **Article submitted by hand search.**
Evidence level 3: Non-randomized controlled cohort/follow up study.

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

Anderegg, M C J et al. Preoperative Chemoradiotherapy Versus Perioperative Chemotherapy for Patients With Resectable Esophageal or Gastroesophageal Junction Adenocarcinoma. Ann. Surg. Oncol. 24. 2282-2290. 2017

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 4 Study type: Retrospective cohort study.	Funding sources: None declared. Conflict of Interests: There are no conflicts of interest. Randomization: - Blinding: - Dropout rates: -	Total no. patients: 313 Recruiting Phase: April 2005 and November 2011. Inclusion criteria: All patients who started neoadjuvant treatment were included in the analysis. They had World Health Organization (WHO) performance statuses of 0–2. Underlying diseases such as cardiac, vascular, pulmonary, or oncologic	Interventions: Preoperative chemoradiotherapy nCRT (carboplatin/ paclitaxel 41.4 Gy, n = 176) three cycles Comparison: Perioperative Chemotherapy pCT (epirubicin, cisplatin and capecitabine, n = 137) three cycles

	(other than esophageal) disorders had to be stable and under the control of their treating physician. Exclusion criteria: -
Notes:	**Article submitted by hand search.** Evidence level 4: Retrospective Cohort Study Author's conclusion: For patients with esophageal or GEJ adenocarcinoma, chemoradiotherapy with paclitaxel, carboplatin, and concurrent radiotherapy and perioperative chemotherapy with epirubicin, cisplatin, and capecitabin lead to equal oncologic outcomes in terms of radical resection rates, lymphadenectomy, patterns of recurrent disease, and (disease-free) survival. However, neoadjuvant chemoradiotherapy is associated with a considerably lower level of severe adverse events and should therefore be the preferred protocol until a well-powered randomized controlled trial provides different insights.
Outcome Measures/results	Primary Toxicity. Source data verification of all grade 3 and higher adverse events was performed by two separate observers according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.11. Grades 3, 4, and 5 adverse events were graded by consensus of two authors. Secondary Postoperative complications, pathologic response, longterm survival, and disease recurrence.
	Results: **Study population:** Between 2005 and 2011, patients with resectable esophageal or junctional adenocarcinoma were treated at three high-volume referral centers in the Netherlands with two different neoadjuvant regimens. All patients who started neoadjuvant treatment were included in the analysis. They had WHO performance statuses of 0–2. Underlying diseases such as cardiac, vascular, pulmonary, or oncologic (other than esophageal) disorders had to be stable and under the control of their treating physician. 176 patients underwent nCRT, and 137 patients underwent pCT followed by esophagectomy. Baseline characteristics did not differ significantly . The baseline characteristics were representative for patients with esophageal or junctional adenocarcinoma in West European countries. **Results: Primary:** Toxicity Profile The full five cycles of nCRT were administered to 162 (92%) of 176 patients. Of 137 patients, 105 (76.6%) received the full treatment regimen of three preoperative cycles of

chemotherapy (p = 0.000). Postoperative continuation of chemotherapy was started for 60 patients (43.8%). The proportion of patients who underwent surgery after initiation of neoadjuvant therapy with curative intent was comparable in the two groups (97.7% after nCRT vs. 95.6% after pCT; p = 0.293). Whereas nCRT was associated with a higher rate of grades 3 and 4 esophagitis (p = 0.000), pCT was associated with a higher rate of grades 3 and 4 thromboembolic events (p = 0.000), febrile neutropenia (p = 0.038), nausea (p = 0.001), vomiting (p = 0.001), diarrhea (p = 0.001), hand–foot syndrome (p = 0.005), mucositis (p = 0.005), cardiac complications (p = 0.002), and electrolyte imbalances. Two patients in the pCT group died during neoadjuvant treatment due to febrile neutropenia (grade 5 toxicity). **Secondary:** More postoperative cardiac complications occurred in the nCRT group. All other postoperative complications and the in-hospital mortality rate (nCRT, 4.7%; pCT, 2.3%) were comparable. The pathologic complete response (pCR) rate was 15.1% after nCRT and 6.9% after pCT. Radicality of surgery was comparable (R0: 93.0 vs. 91.6%). The median overall survival was 35 months after nCRT versus 36 months after pCT."

Seesing, Maarten F J et al. A Propensity Score Matched Analysis of Open Versus Minimally Invasive Transthoracic Esophagectomy in the Netherlands. Ann. Surg. 266. 839-846. 2017

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 3 Study type: Propensity Score Matched	Funding sources: Not disclosed. Conflict of Interests: The authors report no conflicts of interest. Randomization: -	Total no. patients: 1727 Recruiting Phase: 2011 and 2015 selected from the national Dutch Upper Gastrointestinal Cancer Audit.	Interventions: Open esophagectomy OE. Comparison: Minimally

Analysis (population-based Cohort)	Blinding: - Dropout rates: -	Inclusion criteria: Patients who underwent a transthoracic esophagectomy with a 2-field lymphadenectomy for cT1-4a N0-3 M0 esophageal or gastroesophageal junction cancer between 2011 and 2015 were included. Participation in the DUCA is obligatory; hence, all hospitals in the Netherlands performing esophagogastric surgery are included. Only patients who underwent a combined thoracoscopic and laparoscopic esophagectomy were included in the MIE group. In the open group, the thoracic and the abdominal phase were performed via a thoracotomy and laparotomy. Only 3-stage McKeown (anastomosis in the neck) or 2-stage Ivor Lewis procedures (anastomosis in the chest) with a 2-field lymph node dissection and gastric conduit reconstruction were selected. Patients who underwent a hybrid or transhiatal procedure were excluded and patients with an ASA-IV status or patients who underwent emergency surgery. When the operations started as an MIE and it was converted to open, the procedure was still counted as an MIE. Exclusion criteria: Hybrid, transhiatal, and emergency procedures were excluded.	invasive esophagectomy MIE.

Notes:

Article submitted by hand search.
Evidence level 3: non-randomized controlled cohort/follow-up study.

Author's conclusion: "Within the context of these limitations, the present study shows that MIE was associated with a

		shorter hospital stay and resulted in a higher lymph node yield and a similar percentage of R0 resections. However, MIE did not reduce pulmonary complications and resulted in a higher anastomotic leakage and reintervention rate. Therefore we would advocate further analyses and more extensive proctoring during the further introduction of MIE to reduce potential avoidable harm to the patient."
Outcome Measures/results	Primary Postoperative pulmonary complications (defined as clinically proven pneumonia, pleural effusion leading to drainage, pleural empyema, acute respiratory distress syndrome, or reintubation.) Secondary Clinically or radiologically proven anastomotic leakage, chylothorax, cardiac complications, postoperative bleeding, wound infection, fascial dehiscence, intra-abdominal abscess, gastric conduit necrosis, and recurrent laryngeal nerve injury.	Results: **Patients characteristics:** 2202 patients who underwent a transthoracic esophagectomy for cancer with a 2-field lymph node dissection and gastric reconstruction with curative intent in the Netherlands between 2011 and 2015. Some 1727 patients were included in the study (OE n = 500, MIE n = 1227). The differences in baseline characteristics between the OE and the MIE group were statistically significant across most covariates before adjusting however, these differences were all eliminated after adjusting with propensity score matching . Median (range) age of the patients was 64 (34–84) years, with 66% of patients having an ASA II status and 72% of the patients were diagnosed with a cT3 tumor. In more than half of patients a cervical esophagogastric anastomosis was created. **Results: Primary:** postoperative pulmonary complications:, did not differ between groups: 148 of 433 patients (34.2%) of the OE group and 154 of 433 (35.6%) patients in the MIE group had a pulmonary complication (P = 0.669). **Secondary:** Also in subgroup analyses after exclusion of patients who developed an anastomotic leak (67 leaks in the OE and 92 leaks in the MIE group), the incidence of pulmonary complications was still not statistically different between both groups [OE = 115 (31.4%) vs MIE = 95 (27.9%), P =0.300]. postoperative complication rate was almost similar between the groups: 271 of 433 patients (62.2%) in the OE group and 260 of 433 (60.2%) patients in the MIE group (P = 0.468) had one or more complications. Mortality was not statistically significant different between the groups: 3.0% (OE) versus 4.7%

(MIE) (P = 0.209). Anastomotic leakage (15.5% vs 21.2%, P = 0.028), reinterventions (21.1% vs 28.8%, P = 0.017) and gastric conduit necrosis (0.2% vs 3.2%, P = 0.001) were more frequently observed in the MIE group. Subgroup analyses showed that an anastomotic leak after MIE was more frequently seen after an Ivor Lewis esophagectomy (21% (MIE) versus 10% (OE), P = 0.010) compared to the McKeown group [23% (MIE) vs 17% (OE), P = 0.056]. Hospital stay: was a statistically significant shorter in the MIE group (13 vs 14 days, P = 0.001). The readmission rate was similar for patients after OE compared to MIE (12.5% vs 12.9%, respectively; P = 0.704).

12 Chirurgische Therapie - Ausmaß der Lymphadenektomie

Inhalt: *4 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Kurokawa, Yukinori 2019	3	Prospective Cohort (Nationwide Multicentic Study)
Li, Bin 2018	2	Prospective randomized single-center open-label trial.
Visser, E. 2019	1	Systematic review and meta-analysis. (26 studies)
Yamashita, Hiroharu 2017	4	questionnaire-based national retrospective study

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

Visser, E. et al. Prognostic Value of Lymph Node Yield on Overall Survival in Esophageal Cancer Patients: A Systematic Review and Meta-analysis. Ann Surg. 269. 261-268. 2019

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: Systematic review and meta-analysis. (26 studies) Databases: Embase, Medline (via Pubmed), and the Cochrane library databases Search period: 2000-09/2017.	Population: Esophageal cancer patients undergoing esophagectomy with lymphadenectomy. Intervention: lymph node yield as a prognostic factor. Comparison: -	Primary: Overall survival. Secondary: Disease-free survival. Results: **Included studies:** 25 studies were included; studies were published between 2007 and 2017, with sample sizes ranging from 84 to 18,777 patients. 10 studies included patients who underwent primary esophagectomy, 6 studies	26 studies, see article for details.

Inclusion Criteria: Primary articles with esophageal cancer patients undergoing esophagectomy with lymphadenectomy. Only comparative studies investigating the effects of low and high LNY on OS or disease-free survival were included

Exclusion Criteria: Case reports, studies with fewer than 10 patients, reviews, posters abstracts, animal studies, studies published before 2000, and studies in a language other than English; noncomparative studies or studies not concerning lymphadenectomy and esophageal cancer.

investigated patients who underwent neoadjuvant therapy followed by esophagectomy, and 9 studies investigated both patients who underwent neoadjuvant therapy followed by esophagectomy and primary esophagectomy. Median follow-up was reported in 17 studies and ranged from 15 to 94 months. Median LNY was reported in 17 studies and ranged from 21 to 78 resected nodes. A LNY of ≥15 resected nodes and ≥20 resected nodes was achieved in 8 and 4 studies respectively.
Results: Primary Lymph Node Yield and Overall Survival: 23 Studies , median follow-up ranging from 21 to 94 months compared OS from low and high LNY groups. High LNY was associated with significantly improved OS (HR = 0.81; 95% CI = 0.74–0.87; P < 0.01) with moderate heterogeneity for this result (I^2 = 70.4%). Lymph Node Yield and Disease-Free Survival: 10 studies, median follow-up ranging from 25 to 78 months compared disease free survival from low and high LNY groups. High LNY was associated with significantly improved disease-free survival (HR = 0.72; 95% CI 0.62–0.84; P < 0.01); with moderate heterogeneity (I^2 = 63.5%). Lymph Node Yield and Overall Survival Neoadjuvant Therapy Followed by Esophagectomy; 7 studies; median follow-up ranging from 21 to 94

months compared OS from low and high LNY groups in patients receiving neoadjuvant therapy followed by esophagectomy. High LNY was associated with significantly improved OS (HR = 0.82; 95% CI = 0.73–0.92; P < 0.01), moderate heterogeneity for this result (I^2 = 56.7%).

Author's Conclusion: This meta-analysis demonstrates the benefit of an increased lymph node yield from esophagectomy on overall and disease-free survival. In addition, a survival benefit of a high lymph node yield was demonstrated in patients receiving neoadjuvant therapy followed by esophagectomy.

Methodical Notes

Funding Sources: No means of funding were received for this contribution.

COI: The authors declare no conflict of interests.

Study Quality: No evaluation of study quality.

Heterogeneity: Inter-study heterogeneity was assessed using the I^2 value to measure the degree of variation not attributable to chance alone. This was graded as low (I^2 <25%), moderate (I^2 = 25% to 75%), or high(I^2 >75%).

Publication Bias: Publication bias was explored graphically with funnel plots to detect asymmetry and any outliers. The Egger bias test was used to assess the degree of statistical bias. The significance level was set at P < 0.05. There was no significant publication bias for any of the outcomes.

Notes:
No evaluation of study quality.

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

Li, Bin et al. Extended Right Thoracic Approach Compared With Limited Left Thoracic Approach for Patients With Middle and Lower Esophageal Squamous Cell Carcinoma: Three-year Survival of a Prospective, Randomized, Open-label Trial. Ann. Surg. 267. 826-832. 2018

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 Study type: Prospective randomized single-center open-label trial. Number of Patient: 286 Recruitung Phase: 05/2010 and 07/2012 Inclusion Criteria: Resectable esophageal cancer (cT1-T3, N0-N1, M0) in the middle or lower third of the thoracic esophagus (inferior to the carina and 3 cm superior to the cardia) and no evidence of distant metastases (including the absence of histologically confirmed tumor-positive cervical lymph nodes and unresectable celiac lymph nodes).	Intervention: Esophagectomy through either the right thoracic approach (extended lymphadenectomy) Comparison: Esophagectomy through either the left thoracic approach (limited lymphadenectomy)	Primary: Disease-free survival (DSF), minimal follow-up of 3 years. Secondary: Overall survival (OS). minimal follow-up of 3 years. Results: **Patient Characteristics** 300 patients were recruited between 05/2010 and 07/2012. 14 patients were excluded due to other postoperative pathological diagnoses. Characteristics of the 286 patients were generally comparable between the 2 arms Based on postoperative pathological examination of the resection specimens, 102 patients(35.7%) had R1–2 resection margins [100, R1 (35.0%) and 2, R2 (0.7%) resections]. Of these, 99 patients had positive radial resection margins with the tumor at or within 1mm of the cut margin [46 (31.5%)

Exclusion Criteria: Age older than 75 years, the presence of enlarged lymph nodes in the upper mediastinum (>5 mm), history of other malignant diseases, previous gastric or esophageal surgery, neoadjuvant chemotherapy or radiotherapy, severe major organ dysfunction, and a Karnofsky index of less than 80.

in the right thoracic arm vs 53 (37.9%) in the left thoracic arm, P = 0.259]. Four patients had positive proximal margins [1 (0.7%) in the right thoracic arm vs 3 (2.1%) in the left thoracic arm, P = 0.362]. The median number of lymph nodes removed in the upper mediastinum was 3 [IQR 1–6] in the right thoracic arm. The total numbers of lymph nodes retrieved were 22 (IQR, 17–33) and 18 (IQR, 13–26) in the right and left thoracic arms, respectively (P < 0.001, Mann-Whitney test). **Results:** Median follow-up time was 55.9 months [95% CI: 53.1–58.6]. 13 patients (4.5%) were lost to follow-up, 7 (4.8%) and 6 (4.3%) per arm. Recurrent disease was observed in 113 (39.5%) patients. **Primary:** DFS: The cumulative probability of DFS was higher in the right compared with left thoracic arm (HR, 0.709; 95% CI, 0.65–0.995, P = 0.047). The cumulative DFS rates at 1, 2, and 3 years were 84%, 68%, and 62% in the right thoracic arm, as compared with 73%, 59%, and 52% in the left thoracic arm. **Secondary:** OS: Cumulative OS probability was higher in the right thoracic arm (HR, 0.663; 95% CI, 0.457–0.961, P = 0.029). The cumulative OS rates at 1, 2, and 3 years were 92%, 85%, and 74% in the right thoracic arm, as compared with 86%, 73%, and 60% in the left thoracic arm. Regression analysis of all study subjects using a multivariable Cox proportional hazards model revealed independent associations of reduced DFS

with the following 3 factors: the left thoracic approach (HR, 1.420; 95% CI, 1.006–2.004, P = 0.046), R1–2 resection margins (HR, 2.052; 95% CI, 1.238–3.400, P=0.005), and positive lymph nodes (HR, 3.442; 95% CI, 2.211–5.360, P < 0.001) (Table 3).

Author's Conclusion: Compared with the left thoracic approach, the right thoracic approach associated with increased DFS and OS in esophageal squamous cell carcinoma patients, particularly in those with lymph node involvement and/ or R1–2 resection margins.

Methodical Notes

Funding Sources: This study was funded by the Key Construction Program of the National ‘‘985’’ Project (985III-YFX0102).

COI: The authors report no conflicts of interest.

Randomization: The subjects were allocated using simple randomization with a computer-generated sequence to undergo either the right thoracic or the left thoracic procedure at a 1:1 ratio. Concealment was carried out using opaque sealed envelopes. The envelopes were opened on the morning of the day of the planned resection.

Blinding: Open label trial. The patients, surgeons, and assessors were aware of the assigned treatment. Randomized patients with cancer other than squamous cell carcinoma, as determined by postoperative pathology (n = 14), were excluded from the data analysis. Thus, the remaining 286 subjects were included in the final data analysis, regardless of the follow-up duration.

Dropout Rate/ITT-Analysis: No intention to treat analysis was performed. Randomized patients with cancer other than squamous cell carcinoma, as determined by postoperative pathology (n = 14), were excluded from the data analysis.

Notes:
Article submitted by hand search.
Evidence level 2: Randomized trial
No intention to treat analysis was carried out.

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

Kurokawa, Yukinori et al. Mapping of Lymph Node Metastasis From Esophagogastric Junction Tumors: A Prospective Nationwide Multicenter Study. Ann. Surg. . . 2019

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 3 Study type: Prospective Cohort (Nationwide Multicentic Study)	Funding sources: The study was funded in part by the Japanese Gastric Cancer Association and the Japan Esophageal Society. Conflict of Interests: The authors report no conflicts of interest. Randomization: - Blinding: - Dropout rates: -	Total no. patients: 371. Recruiting Phase: 2014 and 2017 Inclusion criteria: (1) tumor epicenter located within 2.0 cm of the EGJ; (2) histologically proven adenocarcinoma, SCC, or adenosquamous carcinoma; (3) cT2-T4; (4) tumor deemed to be resectable; (5) patient age 20 years or older; (6) Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2; (7) no prior history of gastrectomy; (8) adequate organ function; and (9) provision of written informed consent.	Interventions: Surgery via the abdominal transhiatal (TH) approach, according to the study protocol. We selected the TH approach for adenocarcinoma patients who did not have esophageal involvement of more than 3.0 cm, and employed the RT approach in other patients. BSurgery via the abdominal transhiatal (TH) or right transthoracic (RT) approach, oth approaches always entailed lymph node dissection in the perigastric field (stations 1, 2, 3a), the suprapancreatic field (stations 7, 8a, 9, 11p, 11d), the para-aortic field (station 16a2lat), the abdominal hiatal field (stations 19, 20), and the lower mediastinal field (stations 110, 111, 112). Only the RT approach required thorough mediastinal

		Exclusion criteria: The full analysis set (FAS) was defined as all eligible patients. Patients who withdrew their consent were excluded from the FAS.	lymph node dissection, including the upper (stations 105, 106recL, 106recR) and middle mediastinal nodes (stations 107, 108, 109L, 109R). If a patient was diagnosed as clinically node positive in the upper or middle mediastinal field, we selected the RT approach and dissected the upper and middle mediastinal nodes with therapeutic intent. The left transthoracic approach was acceptable instead of the TH approach. Total gastrectomy was not required in either approach. Comparison: Surgery via right transthoracic (RT) approach,.
Notes:	**Article submitted by hand search.** Evidence level 3: Non-randomized controlled cohort/follow up study. Author's conclusion: The study accurately identified the distribution of lymph node metastases from EGJ tumors and the optimal extent of subsequent lymph node dissection.		
Outcome Measures/results	Primary Metastasis rate of each lymph node station. All lymph nodes were classified into 3 categories according to the metastasis rate, as follows: category-1 (strongly recommended for dissection) nodes, for rates exceeding	Results: **Study population:** Patients with an EGJ tumor were screened, 371 patients were enrolled from 42 institutes between April 22, 2014, and September 29, 2017. Two patients withdrew their consent after enrolment and there were 6 ineligible patients. The remaining 363 patients comprised the FAS population. In the 363 FAS patients, the median tumor size at baseline was 4.6 cm, and the median length of esophageal involvement at baselinewas 2.0 cm. The majority of tumors were	

10%; category-2 (weakly recommended for dissection) nodes, for rates between 5% and 10%; and category-3 (not recommended for dissection) nodes, for rates less than 5%. These cut off values were determined referring to the grouping of the regional lymph nodes in the Japanese Classification of Gastric Carcinoma.

Secondary R0 resection rate, recurrence- free survival, overall survival, postoperative complications, sites of recurrence, and the therapeutic value index calculated by multiplying the metastasis rate by the 5-year overall survival rate in patients with metastasis in each node.

adenocarcinoma, and only 31 (8.5%) were SCC. Neoadjuvant treatments were given to 99 (29.8%) of 332 adenocarcinoma patients and 22 (71.0%) of 31 SCC patients. The most frequent regimens were as follows: docetaxel plus cisplatin plus 5-fluorouracil (n=32), docetaxel plus cisplatin plus S-1 (n=19), cisplatin plus S-1 (n=16), and oxaliplatin plus S-1 (n=15). Although 63.1% of the FAS patients were clinically node positive, only 14 patients (3.9%) had distant lymph node metastasis (M1). 1/3 of the FAS patients were treated by the RT, 2/3 were treated by the TH approach. Half of the FAS patients underwent total gastrectomy. Five patients received simple laparotomy (no resection). **Results:** Of the 358 patients who underwent surgical resection, 69.0% were judged to be pathologically node positive, despite the fact that neoadjuvant treatment was administered to one third of the patients and may have affected the results. Pathological responses of the primary tumors in the 121 patients who underwent neoadjuvant treatment were grade 3 (no viable tumor cells) in 16 (13.2%), grade 2 (viable tumor cells <1/3) in 22 (18.2%), grade 1b (viable tumor cells 1/3–2/3) in 26 (21.5%), grade 1a (viable tumor cells >2/3) in 51 (42.1%), and grade 0 (no histological treatment effect) in 6 (5.0%). Since R0 resection was achieved in 214 (88.4%) of the 242 patients without neoadjuvant treatment and in 114 (94.2%) of the 121 patients with neoadjuvant treatment, the R0 resection rate in the 363 FAS patients was 90.4% (95% CI 86.8–93.2). **Primary:** Metastasis Rates of Each Lymph Node Station We estimated the metastasis rates of the abdominal nodes in the 358 patients who underwent surgical resection. Category-1 nodes, whose rates exceeded 10%, were perigastric stations 1, 2, and 3, and supra-pancreatic stations 7, 9, and 11p. Category-2 nodes, whose rates were between 5% and 10%, were suprapancreatic station 8a and abdominal hiatal station 19. The metastasis rate of para-aortic station 16a2 was 4.7% (95% CI 2.7– 7.4), and was thus classified as category-3, with a rate less than 5%. These results were similar after neoadjuvant treatment and between adenocarcinoma and SCC. Subgroup analysis

according to the baseline tumor size showed that the metastasis rates of station 16a2 was 10.1% (95% CI 4.2–19.8) if the tumor size exceeded 6.0 cm. Similarly, the metastasis rate of at least 1 of perigastric stations 4d, 5, or 6 reached 10.7% (95% CI 2.3–28.2) in cases with a tumor size bigger than 6.0 cm.

Yamashita, Hiroharu et al. Results of a nation-wide retrospective study of lymphadenectomy for esophagogastric junction carcinoma. Gastric Cancer. 20. 69-83. 2017

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 4 Study type: questionnaire-based national retrospective study	Funding sources: - Conflict of Interests: The authors have no conflicts of interest to disclose. Randomization: - Blinding: - Dropout rates: -	Total no. patients: Recruiting Phase: 01/2001 and 12/2010 Inclusion criteria: National questionnaire survey included patients with EGJ carcinoma who had undergone R0 resection between 01/2001 and 12/2010. EGJ carcinoma in this survey was defined as having its epicenter within 2 cm proximal or 2 cm distal to the anatomical EGJ, according to the definition promulgated by the Japanese Gastric Cancer Association and the Japan Esophageal Society. We selected tumors of 40 mm or less in dimension since large tumors were apparently associated with poor macroscopic recognition of the anatomical EGJ. Tumor histology was classified into five subtypes: SCC, differentiated AC, undifferentiated AC, adenosquamous carcinoma and other type. Pre- and postoperative treatments were defined as chemotherapy, radiation, chemoradiation, no therapy or unknown;	Interventions: This national questionnaire survey included patients with EGJ carcinoma who had undergone R0 resection between January 2001 and December 2010. Comparison: -

	chemotherapeutic regimens and radiation doses were not specified. Tumor depth was pathologically classified into four groups as pT1a, tumor confined to the mucosa; T1b, tumor confined to the submucosa; T2, tumor invasion of the muscularis propria but not deeper layers; T3/T4, tumor invasion beyond the muscularis propria. T3 and T4 were classified as one category since the definitions of T3 and T4 provided by the Japanese Gastric Cancer Association and the Japan Esophageal Society were not entirely consistent. Lymph node station numbers were determined according to the uniform definition established by the Japanese Gastric Cancer Association and the Japan Esophageal Society. Exclusion criteria: -
	Article submitted by handsearch. Evidence level 4: Case-series, case control study or historically controlled study.
Notes:	Author's conclusion: Complete nodal clearance along the distal portion of the stomach offers marginal survival benefits for patients with EGJ cancers less than 4 cm in diameter. The optimal extent of esophageal resection and the benefits of mediastinal node dissection remain issues to be addressed in managing patients with esophagus-predominant EGJ cancers.
Outcome Measures/results	Primary Rate of dissection according to the tumor epicenter
	Results: **Patient Characteristics** 273 Japanese institutions Japane, providing 2807 patients without prior gastrectomy or preoperative therapy. Tumor histology was differentiated adenocarcinoma in 1926 (68.6%),

Secondary Rate of lymph node metastasis according to the tumor epicenter	undifferentiated adenocarcinoma in 458 (16.3%), SCC in 370 (13.2%), adenosquamous carcinoma in 16 (0.6%) and other type in 37 patients. The median follow-up duration of 2114 surviving patients was 4.5 years (interquartile range: 2.7–6.2). Mean age was 67.1 years, majority was male (male:female, 4:1). Adjuvant postoperative therapy was not given to 2222 (79.2%) patients. The tumor epicenters were mainly at the gastric side (GE, G) in AC (73.4%) and at the esophageal side (E, EG, E = G) in SCC (88.4%) cases. **Results: Primary:** Rate of dissection according to the tumor epicenter Pathological T classification of 989 esophagus-predominant EGJ cancers was T1a in 141, T1b in 421, T2 in 166 and T3/4 in 261 patients. Perigastric nodes (nos. 1, 2, 3, 7) were constantly dissected, followed by lower mediastinal (nos. 110, 111), suprapancreatic (nos. 8a, 9, 11p) and other perigastric (nos. 4sa, 4sb) nodes in incidence of dissection. Dissection of other lymph node areas appeared to be performed on a highly selective basis, since the frequency of dissection for the cervical, upper mediastinal and middle mediastinal nodes, except no. 108, as well as the nodes along the distal portion of the stomach (nos. 4d, 5, 6), was less than 40% even in patients with T3/4 tumors. In marked contrast, the frequency of nodal dissection in the mediastinum and parahiatal area was very low for tumors located predominantly in the stomach, regardless of their histology. Secondary Rate of nodal metastases frequently involved the abdominal nodes, especially those at the right and left cardia, lesser curvature and along the left gastric artery. Nodes along the distal portion of the stomach were much less often metastatic, and their dissection seemed unlikely to be beneficial.

13 Multimodale Therapie - Radiotherapie

Inhalt: *6 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Fuchs, C. S. 2017	2	Randomized controlled trial
Kang, J. 2018	1	Systematic review and meta-analysis.(13 studies)
Li, F. 2018	1	Systematic review and meta-analysis
Liu, T. 2018	1	Systematic review and meta analysis (19 studies)
Montagnani, F. 2017	1	Systematic review and network meta-analysis (25 articles)
Zhao, P. 2018	1	Systematic review and meta-analysis (9 studies)

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

Kang, J. et al. Role of Postoperative Concurrent Chemoradiotherapy for Esophageal Carcinoma: A meta-analysis of 2165 Patients. J Cancer. 9. 584-593. 2018

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: Systematic review and meta-analysis.(13 studies) Databases: PubMed, PMC, EMBASE, Cochrane Central Register of Controlled Trials, Chinese National Knowledge	Population: Esophageal carcinoma patients who have underwent esophagectomy and lymphadenectomy. Intervention: postoperative concurrent chemoradiotherapy (post-	Primary: Overall survival 1,3,5 year Secondary: local-regional recurrence, distant metastasis rate and adverse-event rate. Results: **Population characteristics:** 13	Saito 2993; Mukaida 1998, Bedard 2001, Rice 2003, Tachibana 2003, Liu 2005, Lv 2010; Cao 2010; Chen 2011; Wang 2014; Hsu 2014;

Infrastructure and Wanfang Search period: Inception - 07/2017 Inclusion Criteria: Clinical trials comparing post-CCRT with one of the following non-CCRT strategies: observation, postoperative CT (post-CT), postoperative RT (post-RT) or postoperative sequential chemoradiotherapy (post-SCRT) in the treatment of esophageal carcinoma after surgery; available data on survival, recurrence or toxicities had to be reported; 3. the language of publication was limited to English and Chinese with English abstract. RCTs and non-randomized controlled trials (NRCTs) were eligible. Exclusion Criteria: Articles for which the full text was not available were excluded.	CCRT) Comparison: one of the following non-CCRT strategies: observation, postoperative CT (post-CT), postoperative RT (post-RT) or postoperative sequential chemoradiotherapy (post-SCRT)	studies (3 RCTs, one prospective non-randomized controlled study, one prospective historical controlled study and 8 retrospective control studies). Total n=2165 (998 treated with post-CCRT, 1167 with non-CCRT treatment after surgery). 10 studies enrolled patients with squamous cell carcinoma (SCC) only, 3 studies both SCC and adenocarcinoma (AC) were eligible. The type of SCC comprised 94.6% of all cases and AC accounted for 5.4%. Tumor stage of the patients ranged from phase Ⅱ to phase Ⅳ. Eleven out of 13 studies were conducted in Asian countries, including eight in China, three in Japan. **Results: Primary** <u>Effects of post-CCRT on survival</u> There was significant benefit on overall survival in the post-CCRT group. The values of OR for CCRT comparing with non-CCRT were 1.66 (95% CI=1.30–2.11, P<0.0001) for 1-year survival, 1.50 (95% CI=1.24–1.81, P<0.0001;) for 3-year survival, and 1.54 (95% CI=1.22–1.94, P=0.0003;) for 5-year survival in fixed effects-model. Subgroup analysis per	Hwang 2016, Hsu 2017.

treatment see article. **Secondary:** Effects of post-CCRT on recurrence available in 11 studies. Local-regional recurrence rate was significantly lower in the CCRT group compared with non-CCRT group (OR=0.58, 95% CI=0.46–0.72, P<0.00001). Metastasis rate: Since there was heterogeneity regarding the distant metastasis among the eleven studies (I^2=60%), a random-effects model of analysis was used. There was no significant difference in the comparison of distant metastasis rate between the two groups (OR=0.94, 95% CI=0.68–1.30 P=0.70;). Toxicity of post-CCRT available in 3 studies which compared post-CCRT with post-CT or post-RT [13, 18, 23]. The pooled analysis results revealed that post-CCRT didn't increase the risk of grade 3-4 anemia (OR=1.26, 95% CI=0.34–4.73, P=0.73) and thrombocytopenia (OR=0.84, 95% CI=0.25–2.82, P=0.77) compared with post-CT or post-RT. Compared with post-RT, post-CCRT increased the risk of esophagitis (OR=1.71, 95% CI=1.09–2.66, P=0.02) but not pneumonitis (OR=0.89,

95% CI=0.55–1.44, P=0.63) or anastomotic stenosis (OR=0.54, 95% CI=0.18–1.59, P=0.26).

Author's Conclusion: "Meta-analysis .. confirms that post-CCRT yields significant survival benefit and improves local-regional control with tolerable toxicity for patients with esophageal carcinoma."

Methodical Notes

Funding Sources: This work was supported by grants from National Natural Science Foundation of China (No. 81372418).

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

Study Quality: The quality of RCTs was assessed using the Jadad scale, the scores of which range from 0 to 5, with higher scores indicating better reporting.
"the overall methodological quality of included studies was relatively high."

Heterogeneity: The statistical heterogeneity of each study was assessed by I2 statistic with planned cut-off for significance of I^2 =50%. If $I^2 \leq 50\%$ which indicated no significant heterogeneity existing between the included studies, a fixed-effects model was adopted; otherwise, a random-effects model was employed and sensitivity analysis was further carried out using the leave one-out approach if there were more than two studies.

Publication Bias: The Begg's and Egger's test in STATA were used to assess the potential publication bias. "There was no publication bias for the pooled estimates of 1-year and 3-year survival." Publication bias was detected in the 5-year survival
result since the P values for the Begg's and Egger's test were both less than 0.05."

Notes:
Evidence level 1: Systematic review and meta-analysis.

Li, F. et al. The current optimal multimodality treatments for oesophageal squamous-cell carcinoma: A systematic review and meta-analysis. Int J Surg. 60. 88-100. 2018

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: Systematic review and meta-analysis Databases: PubMed, Embase, Ovid, Cochrane library Search period: Inception - 04/2018 Inclusion Criteria: Rcts and non-randomized controlled studies, studies containing patients with histologically proven locally advanced esophageal squamous cell carcinoma LAESCC, application of nCRT or nCT or DCRT on LAESCC, available data for meta-analysis. Exclusion Criteria: studies without comparison between nCT+S and nCRT+S or nCRT+S and dCRT for LAESCC. Studies containing patients with distant	Population: Patients with histologically proven locally advanced esophageal squamous cell carcinoma LAESCC Intervention: definitive chemoradiotherapy dCRT, neoadjuvant chemotherapy nCT followed by surgery, neoadjuvant radiochemotherapy nCRT followed by surgery. Comparison: One of the interventions.	Primary: Overall survival, as hazard ratio Secondary: local recurrence rate. Results: **Study characteristics:**14 studies compared nCRT+S with dCRT, 5 studies compared nCRT+S with nCT+S. **Results:** nCRT+S vs. nCT+S: nCRT+S had higher rates of R0 resection (OR 1.84, 95% CI 1.03-3.29), pCR (OR 2.90, 95%CI 1.37-6.14) and pN0 (OR 2.55, 95%CI 1.54-4.24) and survival advantage (HR 0.72, 95%CI 0.52-0.99) when compared to nCRT+S. nCRT+S was compared to dRCT: nCRT+S had had better survival (HR 0.65, 95%CI 0.56-0.76) and had a significantly lower rate of local recurrence (OR 0.35, 95%CI 0.22-0.57) Author's Conclusion: "Current evidence suggests that CRT+S may the optimal	Nakadi 2001, Delcambre 2001, Kim 2003, Fujita 2005, Nagata 2006, Cheng 2008, Shao 2015, Hategan 2015, Wang 2016, Wu 2017, Reynold 2017, Liu 2017, Molena 2018.

metastases (stage IV) or with very early disease (stage 0), Studies with without comparability between groups, Studies reported as abstracts, conference reports, reviews and reports,

potential curative treatment mode for patients with LAESCC as long as they are suitable for this multimodality regimen.

Methodical Notes

Funding Sources: Supported by grants from the National Scieence and Technology Support program

COI: The authors declare tno conflict of interest.

Study Quality: Study quality was assessed by Jadad Scoring ssystem and the Newcastle Ottawa scale for RCTs and non-randomized controlled studies.
The RCTS had moderate quality with Jadad Scroes ranging form 2 to 3. while the NOS scores of the non-randomized studies ranged from 5-8 showing acceptable quality.

Heterogeneity: I^2 was ≥50% in the comparison between nCRT+S and nCT+S regarding overall survival, R0 resection and pN0, despite random-effects models.

Publication Bias: Funnel plot, Egger and Begg's test were used to investiagte sources of publication bias. No sigificant publication bias was found.

Notes:
Eveidence level 1: systematic review and meta-analysis.
Considerable heterogeneity (I≥2 50%) in the analysis comparing nCRT+S and nCT+S regarding overall survival, R0 resection and pN0.

Liu, T. et al. The role of postoperative radiotherapy for radically resected esophageal squamous cell carcinoma: a systemic review and meta-analysis. J Thorac Dis. 10. 4403-4412. 2018

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: Systematic review and meta analysis (19 studies) Databases: PubMed, EMBASE, Web of Science, and Cochrane Library Search period: Inception - 09/2017. Inclusion Criteria: RCT, or prospective or retrospective cohort study; Participants with a histopathological diagnosis of ESCC and resectable disease; Patients with surgery as their initial treatment and compared patients who received radical resection with or without PORT; reported survival [overall survival (OS) and/or disease-free survival (DFS) data. If multiple articles covered the same study population, the study with the most recent and complete survival data was used. Exclusion Criteria: letters, editorials, case reports, and reviews; survival data	Population: Patients with resectable esophageal squamous cell carcinoma ESCC. Intervention: Postoperative radiotherapy (PORT) Comparison: Surgery alone	Primary: Overall survival (OS) and disease-free survival (DFS), reported as hazard ratios (HR) and 95% confidence intervals (CIs). Secondary: locoregional recurrence and distant hematogenous metastasis Results: **Study characteristics:** 6 RCTs and 13 retrospective studies, total n=8,198 patients (2,779 patients receiving PORT and 5,419 patients receiving S alone) were included in the meta-analysis. **Results: Primary** Overall survival OS and and disease free survival DFS Significantly statistical difference was observed between PORT and S alone groups in a pooled analysis of OS for 5,657 patients from all included retrospective studies (HR =0.75, 95% CI: 0.65–0.85, P heterogeneity <0.0001), but not for 1,050 patients from all included RCTs (HR =0.94, 95% CI: 0.81–1.09, P heterogeneity =0.13). PORT was associated with significantly improved DFS compared to S alone both for retrospective studies (5 studies with 1,378 patients; HR =0.72, 95% CI:	Lv 2010, Xiao 2003, Zieren, 1995, Teniere 1991, Fok 1993, FOk 1994, Yang 2017, Worni 2012, Hwang 2016, XU, 2013, Zhang 2015, Zou 2016, Hsu 2014, Qiu 2017, CHen 2010, Chen 2016, Lyu 2014, Chen 2009, Shimizu 2005

could not be extracted from the literature.	0.62–0.83, P heterogeneity=0.12) and RCTs (3 studies with 414 patients; HR =0.69, 95% CI: 0.54–0.88, P heterogeneity=0.69) **Secondary:** In the subgroup analysis for retrospective studies, PORT gained superior OS in patients with lymph node-positive (pN+), patients with lymph node-negative (pN0) or pT2–3N0, PORT with three-dimensional radiotherapy (3D-RT), PORT with chemotherapy, and patients with R0 resection, respectively. Author's Conclusion: "The present study shows that PORT can improve DFS and decrease risk of loco-regional recurrence in patients with radically resected ESCC, and PORT using 3D-RT or in combination with chemotherapy is likely to be more useful."

Methodical Notes

Funding Sources: not described.

COI: The authors have no conflicts of interest to declare.

Study Quality: Cochrane risk of bias tool was used to assess the quality of RCTs, and the Newcastle-Ottawa Quality Assessment Scale (NOS) was used to assess the quality of retrospective studies. All of the retrospective studies demonstrated a score of ≥6. The qualities of the included RCTs were generally low. One RCT were considered to be in “high risk”, and the remaining RCTs were classified as “unclear” with respect to the risk of bias.

Heterogeneity: A statistical test for heterogeneity was performed by the Chi-square (χ2) and I-square (I^2) test with significance set at P<0.10 and/or I2>50%. If significant heterogeneity existed, a random-effects analysis model was used; otherwise, a fixed-effects model was used. Significant heterogeneity was seen in pooled analysis of OS (I^2=70%) in retrospective studies.

Publication Bias: Although the Begg's test results indicated no publication bias (P=0.511),
Egger's test suggested a borderline significant probability of publications bias (P=0.084). However, the trim and fill method demonstrated that no missing studies were detected, indicating that our results were reliable

Notes:
Evidence level 1: Systematic review and meta-analysis.
Significant heterogeneity in the pooled analysis of OS (I^2=70%) in retrospective studies, which is investigated by the authors. "Subgroup and meta-regression analysis revealed PORT with/ without chemotherapy was identified as evident contributor of heterogeneity."

Montagnani, F. et al. Multimodality treatment of locally advanced squamous cell carcinoma of the oesophagus: A comprehensive review and network meta-analysis. Crit Rev Oncol Hematol. 114. 24-32. 2017

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: Systematic review and network meta-analysis (25 articles) Databases: Pubmed and EMBASE, handsearch of journals Search period: not described. Inclusion Criteria: Studies enrolling oesophageal cancer patients	Population: Oesophageal squamous cell carcinonma (OSCC) Intervention: Multimodality treatment (i.e. [neo-]adjuvant CT or RT or CRT or definitive CRT) Comparison: Surgery	Primary: Overall survival (OS),defined from the time of randomization or the start of treatment to death from any cause. Hazard ratios (HRs) and their 95% confidence intervals (95%CIs) were used to estimate treatment effects. Secondary: - Results: **Study characteristics:** 25	Roth 1988, Schlag 1992, Nygaard 1992, Apinop 1994, Maipang 1994, Le Prise 1994, Ando 1997, Bosset 1997, Law 1997, Ancona 2001, Urba 2001, Ando 2003, Lee 2004, Burmeister 2005, Stahl 2005, Natsugoe 2006, Kelsen 2007, Allum 2009, Cao 2009, Lv 2010, Boonstra 2011, Ando 2012, Van

independently of tumour histology were included if the following criteria were respected: Study design provided for patient stratification according to histology; sufficient data for the OSCC subgroup were reported.

Exclusion Criteria: Studies enrolling less than 25 OSCC patients were not included in the meta analysis, as well as studies testing biologic agents either alone or in combination with CT or CRT.

studies, published between 1988 and 2014, total n=3866 OSCC patients, were included in the meta-analysis. The majority of trials compared surgery with neoadjuvant CRT (total number of patients: 942) or neoadjuvant CT (total number of patients: 997).

Results: Primary

Overall survival

- both neoadjuvant CRT and definitive CRT confer an OS advantage over surgery alone: HRs (95% CI) were 0.73 (0.63–0.86) and 0.62 (0.41–0.96), respectively.
- Adjuvant CRT apparently demonstrated a similar impact on OS, despite lacking significance (HR 0.73; 95%CI 0.47–1.12). A non-significant trend in favour of neoadjuvant CT was found (HR 0.90; 95%CrI 0.76–1.07), whereas adjuvant CT apparently adds no further benefit to surgical resection (HR 1.00;95%CrI 0.70–1.40).
- Rank probability analysis,which provides an estimate of the probability of each treatment modality to be the most effective therapeutic option

Hagen 2012, Teoh 2013, Mariette 2014.

compared with surgery: definitive CRT and neoadjuvant CRT have the highest probability to represent the most effective treatment approaches in locally advanced OSCC, as they have 82.8% and 54.9% probability, respectively, to be the best or second best therapeutic options.

Author's Conclusion: "Our Bayesian analysis supports the role of neoadjuvant CRT as the preferable treatment modality in OSCC, being definitive CRT an appropriate alternative in selected cases. Future studies should focus on the prospective assessment of preoperative CRT or definitive CRT with more modern regimens."

Methodical Notes

Funding Sources: No fundings were used for this manuscript.

COI: All the authors declare no conflicts of interest.

Study Quality: We assessed the risk of bias for each study by the use of the Cochrane tool.
10 studies were at high risk of bias, 6 at low risk and 9 at unclear risk.
There is great heterogeneity among studies with regard to staging procedures, CT administered, CT doses and type of radiation treatment. Most

studies were conducted in single institutions over a large period of time and randomization procedures are often not reported. Moreover, data regarding protocol violations or potential prognostic factors are frequently not specified in the manuscripts.

Heterogeneity: Heterogeneity described in the supplementary section of the article.
- In order to statistically assess heterogeneity, standard pairwise meta-analyses were performed for the following comparisons: surgery vs. neoadjuvant CT, surgery vs. neoadjuvant CRT and surgery vs. definitive CRT. Other comparisons were not possible due to the small number of trials. Despite the aforementioned considerations, significant heterogeneity was present only in the first comparison (surgery vs. neoadjuvant CT): I^2=44%,p=0.056.

Publication Bias: Publication bias was assessed by visual inspection of funnel plots.

Notes:
Evidence level 1: Systematic review and meta-analysis
- Search period for database search not described.
- Details regarding heterogeneity, Publication bias and individual quality evaluation of original studies are reported in online supplementary, which is not available to the assessor. Only a short summary to these analyses can be found in the manuscript, except for results of the publication bias assessment which are not described.

Zhao, P. et al. Efficacy of postoperative adjuvant chemotherapy for esophageal squamous cell carcinoma: A meta-analysis. Thorac Cancer. 9. 1048-1055. 2018

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: Systematic review and meta-analysis (9 studies) Databases: PubMed, Embase, and Cochrane	Population: Esophageal squamous cell cancer patients ESCC Intervention: postoperative chemotherapy	Primary: Overall survival (OS) Secondary: Disease-free survival (DFS) Results: **Study characteristics** 9 studies included the meta-analysis,	Pouiquen 1996, Ando 1997, Herooer 2003, Ando 2003, Lee 2005, Lyu 2014, Hashiguchi 2014,

Search period: Inception - 02/2018 Inclusion Criteria: ESCC patients as subjects; studies that focused on adjuvant therapy for esophageal cancer and included comparisons between adjuvant chemotherapy and surgery alone; independent clinical trials with an analysis of clinical data; and articles that reported prognostic hazard ratios (HRs) and 95% confidence intervals (CIs) of OS and DFS. Exclusion Criteria: -	Comparison: no postoperative chemotherapy (surgery alone)	published between 1996 and 2016, total n = 1684 patients; the pathological type was ESCC for all included patients. All the included literature was evaluated as high quality (NOS ≥ 6). **Results: Primary** <u>Overall survival</u> 9 publications(n = 1684) fixed effect: ESCC patients receiving postoperative chemotherapy could achieve improved OS (HR 0.78, 95% CI 0.66–0.91; P = 0.002) <u>Disease-free survival:</u> 5 publications (n = 1102) fixed effect model: The results showed that ESCC patients receiving postoperative chemotherapy could also achieve improved DFS (HR 0.72, 95% CI 0.6–0.86; P < 0.001). Author's Conclusion: The current meta-analysis supports postoperative chemotherapy as an independent favorable prognostic factor for ESCC, which could improve both OS and DFS.	Pasquer 2015, Qin 2016

Methodical Notes

Funding Sources: This study was financially supported by the Beijing Municipal Administration of Hospitals Incubating Program (PX2018044), the National Natural Science Foundation for Young Scholars (Grant 81301748), the National High Technology Research and Development Program of China (2015AA020403), and the Beijing Municipal Administration of Hospitals Clinical Medicine Development of Special Funding Support (ZYLX201509).

COI: No authors report any conflict of interest.

Study Quality: The quality of the studies in this meta-analysis was assessed using the Newcastle Ottawa Scale (NOS), and papers with scores ≥ 6 were defined as high quality. All the included literature was evaluated as high quality (NOS ≥ 6).

Heterogeneity: Heterogeneity among the included studies was assessed by the Q test and I2 statistic. If $I^2 \leq 50\%$, a fixed effect model was used; if I2 > 50%, a random effect model was applied. $I^2 = 0.0\%$ for both outcomes.

Publication Bias: Risk analysis of publication bias was assessed using Egger's test, and the results showed no obvious publication bias among the included studies, indicating that the levels of heterogeneity and bias were acceptable.

Notes:
Evidence level 1: systematic review and meta-analysis.
No methodological drawbacks.

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

Fuchs, C. S. et al. Adjuvant chemoradiotlherapy with epirubicin, cisplatin, and fluorouracil compared with adjuvant chemoradiotherapy with fluorouracil and leucovorin after curative resection of gastric cancer: results from CALGB 80101 (Alliance). Journal of clinical oncology. 35. 3671?3677. 2017

Population	Intervention - Comparison	Outcomes/Results

Evidence level: 2

Study type: Randomized controlled trial

Number of Patient: 546 (280/ 266 per arm)

Recruitung Phase: April 2002 - May 2009

Inclusion Criteria: Histologically confirmed stage IB through IV (M0) adenocarcinoma of the stomach or gastroesophageal junction, according to the 2002 staging criteria of the American Joint Commission on Cancer; en bloc surgical resection of tumor without residual disease; an Eastern Cooperative Oncology Group (ECOG) performance status of # 2; adequate function of major organs (serum creatinine # 1.5 mg/dL and bilateral renal function; serum bilirubin # 2.0 mg/dL; serum AST # 3 times the upper limit of normal; absolute neutrophil count ≥ 1,500/mL; and platelet count $ 100,000/mL); a caloric intake sufficient to ensure a stable weight (, 2 pounds weight loss) for at least 1 week before registration; and random assignment and treatment initiation no earlier than 21 days and no later than 84 days after surgical resection.

Exclusion Criteria: -

Intervention: Adjuvant Chemoradiotherapy with Epirubicin, Cisplatin, and Fluorouracil (ECF)

Comparison: Adjuvant Chemoradiotherapy with Fluorouracil and Leucovorin (FU LV)

Primary: Overall survival OS.

Secondary: Disease free survival DFS and adverse events.

Results: **Population:** Between 04/2002, and 05/2009, 546 adenocarcinoma of the stomach or gastroesophageal junction patients were randomly assigned to receive either FU plus LV before and after combined FU and radiotherapy (n = 280) or ECF before and after combined FU and radiotherapy (n = 266). Baseline characteristics were largely similar between treatment arms. A slightly higher proportion of patients in the ECF arm (62%) had ≥$ 15 lymph nodes examined in the surgical resection specimen compared with the FU plus LV arm (50%). All planned postoperative adjuvant therapy was completed by 68% of patients
Results: Primary: Overall survival: After a median follow-up duration of 6.5 years, 322 deaths were documented (170 in the FU plus LV arm and 152 in the ECF arm). The estimated 5-year OS rates were 44% in the FU plus LV arm and 44% in the ECF arm (stratified Plogrank = .69;). **Secondary:** Disease free survival: With 358 DFS events observed (186 in the FU plus LV arm and 172 in the ECF arm), the estimated 5-year DFS rates were

39% in the FU plus LV arm and 37% in the ECF arm (stratified Plogrank = .94). Mortality: Adjusting for other known or suspected predictors of patient outcome, the multivariable HR for mortality of 0.98 (95% CI, 0.78 to 1.24) for patients in the ECF arm, compared with those treated in the FU plus LV arm. Recurrence: The multivariable HR for cancer recurrence or mortality (DFS) was 0.96 (95% CI, 0.77 to 1.20) comparing treatment arms.

Author's Conclusion: After a curative resection of gastric or gastroesophageal junction adenocarcinoma, postoperative chemoradiotherapy using amultiagent regimen of ECF before and after radiotherapy does not improve survival compared with standard FU and LV before and after radiotherapy.

Methodical Notes

Funding Sources: Extensive list of funding and diclosures for each author, see article.

COI: Extensive list of funding and diclosures for each author, see article.

Randomization: randomization 1:1 to treatment arms. Stratification factors were depth of tumor penetration (T1/T2; T3; T4), nodal status (no positive nodes; one to three positive nodes; four or more positive nodes), and total number of lymph nodes examined in the surgical resection specimen (< 7; 7 - 14; or ≥$ 15). Randomization method not described.

Blinding: No blinding was performed.

Dropout Rate/ITT-Analysis: All randomized participants were analyzed in ITT analysis. Dropouts were 15/280 in FULV group and 29/266 in RCF group.

Notes:
Randomization method inadequately described. Dropouts were lower in the FULV group 15/280 (5%) than in ECF group 29/266 (11%). At least partial blinding could have been achieved but was not used.

14 Multimodale Therapie - Chemotherapie

Inhalt: *4 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Li, F. 2018	1	Systematic review and meta-analysis
Montagnani, F. 2017	1	Systematic review and network meta-analysis (25 articles)
Ruhstaller, T. 2018	1	This open-label, phase III randomized controlled trial
Zhao, P. 2018	1	Systematic review and meta-analysis (9 studies)

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

Li, F. et al. The current optimal multimodality treatments for oesophageal squamous-cell carcinoma: A systematic review and meta-analysis. Int J Surg. 60. 88-100. 2018

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: Systematic review and meta-analysis Databases: PubMed, Embase, Ovid, Cochrane library Search period: Inception - 04/2018 Inclusion Criteria: Rcts and non-	Population: Patients with histologically proven locally advanced esophageal squamous cell carcinoma LAESCC Intervention: definitive chemoradiotherapy dCRT, neoadjuvant chemotherapy nCT followed by surgery, neoadjuvant radiochemotherapy nCRT	Primary: Overall survival, as hazard ratio Secondary: local recurrence rate. Results: **Study characteristics:**14 studies compared nCRT+S with dCRT, 5 studies compared nCRT+S with nCT+S. **Results:** nCRT+S vs. nCT+S: nCRT+S had higher rates of R0 resection (OR 1.84, 95% CI 1.03-3.29), pCR (OR 2.90, 95%CI 1.37-	Nakadi 2001, Delcambre 2001, Kim 2003, Fujita 2005, Nagata 2006, Cheng 2008, Shao 2015, Hategan 2015, Wang 2016, Wu 2017, Reynold 2017, Liu 2017, Molena 2018.

randomized controlled studies, studies containing patients with histologically proven locally advanced esophageal squamous cell carcinoma LAESCC, application of nCRT or nCT or DCRT on LAESCC, available data for meta-analysis.

Exclusion Criteria: studies without comparison between nCT+S and nCRT+S or nCRT+S and dCRT for LAESCC. Studies containing patients with distant metastases (stage IV) or with very early disease (stage 0), Studies with without comparability between groups, Studies reported as abstracts, conference reports, reviews and reports,

followed by surgery.

Comparison: One of the interventions.

6.14) and pN0 (OR 2.55, 95%CI 1.54-4.24) and survival advantage (HR 0.72, 95%CI 0.52-0.99) when compared to nCRT+S. nCRT+S was compared to dRCT: nCRT+S had had better survival (HR 0.65, 95%CI 0.56-0.76) and had a significantly lower rate of local recurrence (OR 0.35, 95%CI 0.22-0.57)

Author's Conclusion: "Current evidence suggests that CRT+S may the optimal potential curative treatment mode for patients with LAESCC as long as they are suitable for this multimodality regimen.

Methodical Notes

Funding Sources: Supported by grants from the National Scieence and Technology Support program

COI: The authors declare tno conflict of interest.

Study Quality: Study quality was assessed by Jadad Scoring ssystem and the Newcastle Ottawa scale for RCTs and non-randomized controlled studies.
The RCTS had moderate quality with Jadad Scroes ranging form 2 to 3. while the NOS scores of the non-randomized studies ranged from 5-8 showing acceptable quality.

Heterogeneity: I^2 was ≥50% in the comparison between nCRT+S and nCT+S regarding overall survival, R0 resection and pN0, despite random-

effects models.

Publication Bias: Funnel plot, Egger and Begg's test were used to investiagte sources of publication bias. No sigificant publication bias was found.

Notes:
Eveidence level 1: systematic review and meta-analysis.
Considerable heterogeneity (I≥2 50%) in the analysis comparing nCRT+S and nCT+S regarding overall survival, R0 resection and pN0.

Montagnani, F. et al. Multimodality treatment of locally advanced squamous cell carcinoma of the oesophagus: A comprehensive review and network meta-analysis. Crit Rev Oncol Hematol. 114. 24-32. 2017

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: Systematic review and network meta-analysis (25 articles) Databases: Pubmed and EMBASE, handsearch of journals Search period: not described. Inclusion Criteria: Studies enrolling oesophageal cancer patients independently of tumour histology were included if the following criteria were respected: Study design provided for patient stratification according to histology; sufficient data	Population: Oesophageal squamous cell carcinonma (OSCC) Intervention: Multimodality treatment (i.e. [neo-]adjuvant CT or RT or CRT or definitive CRT) Comparison: Surgery	Primary: Overall survival (OS),defined from the time of randomization or the start of treatment to death from any cause. Hazard ratios (HRs) and their 95% confidence intervals (95%CIs) were used to estimate treatment effects. Secondary: - Results: **Study characteristics:** 25 studies, published between 1988 and 2014, total n=3866 OSCC patients, were included in the meta-analysis. The majority of trials compared surgery with neoadjuvant CRT (total number of	Roth 1988, Schlag 1992, Nygaard 1992, Apinop 1994, Maipang 1994, Le Prise 1994, Ando 1997, Bosset 1997, Law 1997, Ancona 2001, Urba 2001, Ando 2003, Lee 2004, Burmeister 2005, Stahl 2005, Natsugoe 2006, Kelsen 2007, Allum 2009, Cao 2009, Lv 2010, Boonstra 2011, Ando 2012, Van Hagen 2012, Teoh 2013, Mariette 2014.

for the OSCC subgroup were reported.

Exclusion Criteria: Studies enrolling less than 25 OSCC patients were not included in the meta analysis, as well as studies testing biologic agents either alone or in combination with CT or CRT.

patients: 942) or neoadjuvant CT (total number of patients: 997).

Results: Primary

Overall survival

- both neoadjuvant CRT and definitive CRT confer an OS advantage over surgery alone: HRs (95% CI) were 0.73 (0.63–0.86) and 0.62 (0.41–0.96), respectively.
- Adjuvant CRT apparently demonstrated a similar impact on OS, despite lacking significance (HR 0.73; 95%CI 0.47–1.12). A non-significant trend in favour of neoadjuvant CT was found (HR 0.90; 95%CrI 0.76–1.07), whereas adjuvant CT apparently adds no further benefit to surgical resection (HR 1.00;95%CrI 0.70–1.40).
- Rank probability analysis,which provides an estimate of the probability of each treatment modality to be the most effective therapeutic option compared with surgery: definitive CRT and neoadjuvant CRT have the highest probability to represent the most effective treatment approaches in locally advanced OSCC, as they have

82.8% and 54.9% probability, respectively, to be the best or second best therapeutic options.

Author's Conclusion: "Our Bayesian analysis supports the role of neoadjuvant CRT as the preferable treatment modality in OSCC, being definitive CRT an appropriate alternative in selected cases. Future studies should focus on the prospective assessment of preoperative CRT or definitive CRT with more modern regimens."

Methodical Notes

Funding Sources: No fundings were used for this manuscript.

COI: All the authors declare no conflicts of interest.

Study Quality: We assessed the risk of bias for each study by the use of the Cochrane tool.
10 studies were at high risk of bias, 6 at low risk and 9 at unclear risk.
There is great heterogeneity among studies with regard to staging procedures, CT administered, CT doses and type of radiation treatment. Most studies were conducted in single institutions over a large period of time and randomization procedures are often not reported. Moreover, data regarding protocol violations or potential prognostic factors are frequently not specified in the manuscripts.

Heterogeneity: Heterogeneity described in the supplementary section of the article.
- In order to statistically assess heterogeneity, standard pairwise meta-analyses were performed for the following comparisons: surgery vs.

neoadjuvant CT, surgery vs. neoadjuvant CRT and surgery vs. definitive CRT. Other comparisons were not possible due to the small number of trials. Despite the aforementioned considerations, significant heterogeneity was present only in the first comparison (surgery vs. neoadjuvant CT): I^2=44%,p=0.056.

Publication Bias: Publication bias was assessed by visual inspection of funnel plots.

Notes:
Evidence level 1: Systematic review and meta-analysis
- Search period for database search not described.
- Details regarding heterogeneity, Publication bias and individual quality evaluation of original studies are reported in online supplementary, which is not available to the assessor. Only a short summary to these analyses can be found in the manuscript, except for results of the publication bias assessment which are not described.

Zhao, P. et al. Efficacy of postoperative adjuvant chemotherapy for esophageal squamous cell carcinoma: A meta-analysis. Thorac Cancer. 9. 1048-1055. 2018

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: Systematic review and meta-analysis (9 studies) Databases: PubMed, Embase, and Cochrane Search period: Inception - 02/2018 Inclusion Criteria: ESCC patients as subjects; studies that focused on adjuvant therapy for esophageal cancer and included comparisons	Population: Esophageal squamous cell cancer patients ESCC Intervention: postoperative chemotherapy Comparison: no postoperative chemotherapy (surgery alone)	Primary: Overall survival (OS) Secondary: Disease-free survival (DFS) Results: **Study characteristics** 9 studies included the meta-analysis, published between 1996 and 2016, total n = 1684 patients; the pathological type was ESCC for all included patients. All the included literature was evaluated as	Pouiquen 1996, Ando 1997, Herooer 2003, Ando 2003, Lee 2005, Lyu 2014, Hashiguchi 2014, Pasquer 2015, Qin 2016

between adjuvant chemotherapy and surgery alone; independent clinical trials with an analysis of clinical data; and articles that reported prognostic hazard ratios (HRs) and 95% confidence intervals (CIs) of OS and DFS.

Exclusion Criteria: -

high quality (NOS ≥ 6). **Results: Primary** Overall survival 9 publications(n = 1684) fixed effect: ESCC patients receiving postoperative chemotherapy could achieve improved OS (HR 0.78, 95% CI 0.66–0.91; P = 0.002) Disease-free survival: 5 publications (n = 1102) fixed effect model: The results showed that ESCC patients receiving postoperative chemotherapy could also achieve improved DFS (HR 0.72, 95% CI 0.6–0.86; P < 0.001).

Author's Conclusion: The current meta-analysis supports postoperative chemotherapy as an independent favorable prognostic factor for ESCC, which could improve both OS and DFS.

Methodical Notes

Funding Sources: This study was financially supported by the Beijing Municipal Administration of Hospitals Incubating Program (PX2018044), the National Natural Science Foundation for Young Scholars (Grant 81301748), the National High Technology Research and Development Program of China (2015AA020403), and the Beijing Municipal Administration of Hospitals Clinical Medicine Development of Special Funding Support (ZYLX201509).

COI: No authors report any conflict of interest.

Study Quality: The quality of the studies in this meta-analysis was assessed using the Newcastle Ottawa Scale (NOS), and papers with scores ≥ 6 were defined as high quality. All the included literature was evaluated as high quality (NOS ≥ 6).

Heterogeneity: Heterogeneity among the included studies was assessed by the Q test and I2 statistic. If I^2 ≤ 50%, a fixed effect model was used; if I2 > 50%, a random effect model was applied. I^2 = 0.0% for both outcomes.

Publication Bias: Risk analysis of publication bias was assessed using Egger's test, and the results showed no obvious publication bias among the included studies, indicating that the levels of heterogeneity and bias were acceptable.

Notes:
Evidence level 1: systematic review and meta-analysis.
No methodological drawbacks.

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

Ruhstaller, T. et al. Neoadjuvant chemotherapy followed by chemoradiation and surgery with and without cetuximab in patients with resectable esophageal cancer: a randomized, open-label, phase III trial (SAKK 75/08). Annals of oncology. 29. 1386?1393. 2018

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 1 Study type: This open-label, phase III randomized controlled trial Number of Patient: 300 patients: cetuximab (n=149) or control (n=151).	Intervention: chemoradiation followed by surgery with neoadjuvant and adjuvant cetuximab Comparison: chemoradiation followed by surgery without neoadjuvant and adjuvant cetuximab (control)	Primary: Progression-free survival (PFS) defined as time from randomization to tumor progression, recurrence after surgery, or death from any cause, whichever came first. Secondary: Secondary outcomes were OS, histologic remission, R0-resection rate, and in-hospital mortality.

Recruitung Phase: 05/2010 and 12/2013

Inclusion Criteria: Previously untreated patients with histologically confirmed squamous cell carcinoma SCC (from 5 cm below the entrance of the esophagus into the thorax) or adenocarcinoma of the thoracic esophagus, including the gastro-esophageal junction AEG types I and II according to Siewert were included. Tumors had to be locally advanced, but resectable. Eligible patients were aged 18–75 years, with a WHO performance status of ≤1, with adequate hematologic, renal and hepatic function and a normal lung function.

Exclusion Criteria: Patients with metastases (including cervical or celiac lymph node involvement [M1a]), concurrent cancer, uncontrolled significant comorbidity, or infiltration of the tracheo-bronchial tree were not eligible.

Results: **Population:** 300 ESCC patients were randomly assigned to receive cetuximab (n=149) or control (n=151) at 53 centers in four European countries between 05/2010 and 12/2013. 3 patients were recognized to have metastatic disease after treatment had already started . These patients were included in the safety analyses, but excluded from the ITT efficacy analysis. The median age of all enrolled patients was 61 years, 263 (88%) of 300 patients were men, 246 (82%) had uT3 disease, and 269 (90%) were node-positive. Baseline characteristics were generally well balanced between the two groups.
Results: Primary: PFS: Median follow-up time for all patients was 4.0 years. Median PFS was 2.9 years (95% CI, 2.0 to not reached) and 2.0 years (95% CI, 1.5–2.8) for the cetuximab and control groups, respectively (HR 0.79; 95% CI, 0.58–1.07, P=0.13). In total, 76 patients (51%) in the cetuximab group and 90 (60%) of controls experienced an event. The respective PFS rates at 1, 2, 3, and 4 yearswere 74%, 58%, 50%, and 48% in arm A and 73%, 50%, 41%, and 37% in arm B. **Secondary:** OS: Median OS in the cetuximab group was 5.1 years (95% CI, 3.7 to not reached) and 3.0 years (95% CI, 2.2–4.2) in the control group (HR 0.73; 95% CI, 0.52–1.01, P=0.055; Figure 2). The respective OS rates at 1, 2, 3, and 4 years were 85%,

71%, 62%, and 56% in arm A and 79%, 63%, 51%, and 43% in arm B.

Author's Conclusion: "Adding cetuximab to multimodal therapy significantly improved loco-regional control, and led to clinically relevant, but not-significant improvements in PFS and OS in resectable esophageal carcinoma."

Methodical Notes

Funding Sources: This trial was supported by the Swiss State Secretariat for Education, Research and Innovation (SERI) and Merck KGaA, Darmstadt, Germany (no grant number applies).

COI: Extensive list, see article (Pfizer, Novartis, Roche, Astra- Zeneca, Lilly and Amgen...

Randomization: Patients were randomly assigned (1 : 1) to receive multimodal therapy (control) with or without neoadjuvant and adjuvant cetuximab. Randomization was centralized at the SAKK Coordinating Center with stratification by center, histological type (i.e. adenocarcinoma or SCC), stage (T2 versus T3/4), and gender using the minimization method with 90% allocating probability.

Blinding: open-label trial.

Dropout Rate/ITT-Analysis: All efficacy analyses were based on the intention-to-treat (ITT) population,
defined as all randomized, eligible patients who received at least one dose of trial therapy. All safety analyses were based on the safety population, defined as all randomized patients who received at least one dose of trial therapy.
33 participants in the treatment arm did not receive adjuvant cetuximab, due to complication, refusal, death or mistake.

Notes:

Evidence level 2: randomized controlled trial.
Partial blinding could have been achieved.

15 Multimodale Therapie - prä/postoperative Chemotherapie

Inhalt: *7 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Al-Batran, Salah-Eddin 2019	2	investigator-initiated multicentre (hospitals and practice-based oncologists), randomised, unmasked, controlled trial.
Cai, Z. 2018	1	Systematic review and meta-analysis (9 articles)
Chan, K. K. W. 2018	1	Systematic review and network meta-analysis
Cheng, J. 2019	1	Sytematic review and network meta-analysis (8 studies)
Coccolini, F. 2018	1	Systematic review and meta-analysis (15 studies).
Li, F. 2018	1	Systematic review and meta-analysis
Montagnani, F. 2017	1	Systematic review and network meta-analysis (25 articles)

OXFORD (2011) Appraisal Sheet: Systematic Reviews: *6 Bewertung(en)*

Cai, Z. et al. Comparative Effectiveness of Neoadjuvant Treatments for Resectable Gastroesophageal Cancer: A Network Meta-Analysis. Front Pharmacol. 9. 872. 2018

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: Systematic review and meta-analysis (9 articles) Databases: PubMed, Embase (Ovid),	Population: Resectable gastroesophageal cance Intervention: Two or more of the following treatments:	Primary: Overall survival Secondary: Progression-free survival Results: **Study characteristics:** 8 studies were	Ychou 2011, Shapiro 2014, Schuhmacher 2010, Al-Batran 2017, Klevebro 2016, Cunnningham 2006,

Cochrane Library (Ovid) Search period: 09/ 2017 Inclusion Criteria: RCTs that compared at least two arms of following treatments: surgery alone, perioperative FLOT, surgery combined with neoadjuvant treatments involving chemotherapy or chemoradiotherapy listed in the NCCN guidelines. Patients had been histologically proven gastric or lower third of the esophagus cancer with no evidence of distant metastasis. Exclusion Criteria: We excluded studies if they were non-RCTs. Trials without enough data for us to estimate hazard ratios (HR) for survival were also excluded. Studies enrolling patients with esophageal cancer were excluded when data for gastric and lower third of the esophagus cancer were not separately extractable and/or the study included a limited number of patients with gastroesophageal cancer (<80%).	surgery alone, perioperative docetaxel, oxaliplatin, leucovorin, and fluorouracil (FLOT), and neoadjuvant treatments Comparison: -	included, total n = 2434 in 7 different treatments 701 treated with surgery alone; 113 perioperative cisplatin with fluorouracil (CF); 207 preoperative CF; 610 perioperative epirubicin, cisplatin, and fluorouracil or capecitabine (ECF/ECX); 356 perioperative FLOT; 234 preoperative radiotherapy combined with CF (RT/CF); 213 preoperative radiotherapy, paclitaxel, and carboplatin (RT/PC). **Results: Primary:**<u>overall survival:</u> 8 trials contributed to the analysis, comparing the 7 treatments. HRs were explicitly reported in all the eight trials. The treatment with the highest probability of benefit on OS as compared with surgery alone was perioperative FLOT [HR = 0.58 with 95% CrI: (0.43, 0.78), SUCRA = 93%], followed by preoperative radiotherapy, paclitaxel, and carboplatin (RT/PC) [HR = 0.68 with 95% CrI: (0.53, 0.87), SUCRA = 72%], perioperative cisplatin with fluorouracil (CF) [HR = 0.70 with 95% CrI: (0.51, 0.95), SUCRA = 68%], and perioperative epirubicin, cisplatin, and fluorouracil or capecitabine (ECF/ECX) [HR = 0.75 with 95% CrI: (0.60, 0.94), SUCRA = 56%].	Stahl 2017, Burmeister 2005.

Secondary: Progression-Free Survival 7 treatments were compared, and 6 trials. 5 treatments which reached statistical significance in terms of PFS as compared with surgery alone were perioperative FLOT [HR = 0.50 with 95% CrI: (0.37, 0.66)], preoperative RT/CF [HR = 0.49 with 95% CrI: (0.25, 0.94)], preoperative RT/PC [HR = 0.64 with 95% CrI: (0.49, 0.84)], perioperative ECF/ECX [HR = 0.66 with 95% CrI: (0.53, 0.82)]. R0 rescetion rate: 4 trials , comparing 3 pre-operative treatments. Perioperative/Preoperative CF was shown to have a significantly increased curative resection rate compared with surgery alone group [OR = 2 with 95% CrI: (1.2, 3.4)]. Preoperative RT/CF showed a trend to better resection rate as compared surgery alone [OR = 2.3 with 95% CrI: (0.88, 5.9)]. Perioperative ECF/ECX did not significantly improve R0 resection rate as compared with surgery alone [OR = 1.1 with 95% CrI: (0.78, 1.7)]. Perioperative/Preoperative CF also showed a statistically non-significant trend to better R0 resection rate as compared with perioperative ECF/ECX [OR = 1.8 with 95% CrI: (0.95, 3.4)].

Author's Conclusion: "The NMA provides the

first comparison between neoadjuvant treatments for resectable gastroesophageal cancer. In the absence of head to head clinical trials to guide the choice of treatment, it has been unclear which treatment is optimal. The results show that OS is improved with perioperative CF, perioperative ECF/ECX, perioperative FLOT, and preoperative RT/PC. Perioperative FLOT is likely to be the most effective neoadjuvant treatment for the disease. Still, large prospective studies are required to investigate the optimal neoadjuvant treatment for the disease."

Methodical Notes

Funding Sources: This work was supported by National Natural Science Foundation of China (No. 81572931).

COI: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest

Study Quality: The assessment of the risk of bias for selected studies in the Network meta-analysis was investigated using the Cochrane risk-of-bias tool, indicating low risk of bias.

Heterogeneity: Heterogeneity not investigated, just discussed: "First, based on metaanalyses of summary data, it was difficult for us to explore the impact of tumor location which might be the potential source of heterogeneity."

Publication Bias: Publication bias not investigated

Notes:
Publication bias and Heterogeneity not investigated.
Evidence level 1: Systematic review and meta-analysis.

Chan, K. K. W. et al. Neoadjuvant treatments for locally advanced, resectable esophageal cancer: A network meta-analysis. Int J Cancer. 143. 430-437. 2018

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: Systematic review and network meta-analysis Databases: MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL) databases and journal abstracts of ASCO and ASTRO. Search period: Inception - 05/2016. Inclusion Criteria: RCTs that compared at least two of the following treatments for resectable esophageal cancer were included: surgery alone, surgery preceded by neoadjuvant CT, neoadjuvant RT or neoadjuvant CRT. All types of surgery, CT and RT were included. However, only treatments that administered CT and/or RT prior to surgery, and for which the treatments	Population: Resectable esophageal cancer (squamous cell carcinoma, adenocarcinoma or undifferentiated carcinoma) Intervention: surgery alone, surgery preceded by neoadjuvant CT, neoadjuvant RT or neoadjuvant CRT. Comparison: all other interventions.	Primary: Overall survival Secondary: - Results: **Study characteristics** 31 studies were obtained for the final quantitative metaanalysis (N=55496 patients). All trials included were randomized and followed intention-to-treat analysis for the primary endpoints. Two publications were a 2X2 factorial comparison of neoadjuvant CT, neoadjuvant RT, neoadjuvant CRT and surgery alone. Adverse effects of the four-neoadjuvant treatments were not consistently reported. In general, the most common adverse effect of treatment was postoperative 30-day mortality, for which the risk ratio was included in our analysis. **Results:**	31 articles, see article for details. Allum 2009, Boonstra 2011, Burmeister 2005, Kelsen 2007, Urba 2001, Burmeister BH, Thomas JM, Burmeister 2009, Stahl 2009, Klevebro 2016, Maipang 1994, Ancona 2001, Apinop 1994, Arnott 1992, Baba 2000, Bosset 1997, Cao 2009, Fok 1994, Gignoux 1982, Launois 1981, Law 1997, Le Prise 1994, Lee 2004, Lv 2010, Mariette 2014, Natsugoe 2006, Nygaard 1992, Roth 1988, Schlag 1992, Tepper 2008, Shapiro 2015, Walsh 2002, Wang 1989

received were the primary care, were considered. All eligible patients had esophageal cancer with squamous cell carcinoma, adenocarcinoma or undifferentiated carcinoma.

Exclusion Criteria: Nonresectable or metastatic esophageal cancer, any postoperative treatment, any prior intervention other than diagnostic biopsy and nonrandomized trials.

Overall survival:Bayesian analysis shows a strong and favorable OS to both resection alone and the other neoadjuvant interventions benefit toward neoadjuvant CRT compared to both Our NMA has established a significant survival advantage of neoadjuvant CRT over neoadjuvant CT (HR 0.83, 95% CR 0.70–0.96), which had not been previously demonstrated in the direct pairwise analysis. In fact, the Bayesian analysis found a 97.5% probability of neoadjuvant CRT being the best treatment with regards to OS. Neoadjuvant CT and RT were comparable as second-best regimens according to the calculated probabilities, with no significant difference between the two (HR 0.99, 95% CR 0.83–1.22). Last, the NMA was also consistent with the pairwise analysis in showing a trend but not a statistically significant OS benefit of neoadjuvant CT compared to surgery alone (HR 0.91, 95% CR 0.81–1.04). Although OS was improved for neoadjuvant CRT compared to other

interventions, the NMA did reveal an increased risk for postoperative mortality when comparing neoadjuvant CRT to either surgery alone (RR 1.46, 95% CR 1.00–2.14) or to neoadjuvant CT (RR 1.58, 95% CR 1.00– 2.49). The NMA also showed improvement in locoregional recurrence when comparing neoadjuvant CRT to surgery alone (RR 0.57, 95% CR 0.45–0.72) and to neoadjuvant CT (RR 0.72, 95% CR 0.54–0.95).

Author's Conclusion: "In conclusion, our synthesis of the 31 trials demonstrates that neoadjuvant CRT provides a survival advantage for patients with locally advanced, resectable esophageal cancer. For clinical practice, our results provide statistical evidence based on the totality of the literature to support the use of neo-adjuvant chemoradiotherapy as the standard of care for the treatment of locally advanced, resectable esophageal

cancer for patients who are fit for such treatment, and where clinicians and patients are willing to accept a slight increased risk of postoperative mortality.

Methodical Notes

Funding Sources: The Canadian Centre for Applied Research in Cancer Control (ARCC) is funded by the Canadian Cancer Society Research Institute.

COI: The authors declare no competing interests.

Study Quality: Two independent reviewers evaluated the quality of evidence reported in each study using the Cochrane risk of bias tool. As all the studies included in the NMA were randomized, selection and attrition bias were minimized. Moreover, there was no significant imbalance in loss to follow-up between the intervention and control groups of the included trials, further reducing attrition bias. As expected, blinding of outcome assessors was not explicitly indicated. The majority of studies had OS as the primary endpoint, reducing detection bias as the outcome assessor would not influence this endpoint. However, there is
potential for some selection bias, as allocation concealment was not explicitly mentioned in majority of the studies.

Heterogeneity: The significance of any discrepancies in the estimates of the treatment effects from the different trials was assessed by means of Cochran's test for heterogeneity and the I^2 statistic.

Publication Bias: not investigated.

Notes:
Heterogeneity not reported. Publication bias not investigated.
Evidence level 1: Systematic review and meta-analysis.

Cheng, J. et al. Multimodal treatments for resectable esophagogastric junction cancer: a systematic review and network meta-analysis. Ther Adv Med Oncol. 11. 1758835919838963. 2019

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: Sytematic review and network meta-analysis (8 studies) Databases: PubMed, Web of Science, Cochrane Central Register of Controlled Trials, Embase, ASCO and ESMO Meeting Library Search period: Inception - 09/2018 Inclusion Criteria: Participants: Patients with previously untreated resectable esophagogastric junction cancer, not including specific pathological type, targeted positivity or resectable superficial lesions. Intervention: Different multimodal treatments against resectable esophagogastric junction cancer, including preoperative, postoperative and perioperative chemotherapy, radiotherapy or chemoradiotherapy.	Population: Patients with previously untreated resectable esophagogastric junction cancer, not including specific pathological type, targeted positivity or resectable superficial lesions. Intervention: preoperative chemoradiotherapy PreCRT, perioperative chemotherapy plus targeted medication PeriCTT, perioperative chemotherapy Peri CT, perioperative chemoradiotherapy Peri CRT, postoperative chemotherapy Post CT, preoperative chemotherapy PreCT, Surgery alone S. Comparison: Preoperative chemoradiotherapy PreCRT was the common comparator node in the network meta-analysis.	Primary: Overall survival Secondary: - Results: **Population characteristics** 8 phase III RCTs were eligible, total n = 1218 participants. 7 studies were based on western populations while only one eligible trial originated from eastern countries. 4 trials featured comparisons between multimodal strategies against surgery alone, while the remaining investigations focused on comparisons between different multimodal treatments. 1 trial specifically reported junctional cases, 7 studies contained both junctional and gastric or esophageal cancer patients; therefore the median age and gender ratio of junctional cases across different studies could not be precisely compared. Predominantly, studies only recruited patients with a performance status of either 0 or 1. All studies made general	8 recruiting and ongoing trials,see article for Clinicaltrials.gov identifier.

Targeted medications among unselected patients were also eligible. In terms of chemotherapeutic types, oral and intravenous chemotherapeutic regimens. Comparator: 'PreCRT' (preoperative chemoradiotherapy) was the common comparator node in the network meta-analysis. Outcome: time-to-event overall survival data (hazard ratio or Kaplan–Meier curves) on junctional cases were mandatory; timeto- event recurrence-free survival data or safety analysis on junctional cases were dispensable. Study design: phase II and phase III RCTs reported from inception to September 2018 without language limitations.

Exclusion Criteria: Interim or repetitive reports from the same registered study (we only included the one with the longest follow-up period).
Additionally, the comparisons between different regimens of chemotherapy were qualified while enrollment of junctional cases without indication of certain Siewert types. Therefore, the demographic characteristics of included trials were generally comparable. **Results: Primary:** Overall survival
Network geometry. 7 RCTs merged into the quantitative analysis, corresponding to seven network nodes. Due to failure to form a network with other studies, one study was removed from the quantitative analysis. 'PreCRT' topped the hierarchy (HR 1.00, P-score = 0.823), better than 'PeriCT' HR 1.32, P-score = 0.591 and PreCT HR 1.54, P-score = 0.428.
In sensitivity analyses, irrespective of interchanging to fixed-effects model or removing potentially heterogeneous studies, relative rankings remained stable and 'PreCRT' was still the optimal node.

Author's Conclusion: "Preoperative chemoradiotherapy could potentially be the optimal multimodal
treatment, which displayed more overall survival benefits than perioperative chemotherapy and preoperative

the comparisons between different dosages or methods of administration by the same chemotherapeutic regimen were not eligible.
Comparison of surgery with auxiliary therapeutics (such as anti-inflammatory medications, nutritional supportive methods, unspecified herbal medicine and immunomodulators) were not qualified.

chemotherapy among resectable esophagogastric junction cancer patients.
To further verify our pooled results, more randomized trials will be needed to compare preoperative chemoradiotherapy with perioperative chemotherapy (especially FLOT-based regimens)."

Methodical Notes

Funding Sources: The meta-analysis was funded by Scientific Research Training Program for Young Talents (Union Hospital, Tongji Medical College, Huazhong University of Science and Technology) to Ji Cheng and National Natural Science Foundation of China (grant no. 81572413) to Kaixiong Tao.

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

Study Quality: The quality of each eligible study was evaluated by The Cochrane Risk of Bias Tool. studies were defined to be low quality if 4 (out of 7)or more items were scored as high risk of bias.
Overall, the included studies had low risk of bias since more than half of the assessment parameters were scored as low risk of bias (75%).

Heterogeneity: The I2 statistic was the chief indicator of statistical heterogeneity, with its value <25%, 25–50% and >50% indicating low, moderate and high heterogeneity respectively. The Q statistic of heterogeneity and its p value also facilitated the assessment of statistical heterogeneity. If the p value of the Q statistic was
less than 0.05, it suggested that there was a significant heterogeneity within.
"In terms of statistical heterogeneity, both the I^2 = 0% and Q statistic (Q-heterogeneity: p = 0.632) implied that there was no significant

heterogeneity across the network."

Publication Bias: A network plot and comparison-adjusted funnel plot were applied to display the network structure and examine the publication bias across the included trials respectively, where the more symmetrical it was, the less probability of publication bias the merged results would have.

Notes:
Evidence level 1: Systematic review and meta-analysis.

Coccolini, F. et al. Neoadjuvant chemotherapy in advanced gastric and esophago-gastric cancer. Meta-analysis of randomized trials. Int J Surg. 51. 120-127. 2018

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: Systematic review and meta-analysis (15 studies). Databases: Medline, Embase, PubMed, Cochrane databases, CINAHL. Search period: Medline, Embase (1988–March 2017), PubMed (January 1980–March 2017), Cochrane Central Register of Controlled Trials (CCTR), Cochrane Database of Systematic Reviews (CDSR) and CINAHL from (1966–March 2017). Inclusion Criteria: Patients with	Population: Patients with advanced gastric AGC or or esophageal gastric cancer EGC both without peritoneal carcinosis Intervention: Neoadjuvant chemotherapy NACT + surgery Comparison: Surgery alone	Primary: 1, 2, 3 and 5-year mortality. Secondary: Perioperative mortality, morbidity and recurrence in AGC and EGC. Results: **Study population:** 15 RCTs fulfilled the inclusion criteria and were included in the meta-analysis (publication dates 1987–2014). Total n=2001 patients (977 randomized to receive NACT + radical resection and 1024 randomized to receive radical resection without NACT). **Results: Primary:** 1-year mortality8 studies reported 1-year in AGC, 3 in EGC; 291 and 436 patients received the surgical treatment alone and 236 and 435 NACT +	Imano 2010, Cunningham 2006, Schumacher 2010, Hartgrink 2004, Ychou 2011, Hashemzadeh 2014, Zhang 2004, Biffi 2010, Yonemura 1993, Nio 2004, Sun 2011, Kobayashi 2000, Lygidakis 1999, Shchepotin 1999, Wang 2000

advanced gastric AGC or or esophageal gastric cancer EGC both without peritoneal carcinosis were randomly assigned to receive either NACT + surgery or surgery without NACT. All included patients must have histologically-proven gastric or gastro-oesophagealjunction adenocarcinoma and underwent potentially curative resection. All forms of NACT in addition to surgery were included. No language restrictions have been applied.

Exclusion Criteria: -

surgery in the two groups respectively. There was no statistical heterogeneity between studies. Fixed-effects model, 1-year mortality rate was significantly favourable to the NACT + surgery arm in the cumulative analysis (RR = 0.78, 95%CI = 0.67–0.94) in the EGC (RR = 0.79, 95%CI = 0.64–0.97) and was not significantly favourable to the NACT + surgery arm in AGC (RR = 0.81, 95%CI = 0.61–1.09). 2-years mortality

3 studies reported 2-years mortality in EGC 436 patients received the surgical treatment alone and 435 NACT + surgery (Fig. 1). Fixed-effects model, the 2-years mortality rate was significantly favourable to the NACT + surgery arm (RR = 0.83, 95%CI = 0.73–0.93). 3-years mortality

5 studies reported 3-year mortality in AGC and three in EGC 315 and 436 patients received the surgical treatment alone and 254 and 435 NACT + surgery in the two groups. There was statistical heterogeneity between studies.

Fixed-effects model, the 3-year mortality rate was significantly favourable to the NACT + surgery arm in the cumulative

analysis (RR = 0.81, 95%CI = 0.74–0.89), in the EGC (RR = 0.84, 95%CI = 0.76–0.92) and in AGC (RR = 0.74, 95%CI = 0.60–0.91). 5-year mortality 8 studies AGC and 3 EGC: 472 and 436 patients received the surgical treatment alone and 422 and 435 NACT + surgery in the two groups. There was statistical heterogeneity between studies. In the fixed-effects model, the 5-year mortality rate was favourable to the NACT + surgery arm in the cumulative analysis (RR = 0.88, 95%CI = 0.83–0.93), in the EGC (RR = 0.91, 95%CI = 0.86–0.96) and in AGC (RR = 0.82, 95%CI = 0.71–0.95). Secondary outcomes see article.

Author's Conclusion: "NACT reduces the mortality in gastric and esophago-gastric cancer. Morbidity and perioperative mortality are not influenced by NACT. The overall recurrence rate is reduced by NACT in esophago-gastric cancer."

Methodical Notes

Funding Sources: All authors declare to have no sources of funding for this research.

COI: All authors declare to have no conflict of interest.

Study Quality: The risk of bias was assessed comprehensively according to guidelines of The Cochrane Collaboration. Six items have been considered relevant. With a positive answer to five or four questions the study was considered of fair quality. With a positive answer to three or fewer questions the study was registered as low quality. All fifteen RCTs were considered to be at acceptable risk of bias in the important domains.

Heterogeneity: "Heterogeneity amongst the trials was determined by means of the Cochrane Q value and quantified using the I^2 inconsistency test."
According to the authors statistical heterogeneity was present for 3- and 5-year mortality outcomes. Looking at the forest plots this is not the case for the EGC subgroup in which I^2 is 0%

Publication Bias: Not investigated.

Notes:
Evidence level 1: systematic review and meta-analyis.
Unclear definition of inclusion and exclusion criteria. Publication bias not investigated.
"Heterogeneity amongst the trials was determined by means of the Cochrane Q value and quantified using the I^2 inconsistency test."
According to the authors statistical heterogeneity was present for 3- and 5-year mortality outcomes. Looking at the forest plots this is not the case for the EGC subgroup in which I^2 is 0%.

Li, F. et al. The current optimal multimodality treatments for oesophageal squamous-cell carcinoma: A systematic review and meta-analysis. Int J Surg. 60. 88-100. 2018

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: Systematic review and meta-analysis	Population: Patients with histologically proven locally advanced esophageal squamous cell carcinoma LAESCC	Primary: Overall survival, as hazard ratio Secondary: local recurrence rate.	Nakadi 2001, Delcambre 2001, Kim 2003, Fujita 2005, Nagata 2006, Cheng

Databases: PubMed, Embase, Ovid, Cochrane library Search period: Inception - 04/2018 Inclusion Criteria: Rcts and non-randomized controlled studies, studies containing patients with histologically proven locally advanced esophageal squamous cell carcinoma LAESCC, application of nCRT or nCT or DCRT on LAESCC, available data for meta-analysis. Exclusion Criteria: studies without comparison between nCT+S and nCRT+S or nCRT+S and dCRT for LAESCC. Studies containing patients with distant metastases (stage IV) or with very early disease (stage 0), Studies with without comparability between groups, Studies reported as abstracts, conference reports, reviews and reports,	Intervention: definitive chemoradiotherapy dCRT, neoadjuvant chemotherapy nCT followed by surgery, neoadjuvant radiochemotherapy nCRT followed by surgery. Comparison: One of the interventions.	Results: **Study characteristics:**14 studies compared nCRT+S with dCRT, 5 studies compared nCRT+S with nCT+S. **Results:** nCRT+S vs. nCT+S: nCRT+S had higher rates of R0 resection (OR 1.84, 95% CI 1.03-3.29), pCR (OR 2.90, 95%CI 1.37-6.14) and pN0 (OR 2.55, 95%CI 1.54-4.24) and survival advantage (HR 0.72, 95%CI 0.52-0.99) when compared to nCRT+S. nCRT+S was compared to dRCT: nCRT+S had had better survival (HR 0.65, 95%CI 0.56-0.76) and had a significantly lower rate of local recurrence (OR 0.35, 95%CI 0.22-0.57) Author's Conclusion: "Current evidence suggests that CRT+S may the optimal potential curative treatment mode for patients with LAESCC as long as they are suitable for this multimodality regimen.	2008, Shao 2015, Hategan 2015, Wang 2016, Wu 2017, Reynold 2017, Liu 2017, Molena 2018.

Methodical Notes

Funding Sources: Supported by grants from the National Scieence and Technology Support program

COI: The authors declare tno conflict of interest.

Study Quality: Study quality was assessed by Jadad Scoring ssystem and the Newcastle Ottawa scale for RCTs and non-randomized controlled studies.
The RCTS had moderate quality with Jadad Scroes ranging form 2 to 3. while the NOS scores of the non-randomized studies ranged from 5-8 showing acceptable quality.

Heterogeneity: I^2 was ≥50% in the comparison between nCRT+S and nCT+S regarding overall survival, R0 resection and pN0, despite random-effects models.

Publication Bias: Funnel plot, Egger and Begg's test were used to investiagte sources of publication bias. No sigificant publication bias was found.

Notes:
Eveidence level 1: systematic review and meta-analysis.
Considerable heterogeneity (I≥2 50%) in the analysis comparing nCRT+S and nCT+S regarding overall survival, R0 resection and pN0.

Montagnani, F. et al. Multimodality treatment of locally advanced squamous cell carcinoma of the oesophagus: A comprehensive review and network meta-analysis. Crit Rev Oncol Hematol. 114. 24-32. 2017

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: Systematic review and network meta-analysis (25 articles) Databases: Pubmed and EMBASE, handsearch of journals Search period: not described. Inclusion Criteria: Studies enrolling	Population: Oesophageal squamous cell carcinonma (OSCC) Intervention: Multimodality treatment (i.e. [neo-]adjuvant CT or RT or CRT or definitive CRT) Comparison: Surgery	Primary: Overall survival (OS),defined from the time of randomization or the start of treatment to death from any cause. Hazard ratios (HRs) and their 95% confidence intervals (95%CIs) were used to estimate treatment effects. Secondary: -	Roth 1988, Schlag 1992, Nygaard 1992, Apinop 1994, Maipang 1994, Le Prise 1994, Ando 1997, Bosset 1997, Law 1997, Ancona 2001, Urba 2001, Ando 2003, Lee 2004, Burmeister 2005, Stahl 2005, Natsugoe 2006, Kelsen 2007, Allum 2009, Cao 2009, Lv 2010, Boonstra 2011, Ando 2012, Van

oesophageal cancer patients independently of tumour histology were included if the following criteria were respected: Study design provided for patient stratification according to histology; sufficient data for the OSCC subgroup were reported.

Exclusion Criteria: Studies enrolling less than 25 OSCC patients were not included in the meta analysis, as well as studies testing biologic agents either alone or in combination with CT or CRT.

Results: **Study characteristics:** 25 studies, published between 1988 and 2014, total n=3866 OSCC patients, were included in the meta-analysis. The majority of trials compared surgery with neoadjuvant CRT (total number of patients: 942) or neoadjuvant CT (total number of patients: 997).

Results: Primary

Overall survival

- both neoadjuvant CRT and definitive CRT confer an OS advantage over surgery alone: HRs (95% CI) were 0.73 (0.63–0.86) and 0.62 (0.41–0.96), respectively.
- Adjuvant CRT apparently demonstrated a similar impact on OS, despite lacking significance (HR 0.73; 95%CI 0.47–1.12). A non-significant trend in favour of neoadjuvant CT was found (HR 0.90; 95%CrI 0.76–1.07), whereas adjuvant CT apparently adds no further benefit to surgical resection (HR 1.00;95%CrI 0.70–1.40).
- Rank probability analysis,which provides an estimate of the probability of each treatment modality to be the

Hagen 2012, Teoh 2013, Mariette 2014.

most effective therapeutic option compared with surgery: definitive CRT and neoadjuvant CRT have the highest probability to represent the most effective treatment approaches in locally advanced OSCC, as they have 82.8% and 54.9% probability, respectively, to be the best or second best therapeutic options.

Author's Conclusion: "Our Bayesian analysis supports the role of neoadjuvant CRT as the preferable treatment modality in OSCC, being definitive CRT an appropriate alternative in selected cases. Future studies should focus on the prospective assessment of preoperative CRT or definitive CRT with more modern regimens."

Methodical Notes

Funding Sources: No fundings were used for this manuscript.

COI: All the authors declare no conflicts of interest.

Study Quality: We assessed the risk of bias for each study by the use of the Cochrane tool.
10 studies were at high risk of bias, 6 at low risk and 9 at unclear risk.

There is great heterogeneity among studies with regard to staging procedures, CT administered, CT doses and type of radiation treatment. Most studies were conducted in single institutions over a large period of time and randomization procedures are often not reported. Moreover, data regarding protocol violations or potential prognostic factors are frequently not specified in the manuscripts.

Heterogeneity: Heterogeneity described in the supplementary section of the article.
- In order to statistically assess heterogeneity, standard pairwise meta-analyses were performed for the following comparisons: surgery vs. neoadjuvant CT, surgery vs. neoadjuvant CRT and surgery vs. definitive CRT. Other comparisons were not possible due to the small number of trials. Despite the aforementioned considerations, significant heterogeneity was present only in the first comparison (surgery vs. neoadjuvant CT): I^2=44%,p=0.056.

Publication Bias: Publication bias was assessed by visual inspection of funnel plots.

Notes:
Evidence level 1: Systematic review and meta-analysis
- Search period for database search not described.
- Details regarding heterogeneity, Publication bias and individual quality evaluation of original studies are reported in online supplementary, which is not available to the assessor. Only a short summary to these analyses can be found in the manuscript, except for results of the publication bias assessment which are not described.

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

Al-Batran, Salah-Eddin et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a ran. Lancet. 393. 1948-1957. 2019

Population	Intervention - Comparison	Outcomes/Results

Evidence level: 2

Study type: investigator-initiated multicentre (hospitals and practice-based oncologists), randomised, unmasked, controlled trial.

Number of Patient: 716 randomized (356,360 per arm)

Recruitung Phase: Aug 8, 2010, - Feb 10, 2015

Inclusion Criteria: Patients with histologically confirmed gastric or gastro-oesophageal junction adenocarcinoma of a clinical stage cT2 or higher nodal positive stage (cN+), or both and no clinical evidence of distant metastases according to the 7th Edition of the International Union against Cancer tumour–node–metastasis classification. Adenocarcinomas of the gastro-oesophageal junction were classified according to Siewert. Complete eligibility criteria are listed in the web appendix. We assessed clinical stage by physical examination, oesophagogastroduodenoscopy, endoscopic ultrasound, and CT or MRI of the chest, abdomen, and pelvis. Diagnostic laparoscopy was recommended but was not mandatory in accordance with standard of care in Germany.

Exclusion Criteria: -

Intervention: Surgical resection with perioperative ECF/ECX

Comparison: Surgical resection with perioperative FLOT

Primary: Median overall survival.

Secondary: Margin-free-(R0) resection rate; disease-free survival, defined as time from randomisation to disease progression, relapse, or death; surgical morbidity and mortality; and adverse events.

Results: **Patient characteristics:** This report discusses the results of the phase 3 study. Between Aug 8, 2010, and Feb 10, 2015, 716 patients were randomly assigned to treatment in 38 German cancer sites. Follow-up of the last patient ended March 7, 2017. Baseline characteristics were similar between the groups. Diagnostic laparoscopy at baseline was done in 147 (41%) patients in the ECF/ECX group and 139 (39%) patients in the FLOT group. 353 (98%) of 360 patients started allocated chemotherapy in the ECF/ECX group and 352 (99%) of 356 in the FLOT group. 326 (91%) patients in the ECF/ECX group and 320 (90%) patients in the FLOT group completed all cycles of allocated preoperative chemotherapy. In the ECF/ECX group, 240 (67%) of 360 patients received capecitabine as the fluoropyrimidine (ECX). 186 (52%) of 360 patients in the ECF/ECX group and 213 (60%) of 356 patients in the FLOT group started

allocated postoperative chemotherapy. Of all patients randomised, 132 (37%) patients in the ECF/ECX group and 162 (46%) patients in the FLOT group completed all allocated cycles. The cumulative doses and dose modifications are in the web appendix. Dose delays (>7 days) occurred in 31 (2%) of 1515 cycles in the ECF/ECX group and 56 (3%) of 2101 cycles in the FLOT group. GCSFs were administered with the first cycle in 22 patients (6%) in the ECF/ECX group and 17 patients (5%) in theFLOT group. 77 patients (21%) in the ECF/ECX group and 121 (34%) in the FLOT group received GCSFs at any time-point. **Results: Primary:** Median overall survival was 35 months (95% CI 27.35 to 46.26) in the ECF/ECX group and 50 months (38.33 to not reached) in the FLOT group (HR 0.77; 0.63 to 0.94; p=0.012). The estimated overall survival at 2, 3, and 5 years were 59% (95% CI 53 to 64), 48% (43 to 54), and 36% (30 to 42) in the ECF/ECX group, as compared with 68% (63 to 73), 57% (52 to 62), and 45% (38 to 51) in the FLOT group. **Secondary:** Chemotherapy-associated toxicity was analysed in the safety population comprising 354 patients per group. We observed significantly more grade 3 or 4 nausea (55 [16%] in the ECF/ECX group vs 26 [7%] in the FLOT group. Disease-free survial: Median disease-free survival was 18 months in the ECF/ECX

group and 30 months in the FLOT group (HR, 0·75; 95% CI, 0·62–0·91; p=0·0036). Adverse events: The number of patients with serious adverse events related to treatment was similar in the two groups (96 [27%] in the ECF/ECX group vs 97 [27%] in the FLOT group), as was the number of toxic deaths (two [<1%] in both groups). Hospitalisation for toxicity occurred in 94 patients (26%) in the ECF/ECX group and 89 patients (25%) in the FLOT group. postoperative complications The incidence of was similar in both the surgery population. morbidity and mortality: results were observed in both arms in terms of 30-day postoperative death rates (2% in the FLOT group and 3% in the ECF/ECX group) and surgical complications (51% in the FLOT group and 50% in the ECF/ECX group).

Author's Conclusion: "In locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma, perioperative FLOT improved overall survival compared with perioperative ECF/ECX"

Methodical Notes

Funding Sources: The German Cancer Aid (Deutsche Krebshilfe), Sanofi-Aventis, Chugai, and Stiftung Leben mit Krebs Foundation.

COI: Extensive list of potential COI, see article.

Randomization: Patients were centrally randomised 1:1 to surgical resection with either perioperative ECF/ECX or perioperative FLOT using an interactive web-response system (IWRS) based on a sequence generated with permuted blocks stratified
by Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1 vs 2), location of primary tumour (GEJ Type I vs GEJ type II/III vs. gastric), age (<60 vs 60–69 vs ≥70 years), and suspected lymph node involvement (N+ vs N-). The randomisation system allocated every patient a unique identification number and sent a message that included allocation result to the investigator.

Blinding: The study was open-label and no masking was required.

Dropout Rate/ITT-Analysis: All randomised patients were included in the intention-to-treat population.

Notes:
Article submitted by hand search.
Evidence level 2: randomized controlled trial.
At least partial blinding could have been achieved.
No fit for any of the described PICO questions. Potential downgrade for indirectness.

16 Multimodale Therapie - präoperative Radiochemotherapie

Inhalt: *7 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Feng, H. 2018	2	systematic review and meta-analysis
Li, F. 2018	1	Systematic review and meta-analysis
Meng, X. 2019	1	systematic review and meta analysis
Montagnani, F. 2017	1	Systematic review and network meta-analysis (25 articles)
Noordman, B. J. 2018	2	subanalysis of a multicenter, randomized controlled trial
Noordman, B. J. 2018	2	subanalysis of a multicenter, randomized controlled trial
Petrelli, F. 2019	1	systematic review and meta analysis

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

Feng, H. et al. Traditional and cumulative meta-analysis: Chemoradiotherapy followed by surgery versus surgery alone for resectable esophageal carcinoma. Mol Clin Oncol. 8. 342-351. 2018

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 2 Study type: systematic review and meta-analysis Databases: Embase, PubMed and The Cochrane Library	Population: locoregional resectable esophageal cancer patients who received either CRTS or SA. Intervention: neoadjuvant chemoradiotherapy followed by	Primary: Overall survival rates at 1, 3 and 5 years (OSR1y, OSR3y and OSR5y, respectively) Secondary: R0 resection rate, postoperative mortality, postoperative local recurrence rate and postoperative distant metastasis	Nygaard et al, 1992, World J Surg Apinop et al, 1994, Hepatogastroenterology Le Prise et al, 1994, Cancer Walsh et al, 1996, N Engl

Search period: from inception to October 1st, 2016 Inclusion Criteria: i) Prospective RCTs comparing CRTS vs. SA in the initial management of resectable esophageal cancer; ii) outcome indices containing survival data; iii) no significant differences in baseline characteristics between the CRTS and SA groups; iv) definitive follow-up survival number of cases or survival curve, with a follow-up rate of >95% in the original RCTs. Exclusion Criteria: Studies focusing on patients with esophageal cancer who had been treated with neoadjuvant chemotherapy alone or radiotherapy alone, other studies without usable data, letters, editorials, case reports and reviews were excluded.	surgery (CRTS) Comparison: surgery alone (SA)	rate Results: 22 studies including 3,419 patients selected for meta-analysis **Survival rate** - The heterogeneity test at all the time points had a I^2 value of <55%; thus, the fixed-effects model was used. - no statistically significant difference in OSR1y between the CRTS and SA groups; the pooled OSR1y was 71% (95% CI: 65-78%) vs. 68% (95% CI: 60-76%), respectively, and the OR was 1.06 (95% CI: 0.94-1.19, P=0.348) - compared with the SA group, the OSR3y and OSR5y were significantly higher in the CRTS group. The pooled OSR3y was 44% (95% CI: 37-52%) vs. 30% (95% CI: 23-38%), respectively, and the OSR5y was 36% (95% CI: 32-42%) vs. 24% (95% CI: 19-29%), respectively, with an OR of 1.38 (1.20-1.58, P<0.001) and 1.42 (95% CI: 1.22-1.66, P<0.001), respectively. - The pooled OR of squamous cell carcinoma in terms of OSR3y and OSR5y in the CRTS and SA groups was 1.57 (95% CI: 1.21-2.04, P=0.0006) and 1.69 (95% CI: 1.32-2.16,	J Med Bosset et al, 1997, N Engl J Med Urba et al, 2001, J Clin Oncol An et al, 2003, Zhonghua Zhong Liu Za Zhi Lee et al, 2004, Ann Oncol Burmeister et al, 2005, Lancet Oncol Law et al, 2006, J Gastrointest Surg Natsugoe et al, 2006, Dis Esophagus Cao et al, 2007, Dis Esophagus Jin et al, 2008, China J Cancer Prev Treat Peng et al, 2008, Tumor Chin Tepper et al, 2008, J Clin Oncol Lv et al, 2010, World J Gastroenterol Jin et al, 2011, Zhiyong Zhongliu Zazhi van Hagen et al, 2012, N

P<0.0001), respectively - the OSR1y, OSR3y and OSR5y were significantly higher in CRTS, with an OR of 1.55 (95% CI: 1.09-2.20, P=0.01), 1.77 (95% CI: 1.34-2.36, P<0.0001) and 1.92 (95% CI: 1.34-2.75, P=0.0004), respectively - OSR3y, OSR5y for Asian, European and American populations were significantly higher in the CRTS group compared with those in the SA group, and the differences were all statistically significant (P<0.05). <u>Surgical factors</u> - The CRTS group had a significantly higher R0 resection rate and a lower local recurrence and distant metastasis rate compared with the SA group, with a pooled OR of 2.76 (95% CI: 2.15-3.53, P<0.001, I^2=45%), 0.49 (95% CI: 0.36-6.65, P<0.001, I^2=15%) and 0.76 (95% CI: 0.60-0.97, P=0.02, I^2=38%), respectively; the differences were statistically significant. - However, the incidence of postoperative mortality in the two groups suggested there was no significantly statistical difference, with an OR of 0.97 (95% CI: 0.72-1.32, P=0.87, I^2=59%)	Engl J Med Yang et al, 2012, Natl Med J Chin Bass et al, 2014, Eur J Cancer Mariette et al, 2014, J Clin Oncol Shapiro et al, 2015, Lancet Oncol

Author's Conclusion: In summary, it may be concluded from the cumulative meta-analysis that CRTS may increase OSR3y and OSR5y by 38% (P<0.0001) and 42% (P<0.0001), respectively. From the forest plot, it was observed that the difference in OSR3y and OSR5y was statistically significant, with P-values stable at <0.05, indicating that CRTS may improve the patient survival rate. Therefore, it is recommended that the CRTS regimen is routinely used for patients with early resectable esophageal cancer. There are ongoing studies on this subject and, as the results of those studies are published, it may further elucidate the role of CRTS in the treatment of early resectable esophageal cancer.

Methodical Notes

Funding Sources: no statement

COI: no statement

Study Quality: The methodological quality assessment of individual studies followed the Cochrane risk of bias method
→ no results of quality assessment given

Heterogeneity: results were analysed by adopting the fixed- or random-effects model where heterogeneity was assessed with the inconsistency statistic (I^2<50%, P>0.05; and I^2≥50%, P≤0.05, respectively)
- see results section for individual comparisons

Publication Bias: A funnel plot analysis of all the studies was performed in the meta-analysis of OSR1y, OSR2y and OSR3y between CRTS and SA. This indicated that the publication bias was low in the present meta-analysis

Notes:
evidence level 2: systematic review and meta analysis, downgraded from 1 to 2 due to missing quality assessment results
- 11 out of 22 studies are also included in another meta analysis: Meng et al 2019, Journal of Cancer

Li, F. et al. The current optimal multimodality treatments for oesophageal squamous-cell carcinoma: A systematic review and meta-analysis. Int J Surg. 60. 88-100. 2018

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: Systematic review and meta-analysis Databases: PubMed, Embase, Ovid, Cochrane library Search period: Inception - 04/2018 Inclusion Criteria: Rcts and non-randomized controlled studies, studies containing patients with histologically proven locally advanced esophageal	Population: Patients with histologically proven locally advanced esophageal squamous cell carcinoma LAESCC Intervention: definitive chemoradiotherapy dCRT, neoadjuvant chemotherapy nCT followed by surgery, neoadjuvant radiochemotherapy nCRT followed by surgery.	Primary: Overall survival, as hazard ratio Secondary: local recurrence rate. Results: **Study characteristics:**14 studies compared nCRT+S with dCRT, 5 studies compared nCRT+S with nCT+S. **Results:** nCRT+S vs. nCT+S: nCRT+S had higher rates of R0 resection (OR 1.84, 95% CI 1.03-3.29), pCR (OR 2.90, 95%CI 1.37-6.14) and pN0 (OR 2.55, 95%CI 1.54-4.24) and survival advantage (HR 0.72, 95%CI 0.52-0.99) when compared to nCRT+S.	Nakadi 2001, Delcambre 2001, Kim 2003, Fujita 2005, Nagata 2006, Cheng 2008, Shao 2015, Hategan 2015, Wang 2016, Wu 2017, Reynold 2017, Liu 2017, Molena 2018.

squamous cell carcinoma LAESCC, application of nCRT or nCT or DCRT on LAESCC, available data for meta-analysis.

Exclusion Criteria: studies without comparison between nCT+S and nCRT+S or nCRT+S and dCRT for LAESCC. Studies containing patients with distant metastases (stage IV) or with very early disease (stage 0), Studies with without comparability between groups, Studies reported as abstracts, conference reports, reviews and reports,

Comparison: One of the interventions.

nCRT+S was compared to dRCT: nCRT+S had had better survival (HR 0.65, 95%CI 0.56-0.76) and had a significantly lower rate of local recurrence (OR 0.35, 95%CI 0.22-0.57)

Author's Conclusion: "Current evidence suggests that CRT+S may the optimal potential curative treatment mode for patients with LAESCC as long as they are suitable for this multimodality regimen.

Methodical Notes

Funding Sources: Supported by grants from the National Scieence and Technology Support program

COI: The authors declare tno conflict of interest.

Study Quality: Study quality was assessed by Jadad Scoring ssystem and the Newcastle Ottawa scale for RCTs and non-randomized controlled studies.
The RCTS had moderate quality with Jadad Scroes ranging form 2 to 3. while the NOS scores of the non-randomized studies ranged from 5-8 showing acceptable quality.

Heterogeneity: I^2 was ≥50% in the comparison between nCRT+S and nCT+S regarding overall survival, R0 resection and pN0, despite random-effects models.

Publication Bias: Funnel plot, Egger and Begg's test were used to investiagte sources of publication bias. No sigificant publication bias was

found.

Notes:
Eveidence level 1: systematic review and meta-analysis.
Considerable heterogeneity (I≥2 50%) in the analysis comparing nCRT+S and nCT+S regarding overall survival, R0 resection and pN0.

Meng, X. et al. Neoadjuvant Chemoradiation Treatment for Resectable Esophago-Gastric Cancer: A Systematic Review and Meta-Analysis. J Cancer. 10. 192-204. 2019

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: systematic review and meta analysis Databases: PubMed, Embase, Web of science, the Cochrane Library, the Cochrane Controlled Trials Register, WanFan data, VIP database and China National Knowledge Infrastructure (CNKI) Search period: up to August 7, 2018 Inclusion Criteria: 1.published RCT studies. 2.clear statement in the Materials and Methods section. 3.eligible patients were randomly assigned to treatment and control	Population: patients with resectable, pathologic diagnosis carcinoma of the esophagus, gastroesophageal junction or stomach Intervention: preoperative CRT plus surgery Comparison: surgery alone or preoperative CT plus surgery	Primary: overall survival (OS), disease-free survival (DFS), progression-free survival (PFS), Secondary: R0 resection rate, pathological reaction, metastasis and recurrence rate, perioperative mortality and morbidity. Results: - 17 records were eventually eligible for the meta-analysis, including 4095 patients <u>primary outcomes</u> - 14 records reported 1-year survival, 11 records reported 2-year survival, 14 records reported 3-year survival, 12 records reported 5-year survival - neoadjuvant CRT plus surgery led to a significant increase in 1-year survival, 2-year survival, 3-year survival and 5-year survival when compared to neoadjuvant CT plus surgery or surgery alone. The RR (95%CI, P	<u>CRT-S vs. S</u> Bosset et al, 1997, The New England journal of medicine. Burmeister et al, 2005, The Lancet Oncology. Klevebro et al, 2016, Annals of oncology: official journal of the European Society for Medical Oncology / ESMO. Le Prise et al, 1994, Cancer. Mariette et al, 2014, Journal of Clinical Oncology. Natsugoe et al, 2006, Diseases of the

arms.
4.the treatment arm: preoperative CRT plus surgery; the control arm: surgery alone or preoperative CT plus surgery.
5.included patients with resectable, pathologic diagnosis carcinoma of the esophagus, gastroesophageal junction or stomach.
6.included studies with a low risk of selection, performance, detection, attrition, reporting and other bias.

Exclusion Criteria: Non-RCTs, case reports, reviews, conference presentation and fundamental researches were excluded.

value) was 1.08 (1.03-1.14, 0.002), 1.21(1.12-1.32, <0.00001), 1.31 (1.09-1.58, 0.004), 1.38(1.17-1.62, <0.001), respectively.
- The heterogneity test was not significant (I^2=48%)
- For the records reporting DFS (n=3) and PFS (n=4) the results of heterogeneity tests (I2,P) were respectively (0%,0.45) and (19%,0.25).
- The meta- analysis yielded RRs (95%CI, P value) of 1.13 (1.00-1.28,0.05), 1.08 (0.90-1.29,0.39), 0.99 (0.78-1.26, 0.94) and 0.91 (0.64-1.30, 0.62) for neoadjuvant CRT plus surgery compared to neoadjuvant CT plus surgery or surgery alone in 1-,2-,3- and 5-year DFS.
- the RRs (95%CI, P value) of 1-,2-,3- and 5-year PFS were separately 1.23 (1.09-1.39, 0.0006), 1.39 (1.18-1.65, <0.0001), 1.26 (0.96-1.66, 0.09), 1.53 (1.20-1.95, 0.0004).
<u>secondary outcomes</u>
- R0 resection: significant difference between neoadjuvant CRT plus surgery and neoadjuvant CT plus surgery (OR 2.11, 95% CI 1.15-3.86, P=0.02) or surgery alone (OR 2.96, 95% CI 1.93-4.55, P<0.00001)
- patients treated with neoadjuvant CRT plus surgery had a lower incidence of local

esophagus: official journal of the International Society for Diseases of the Esophagus.
Nygaard et al, 1992, World J Surg
Shapiro et al, 2015, The Lancet Oncology.
Tepper et al, 2008, J Clin Oncol.
Urba et al, 2001, J Clin Oncol.
van Hagen et al, 2012, New England Journal of Medicine.
Walsh et al, 1996, New England Journal of Medicine.
Zhao et al, 2015, The American journal of the medical sciences
<u>CRT-S vs. CT-S</u>
Klevebro et al, 2016, Annals of oncology: official journal of the European Society for

recurrence compared to neoadjuvant CT plus surgery or surgery alone (OR 0.52, 95% CI 0.39-0.69, P<0.00001), but no significant difference between two arms was shown in the distant metastasis (OR 0.85, 95% CI 0.67-1.08, P=0.19) - There was no evidence that neoadjuvant CRT increased the treatment-related mortality [1.27(0.95-1.71),0.11]. - Neoadjuvant CRT plus surgery did not increase the risk of adverse events morbidity [1.14(0.99-1.32),0.08]. Author's Conclusion: Our meta-analysis result demonstrated that neoadjuvant CRT plus surgery improved survival of patients with the oesophagus or GOJ cancers both in squamous cell carcinomas and adenocarcinomas. The patients with squamous cell carcinomas gained more survival advantage from neoadjuvant CRT. The addition of radiation was efficacy and safe in range. The data emerging from novel neoadjuvant CRT regimens is exciting, but needs further high-quality investigation based on inaccuracy from published prospective RCTs. We hope that our results could promote the continued	Medical Oncology / ESMO. Klevebro et al, 2016, The British journal of surgery. Nygaard et al, 1992, World J Surg Spicer et al, 2016, The Annals of thoracic surgery. Stahl et al, 2009, Clin Oncol. Stahl et al, 2017, Eur J Cancer

development of innovative neoadjuvant CRT with novel methods and schedules of neoadjuvant CRT therapy.

Methodical Notes

Funding Sources: This work was supported by grants from Natural Science Foundation of Liaoning Province (2015020269)

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

Study Quality: - quality assessment based on the Newcastle-Ottawa Scale (NOS) which is a semi quantitative method for assessing the quality of studies, and consisted of three main parts: selection (4 points), comparability (2 points) and outcome (3 points). The quality of study was determined on a scale from zero to nine points. Studies with seven or more points were regarded as “high quality”, studies with the points from four to six were regard as “moderate quality”, and otherwise, the study was regarded as “low quality”.
- The quality score ranged from 5 to 8. 4 records were evaluated as 8 scores, 6 records were evaluated as 7 scores, 4 records were evaluated as 6 scores, 3 records were evaluated as 5 scores. All the included records were regarded as moderate and high quality.

Heterogeneity: Heterogeneity was assessed using I2 statistics. When I2<50% and P>0.1, the fixed model was conducted; Otherwise, the Mantel-Haenszel (M-H) random model was selected
- I2 values are displayed in the results section

Publication Bias: funnel plots were used to evaluate the publication bias of included records. The plots were nearly symmetric. Hence, we didn’t find significant publication bias in our meta-analysis.

Notes:
- evidence level 1: systematic review and meta-analysis
- 11 out of 13 studies from the CRT-S vs. S analysis are already included in another meta-analysis: Feng et al 2018, Molecular and Clinical Oncology
- 4 out of 6 studies from the CRT-S vs. CT-S analysis are already included in another meta-analysis: Petrelli et al 2019, Gastric Cancer

Montagnani, F. et al. Multimodality treatment of locally advanced squamous cell carcinoma of the oesophagus: A comprehensive review and network meta-analysis. Crit Rev Oncol Hematol. 114. 24-32. 2017

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: Systematic review and network meta-analysis (25 articles) Databases: Pubmed and EMBASE, handsearch of journals Search period: not described. Inclusion Criteria: Studies enrolling oesophageal cancer patients independently of tumour histology were included if the following criteria were respected: Study design provided for patient stratification according to histology; sufficient data for the OSCC subgroup were reported. Exclusion Criteria: Studies enrolling less than 25 OSCC patients were not included in the meta analysis, as well as studies testing biologic agents	Population: Oesophageal squamous cell carcinonma (OSCC) Intervention: Multimodality treatment (i.e. [neo-]adjuvant CT or RT or CRT or definitive CRT) Comparison: Surgery	Primary: Overall survival (OS),defined from the time of randomization or the start of treatment to death from any cause. Hazard ratios (HRs) and their 95% confidence intervals (95%CIs) were used to estimate treatment effects. Secondary: - Results: **Study characteristics:** 25 studies, published between 1988 and 2014, total n=3866 OSCC patients, were included in the meta-analysis. The majority of trials compared surgery with neoadjuvant CRT (total number of patients: 942) or neoadjuvant CT (total number of patients: 997). **Results: Primary** <u>Overall survival</u> - both neoadjuvant CRT and definitive CRT confer an OS advantage over surgery alone: HRs (95% CI) were 0.73 (0.63–0.86) and 0.62 (0.41–0.96),	Roth 1988, Schlag 1992, Nygaard 1992, Apinop 1994, Maipang 1994, Le Prise 1994, Ando 1997, Bosset 1997, Law 1997, Ancona 2001, Urba 2001, Ando 2003, Lee 2004, Burmeister 2005, Stahl 2005, Natsugoe 2006, Kelsen 2007, Allum 2009, Cao 2009, Lv 2010, Boonstra 2011, Ando 2012, Van Hagen 2012, Teoh 2013, Mariette 2014.

either alone or in combination with CT or CRT.

respectively.
- Adjuvant CRT apparently demonstrated a similar impact on OS, despite lacking significance (HR 0.73; 95%CI 0.47–1.12). A non-significant trend in favour of neoadjuvant CT was found (HR 0.90; 95%CrI 0.76–1.07), whereas adjuvant CT apparently adds no further benefit to surgical resection (HR 1.00;95%CrI 0.70–1.40).
- Rank probability analysis,which provides an estimate of the probability of each treatment modality to be the most effective therapeutic option compared with surgery: definitive CRT and neoadjuvant CRT have the highest probability to represent the most effective treatment approaches in locally advanced OSCC, as they have 82.8% and 54.9% probability, respectively, to be the best or second best therapeutic options.

Author's Conclusion: "Our Bayesian analysis supports the role of neoadjuvant CRT as the preferable treatment modality in OSCC, being

definitive CRT an appropriate alternative in selected cases. Future studies should focus on the prospective assessment of preoperative CRT or definitive CRT with more modern regimens."

Methodical Notes

Funding Sources: No fundings were used for this manuscript.

COI: All the authors declare no conflicts of interest.

Study Quality: We assessed the risk of bias for each study by the use of the Cochrane tool.
10 studies were at high risk of bias, 6 at low risk and 9 at unclear risk.
There is great heterogeneity among studies with regard to staging procedures, CT administered, CT doses and type of radiation treatment. Most studies were conducted in single institutions over a large period of time and randomization procedures are often not reported. Moreover, data regarding protocol violations or potential prognostic factors are frequently not specified in the manuscripts.

Heterogeneity: Heterogeneity described in the supplementary section of the article.
- In order to statistically assess heterogeneity, standard pairwise meta-analyses were performed for the following comparisons: surgery vs. neoadjuvant CT, surgery vs. neoadjuvant CRT and surgery vs. definitive CRT. Other comparisons were not possible due to the small number of trials. Despite the aforementioned considerations, significant heterogeneity was present only in the first comparison (surgery vs. neoadjuvant CT): I^2=44%,p=0.056.

Publication Bias: Publication bias was assessed by visual inspection of funnel plots.

Notes:
Evidence level 1: Systematic review and meta-analysis

- Search period for database search not described.
- Details regarding heterogeneity, Publication bias and individual quality evaluation of original studies are reported in online supplementary, which is not available to the assessor. Only a short summary to these analyses can be found in the manuscript, except for results of the publication bias assessment which are not described.

Petrelli, F. et al. Neoadjuvant chemoradiotherapy or chemotherapy for gastroesophageal junction adenocarcinoma: A systematic review and meta-analysis. Gastric Cancer. 22. 245-254. 2019

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: systematic review and meta analysis Databases: PubMed, EMBASE, and the Cochrane Library Search period: from inception to 30th June 2018 Inclusion Criteria: (1) investigating patients who had a diagnosis of esophageal or GEJ adenocarcinoma in > 80% of included subjects, and (2) including both patients who underwent neoadjuvant CT and patients who underwent neoadjuvant CTRT.	Population: patients with esophageal or GEJ adenocarcinoma Intervention: neoadjuvant CTRT (cisplatin and 5-FU or platinum-taxanes based (CROSS-like schedule) regimen; radiotherapy doses ranged from 40 to 50 Gy) Comparison: neoadjuvant CT (mostly cisplatin + 5-Fluoro-uracil (5-FU) based)	Primary: overall survival Secondary: DFS, pCR, median OS, 5-year OS, rates of locoregional and distant recurrences. Results: - 22 studies were selected for the meta-analysis, 18,260 patients were included, 14,709 patients received neoadjuvant CTRT, whereas 3551 patients received CT alone. <u>Comparison of CTRT and CT: meta-analysis of OS and DFS</u> - pooled HR and 95% CI by comparing CTRT vs CT alone was 0.95 (95% CI 0.84–1.07; P=0.41) in n=18 studies, demonstrating that the risk of death was similar with combined modalities compared to systemic therapy alone; moderate heterogeneity in the OS result, with I2=48% and P=0.01 - DFS was better with CTRT as compared with	Al Sukhni, 2016, J Am Coll Surg Anderegg, 2017, Ann Surg Oncol Burmeister, 2011, Eur J Cancer Defoe, 2011, Am J Clin Oncol Favi, 2017, Eur J Surg Oncol Ge, 2018, Eur J Surg Oncol Goense, 2017, J Surg Oncol Hoeppner, 2014, J Surg Oncol Hong, 2013, Ann Surg Oncol Klevebro, 2016,

Exclusion Criteria: (1) included patients whose main histology was squamous cell carcinoma in > 20% of patients, (2) did not provide sufficient data to acquire hazard ratio (HR) and its 95% confidence interval (CI) of combined CTRT for OS or did not provide data about other endpoints of interest.	CT (HR 0.85, 95% CI 0.75–0.97; P=0.01) in n=12 studies with data available, heterogeneity: I2=8%, P=0.37 <u>Pooled median OS and 5-year OS</u> - Pooled median OS were 34.4 months (95% CI 31.7–37.2) and 32.1 months (95% CI 27.8–36.8) in CTRT and CT arms, respectively. Pooled 5-year OS rates were 38.7% (95% CI 36.5–41%) and 39% (95% CI 34.5–43.7%) in CTRT and CT arms, respectively. <u>pCR rates</u> - Rates of pCR (defined as ypT0N0 stage after neoadjuvant therapy and surgery) was available in n=17 studies. Odds ratio of pCR was 2.8 in favor of CTRT (95% CI 2.27–3.47; P <0.001) <u>Locoregional and distant failure rates</u> - Compared to CT alone neoadjuvant CTRT improved locoregional recurrences rate (OR 0.6, 95% CI 0.39–0.91; P=0.01) but not distant metastases rate (OR 0.81, 95% CI 0.59–1.11; P=0.19) Author's Conclusion: In conclusion, we demonstrated that both CTRT and CT are associated with similar survival rates when preceded surgery in GEJ or distal esophageal adenocarcinoma. Despite CTRT shows higher

Ann Oncol
Klevebro, 2016, Br J Surg
Lagarde, 2016, Br J Surg
Luc, 2015, Ann Surg Oncol
Luu, 2008, Ann Thorac Surg
Munch, 2018, Strahlentherapie Onkol
Samson, 2016, J Thorac Oncol
Schulze, 2014, Oncol Lett
Spicer, 2016, Ann Thorac Surg
Stahl, 2017, Eur J Cancer
Swisher, 2010, Ann Thorac Surg
Tiesi, 2017, J Surg Res
Visser, 2018, J Surg Oncol

pCR and a better locoregional control than CT alone, it is not associated with an improved outcome nor reduce the risk of distant metastases. However, both treatment modalities are justified for these patients according to current guidelines. Patient preferences, medical conditions, disease characteristics (uncertainty about R0 resection chance), medical confidence with treatment management and related toxicities should also be considered. When defining treatment plan, modern CT combinations such as CROSS-like and FLOT regimens should reasonably be preferred.

Methodical Notes

Funding Sources: no statement

COI: All authors declare that they have no conflict of interest

Study Quality: The risk of bias of retrospective studies was assessed using the Newcastle Ottawa Scale, including the following three factors: patient selection, comparability of the study groups, and assessment of outcomes. Studies with scores greater than or equal to 7 were considered as having a low risk of bias, scores of 4–6 as having a moderate risk of bias, and scores less than 4 as having a high risk of bias.
- overall research quality was moderate as assessed by the Newcastle-Ottawa Scale (mean 6.2)

Heterogeneity: - Heterogeneity among included studies was assessed using the Cochran Q test and the I2 index, significant heterogeneity was denoted by a Cochran Q P value of less than 0.05 or an I2 index >50%
- I2 values only described for OS and DFS (see results section)

Publication Bias: We applied a funnel plot as well as the Egger regression test to assess the possibility of publication bias
- Evidence of publication bias was identified in our meta-analysis for OS [P Begg's=0.02; Egger test, P=0.01]. In addition, the "fill and trim" method identified five hypothetical studies as source of bias. The recalculated overall result continued to display a not significant OS different between CT and CTRT (HR 1.06, 95% CI 0.93–1.22)

Notes:
evidence level 1: systematic review and meta analysis

OXFORD (2011) Appraisal Sheet: RCT: *2 Bewertung(en)*

Noordman, B. J. et al. Effect of Neoadjuvant Chemoradiotherapy on Health-Related Quality of Life in Esophageal or Junctional Cancer: Results From the Randomized CROSS Trial. J Clin Oncol. 36. 268-275. 2018

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 Study type: subanalysis of a multicenter, randomized controlled trial Number of Patient: 368 randomly assigned patients in the CROSS Trial, 363 in this subanalysis Recruitung Phase: not specified Inclusion Criteria: - patients with locally advanced (clinical stage T1N1M0 or T2–3N0–1M0 according	Intervention: <u>nCRT + surgery group</u> - received carboplatin (AUC 2 mg/mL per min) and paclitaxel (50 mg/m2 of body-surface area) intravenously for five cycles on days 1, 8, 15, 22, and 29. - Concurrent radiation therapy of 41.4 Gy was given in 23 fractions of 1.8 Gy, 5 days per week. - preferably had surgery 4 to 6 weeks after completion of nCRT	Primary: Health-related quality of life: primary end points of physical functioning (PF; QLQ-C30) and eating problems (EA; QLQ-OES24) Secondary: Health-related quality of life: Secondary end points were defined as global QOL (GQOL; QLQ-C30), fatigue (FA; QLQ-C30), and emotional problems (EM; QLQ-OES24). Results: Of the 368 randomly assigned patients, 363 were included in the HRQOL analysis - in the nCRT group, PF, EA, GQOL, FA, and EM scores

to the 6th edition of the TNM cancer staging), histologically proven squamous cell carcinoma (SCC), adenocarcinoma (AC) or large-cell undifferentiated carcinoma of the esophagus or esophagogastric junction (EGJ)
- patients were between 18 and 75 years of age
- had adequate pulmonary, hematological, hepatic and renal function
- and a WHO performance score of 2 or better.

Exclusion Criteria: not described

Comparison: Patients in the surgery alone group received surgery as soon as possible

deteriorated 1 week after nCRT (Cohen's d: −0.93, P < .001; 0.47, P < .001; −0.84, P < .001; 1.45, P < .001; and 0.32, P = .001, respectively).
- In both treatment groups, all end points declined 3 months postoperatively compared with baseline (Cohen's d: −1.00, 0.33, −0.47, −0.34, and 0.33, respectively; all P < .001), followed by a continuous gradual improvement.
- EA, GQOL, and EM were restored to baseline levels during follow-up, whereas PF and FA remained impaired 1 year post-operatively (Cohen's d: 0.52 and −0.53, respectively; both P < .001)

Author's Conclusion: In conclusion, although HRQOL declined immediately after nCRT, no effect of nCRT according to CROSS was apparent on postoperative short-term HRQOL compared with surgery alone. In addition to the earlier described improvement in long-term overall and disease-free survival, these results support the view that nCRT according to this effective regimen should be regarded as a standard of care for patients with locally advanced resectable esophageal or esophagogastric junctional cancer.

Methodical Notes

Funding Sources: Supported by the Dutch Cancer Foundation (KWF Kankerbestrijding)

COI: - Hanneke W.M. van Laarhoven: Research Funding: Bayer HealthCare Pharmaceuticals (Inst), Bristol-Myers Squibb (Inst), Eli Lilly (Inst),

Roche (Inst), Philips Healthcare (Inst), Celgene (Inst), Nordic Group (Inst)
- Maurice J.C. van der Sangen: Travel, Accommodations, Expenses: Roche
- Ewout W. Steyerberg: Patents, Royalties, Other Intellectual Property: Royalties from Springer for book on prediction models
- J. Jan B. van Lanschot: Other Relationship: Dutch Cancer Foundation (KWF Kankerbestrijding), Coolsingel Stichting, Erasmus MC/MRace Fund
- all other authors have no relationship to declare

Randomization: Patients were randomized 1:1 to each treatment group, with random permuted block sizes of 4 or 6. All patients were stratified according to treatment center, WHO performance score, histological tumor type and clinical lymph node status.

Blinding: no blinding

Dropout Rate/ITT-Analysis: Data were analyzed on an intention-to-treat basis

Notes:
- evidence level 2: randomized controlled trial
- HRQOL results of long-term survivors are described in Noordman et al 2018, Annals of Oncology

Noordman, B. J. et al. Impact of neoadjuvant chemoradiotherapy on health-related quality of life in long-term survivors of esophageal or junctional cancer: results from the randomized CROSS trial. Ann Oncol. 29. 445-451. 2018

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 Study type: subanalysis of a multicenter, randomized controlled trial Number of Patient: 368 patients included in the CROSS trial, 123 included in this subanalysis	Intervention: <u>nCRT + surgery group</u> - received carboplatin (AUC 2 mg/mL per min) and paclitaxel (50 mg/m2 of body-surface area) intravenously for five cycles on days 1, 8, 15, 22, and 29. - Concurrent radiation therapy of	Primary: Health-related quality of life: primary end points of physical functioning (PF; QLQ-C30) and eating problems (EA; QLQ-OES24) Secondary: Health-related quality of life: Secondary end points were defined as global QOL (GQOL; QLQ-C30), fatigue (FA; QLQ-C30), and emotional problems

Recruitung Phase: not specified

Inclusion Criteria: - patients with locally advanced (clinical stage T1N1M0 or T2–3N0–1M0 according to the 6th edition of the TNM cancer staging), histologically proven squamous cell carcinoma (SCC), adenocarcinoma (AC) or large-cell undifferentiated carcinoma of the esophagus or esophagogastric junction (EGJ)
- patients were between 18 and 75 years of age
- had adequate pulmonary, hematological, hepatic and renal function
- and a WHO performance score of 2 or better.
- Patients who were alive during long-term follow-up assessment (July2015) were included in the analysis

Exclusion Criteria: not described

41.4 Gy was given in 23 fractions of 1.8 Gy, 5 days per week.
- preferably had surgery 4 to 6 weeks after completion of nCRT

Comparison: Patients in the surgery alone group received surgery as soon as possible

(EM; QLQ-OES24).

Results: - 368 patients included in the CROSS trial, 123 (33%) were still alive at long-term follow-up assessment (July 2015, 70 nCRT plus surgery, 53 surgery alone).
- median follow-up of 105 months
- No statistically significant or clinically relevant differential effects in HRQOL end points were found between both groups.
- Compared with 1-year postoperative levels, eating problems, physical functioning, global quality of life and fatigue remained at the same level in both groups.
- Compared with pretreatment levels, eating problems had improved (Cohen's d - 0.37,P=0.011) during long-term follow-up, whereas physical functioning and fatigue were not restored to pretreatment levels in both groups (Cohen's d -0.56 and 0.51, respectively, both P<0.001).

Author's Conclusion: In conclusion, no impact of nCRT is apparent on long-term HRQOL compared with surgery alone. In addition to the improvement in long-term survival and the absent impact on postoperative recovery, these results support the view that nCRT can be considered as a standard care for patients with

locally advanced esophageal or esophagogastric junctional cancer.

Methodical Notes

Funding Sources: Dutch Cancer Foundation (KWF Kankerbestrijding, no grant number applicable)

COI: - EWS: Royalties from Springer for book on prediction models.
- JJBvL: Dutch Cancer Foundation (KWF Kankerbestrijding), the Coolsingel Stichting, Erasmus MC/MRace fund.
- All remaining authors have declared no conflicts of interest.

Randomization: Patients were randomized 1:1 to each treatment group, with random permuted block sizes of 4 or 6. All patients were stratified according to treatment center, WHO performance score, histological tumor type and clinical lymph node status.

Blinding: no blinding

Dropout Rate/ITT-Analysis: not specified

Notes:
- evidence level 2: randomized controlled trial
- HRQOL results of whole trial population are described in Noordman et al 2018, J Clin Oncol

17 Multimodale Therapie - definitive Radiochemotherapie

Inhalt: *5 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Li, F. 2018	1	Systematic review and meta-analysis
Ma, M. W. 2018	2	systematic review and meta-analysis
Montagnani, F. 2017	1	Systematic review and network meta-analysis (25 articles)
Voeten, D. M. 2019	1	systematic review and meta-analysis
Wang, J. 2018	1	systematic review and meta analysis

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

Li, F. et al. The current optimal multimodality treatments for oesophageal squamous-cell carcinoma: A systematic review and meta-analysis. Int J Surg. 60. 88-100. 2018

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: Systematic review and meta-analysis Databases: PubMed, Embase, Ovid, Cochrane library Search period: Inception - 04/2018	Population: Patients with histologically proven locally advanced esophageal squamous cell carcinoma LAESCC Intervention: definitive chemoradiotherapy dCRT, neoadjuvant chemotherapy nCT followed by surgery, neoadjuvant	Primary: Overall survival, as hazard ratio Secondary: local recurrence rate. Results: **Study characteristics:**14 studies compared nCRT+S with dCRT, 5 studies compared nCRT+S with nCT+S. **Results:** nCRT+S vs. nCT+S: nCRT+S had higher rates of R0 resection (OR 1.84, 95%	Nakadi 2001, Delcambre 2001, Kim 2003, Fujita 2005, Nagata 2006, Cheng 2008, Shao 2015, Hategan 2015, Wang 2016, Wu 2017, Reynold 2017, Liu 2017, Molena 2018.

Inclusion Criteria: Rcts and non-randomized controlled studies, studies containing patients with histologically proven locally advanced esophageal squamous cell carcinoma LAESCC, application of nCRT or nCT or DCRT on LAESCC, available data for meta-analysis.

Exclusion Criteria: studies without comparison between nCT+S and nCRT+S or nCRT+S and dCRT for LAESCC. Studies containing patients with distant metastases (stage IV) or with very early disease (stage 0), Studies with without comparability between groups, Studies reported as abstracts, conference reports, reviews and reports,

radiochemotherapy nCRT followed by surgery.

Comparison: One of the interventions.

CI 1.03-3.29), pCR (OR 2.90, 95%CI 1.37-6.14) and pN0 (OR 2.55, 95%CI 1.54-4.24) and survival advantage (HR 0.72, 95%CI 0.52-0.99) when compared to nCRT+S. nCRT+S was compared to dRCT: nCRT+S had had better survival (HR 0.65, 95%CI 0.56-0.76) and had a significantly lower rate of local recurrence (OR 0.35, 95%CI 0.22-0.57)

Author's Conclusion: "Current evidence suggests that CRT+S may the optimal potential curative treatment mode for patients with LAESCC as long as they are suitable for this multimodality regimen.

Methodical Notes

Funding Sources: Supported by grants from the National Scieence and Technology Support program

COI: The authors declare tno conflict of interest.

Study Quality: Study quality was assessed by Jadad Scoring ssystem and the Newcastle Ottawa scale for RCTs and non-randomized controlled studies.
The RCTS had moderate quality with Jadad Scroes ranging form 2 to 3. while the NOS scores of the non-randomized studies ranged from 5-8 showing acceptable quality.

Heterogeneity: I^2 was ≥50% in the comparison between nCRT+S and nCT+S regarding overall survival, R0 resection and pN0, despite random-effects models.

Publication Bias: Funnel plot, Egger and Begg's test were used to investiagte sources of publication bias. No sigificant publication bias was found.

Notes:
Eveidence level 1: systematic review and meta-analysis.
Considerable heterogeneity (I≥2 50%) in the analysis comparing nCRT+S and nCT+S regarding overall survival, R0 resection and pN0.

Ma, M. W. et al. The role of definitive chemoradiotherapy versus surgery as initial treatments for potentially resectable esophageal carcinoma. World J Surg Oncol. 16. 172. 2018

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 2 Study type: systematic review and meta-analysis Databases: PubMed (1985 to May 2016) and Web of Science (1992 to June 2018) Search period: see databases Inclusion Criteria: (1) they were randomised clinical trials (RCTs) or non-randomised clinical trials (nRCTs) that compared dCRT with surgery as the primary treatment in patients with	Population: patients with resectable esophageal carcinoma Intervention: Definitive chemoradiotherapy (dCRT) total doses ranged from 50 to 71.4 Gy. Comparison: surgery	Primary: overall survival Secondary: progression-free survival Results: - a total of 13 studies conducted between 1985 and 2015 that included 2071 patients and that compared dCRT (N= 869) with surgery (N= 1202) <u>overall survival</u> - pooled ORs for the 2-year and 5-year OS were 1.199 (95% CI 0.922–1.560;P= 0.177; I^2=28.9%, P=0.17) and 0.947 (95% CI0.628–1.429;P=0.796; I^2=57.8%, P=0.008), respectively (12 studies) - subgroup analyses with (i) patients with ESCC, (ii) patients with different stages of esophageal cancer, (iii)	Chan 1999, Int J Radiat Oncol Biol Phys Hironaka 2003, Int J Radiat Oncol Biol Phys Sun 2006, Zhonghua Zhong Liu Za Zhi Toh 2006, Anticancer Res Yamashita 2009, J Surg Oncol Yamashita 2008,

resectable esophageal carcinoma, (2) they reported data on overall survival (OS) and progression-free survival (PFS) or if this information could be extracted from survival curves (3) the language of publication was English or Chinese. Exclusion Criteria: Studies that recruited patients who received neoadjuvant chemotherapy were excluded. Articles in which non-standardised scoring systems were used and those that reported insufficient data were also excluded.	patients with and without lymph node metastasis, (iv) patients from Asian and Western countries revealed no significant differences in OS except for a favorable 2-year OS for surgery for patients from North America (OR 1.522 (95% CI 1.035–2.238;P=0.033; I^2=0%, P=0.341; 2 studies)) <u>progression-free survival</u> - dCRT is equivalent to surgery in terms of the 5-year PFS (OR = 1.06, 95% CI 0.79–1.42;P= 0.70; I^2=49.2%, P=0.08, 5 studies) - - subgroup analysis for patients with ESCC revealed no significant differences Author's Conclusion: Our study demonstrates that dCRT is similar to surgery as an initial treatment for esophageal cancer with respect to the long-term survival of patients. Surgery may lead to a better OS in patients from Western countries, but further randomised trials are required to confirm these results.	Dis Esophagus Ariga 2009, Int J Radiat Oncol Biol Phys Morgan 2009, Br J Surg Yamamoto 2011, Am J Gastroenterol Motoori 2012, Ann Surg Oncol Teoh 2013, Ann Oncol Park 2014, Cancer Chemother Pharmacol Matsuda 2015, Ann Surg Oncol

Methodical Notes

Funding Sources: no statement

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

Study Quality: not assessed

Heterogeneity: We assessed and quantified statistical heterogeneity using Cochran's C statistic and the I^2 statistic. If heterogeneity was detected (I^2<50% and P> 0.10), a fixed-effects model was adopted; otherwise, a random-effects model was used.
- Publication bias test for 2-year overall survival: P=0.640 (Begg's test);P= 0.240 (Egger's test)
- Publication bias test for 5-year overall survival: P=0.161 (Begg's test); P=0.236 (Egger's test)
Publication bias test for 5-year progression-free survival: P=0.260 (Begg's test);P=0.350 (Egger's test)

Publication Bias: To assess potential publication bias, Begg's test and Egger's test were performed
- see results section for values of each comparison

Notes:
evidence level 2: systematic review and meta analysis, downgraded due to missing quality assessment

Montagnani, F. et al. Multimodality treatment of locally advanced squamous cell carcinoma of the oesophagus: A comprehensive review and network meta-analysis. Crit Rev Oncol Hematol. 114. 24-32. 2017

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: Systematic review and network meta-analysis (25 articles) Databases: Pubmed and EMBASE, handsearch of journals Search period: not described. Inclusion Criteria: Studies enrolling oesophageal cancer patients	Population: Oesophageal squamous cell carcinonma (OSCC) Intervention: Multimodality treatment (i.e. [neo-]adjuvant CT or RT or CRT or definitive CRT) Comparison: Surgery	Primary: Overall survival (OS),defined from the time of randomization or the start of treatment to death from any cause. Hazard ratios (HRs) and their 95% confidence intervals (95%CIs) were used to estimate treatment effects. Secondary: - Results: **Study characteristics:** 25	Roth 1988, Schlag 1992, Nygaard 1992, Apinop 1994, Maipang 1994, Le Prise 1994, Ando 1997, Bosset 1997, Law 1997, Ancona 2001, Urba 2001, Ando 2003, Lee 2004, Burmeister 2005, Stahl 2005, Natsugoe 2006, Kelsen 2007, Allum 2009, Cao 2009, Lv 2010, Boonstra 2011, Ando 2012, Van

independently of tumour histology were included if the following criteria were respected: Study design provided for patient stratification according to histology; sufficient data for the OSCC subgroup were reported.

Exclusion Criteria: Studies enrolling less than 25 OSCC patients were not included in the meta analysis, as well as studies testing biologic agents either alone or in combination with CT or CRT.

studies, published between 1988 and 2014, total n=3866 OSCC patients, were included in the meta-analysis. The majority of trials compared surgery with neoadjuvant CRT (total number of patients: 942) or neoadjuvant CT (total number of patients: 997).

Results: Primary

Overall survival

- both neoadjuvant CRT and definitive CRT confer an OS advantage over surgery alone: HRs (95% CI) were 0.73 (0.63–0.86) and 0.62 (0.41–0.96), respectively.
- Adjuvant CRT apparently demonstrated a similar impact on OS, despite lacking significance (HR 0.73; 95%CI 0.47–1.12). A non-significant trend in favour of neoadjuvant CT was found (HR 0.90; 95%CrI 0.76–1.07), whereas adjuvant CT apparently adds no further benefit to surgical resection (HR 1.00;95%CrI 0.70–1.40).
- Rank probability analysis,which provides an estimate of the probability of each treatment modality to be the most effective therapeutic option

Hagen 2012, Teoh 2013, Mariette 2014.

compared with surgery: definitive CRT and neoadjuvant CRT have the highest probability to represent the most effective treatment approaches in locally advanced OSCC, as they have 82.8% and 54.9% probability, respectively, to be the best or second best therapeutic options.

Author's Conclusion: "Our Bayesian analysis supports the role of neoadjuvant CRT as the preferable treatment modality in OSCC, being definitive CRT an appropriate alternative in selected cases. Future studies should focus on the prospective assessment of preoperative CRT or definitive CRT with more modern regimens."

Methodical Notes

Funding Sources: No fundings were used for this manuscript.

COI: All the authors declare no conflicts of interest.

Study Quality: We assessed the risk of bias for each study by the use of the Cochrane tool.
10 studies were at high risk of bias, 6 at low risk and 9 at unclear risk.
There is great heterogeneity among studies with regard to staging procedures, CT administered, CT doses and type of radiation treatment. Most

studies were conducted in single institutions over a large period of time and randomization procedures are often not reported. Moreover, data regarding protocol violations or potential prognostic factors are frequently not specified in the manuscripts.

Heterogeneity: Heterogeneity described in the supplementary section of the article.
- In order to statistically assess heterogeneity, standard pairwise meta-analyses were performed for the following comparisons: surgery vs. neoadjuvant CT, surgery vs. neoadjuvant CRT and surgery vs. definitive CRT. Other comparisons were not possible due to the small number of trials. Despite the aforementioned considerations, significant heterogeneity was present only in the first comparison (surgery vs. neoadjuvant CT): I^2=44%,p=0.056.

Publication Bias: Publication bias was assessed by visual inspection of funnel plots.

Notes:
Evidence level 1: Systematic review and meta-analysis
- Search period for database search not described.
- Details regarding heterogeneity, Publication bias and individual quality evaluation of original studies are reported in online supplementary, which is not available to the assessor. Only a short summary to these analyses can be found in the manuscript, except for results of the publication bias assessment which are not described.

Voeten, D. M. et al. Definitive Chemoradiotherapy Versus Trimodality Therapy for Resectable Oesophageal Carcinoma: Meta-analyses and Systematic Review of Literature. World J Surg. 43. 1271-1285. 2019

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: systematic review and meta-analysis Databases: PubMed, Embase and	Population: patients with stages I through IV a histologically proven oesophageal carcinoma adenocarcinoma (AC) or squamous cell carcinoma (SCC)	Primary: (1) 1-, 2-, 3- and 5-year overall survival rates (2) 1-, 2-, 3- and 5-year overall survival rates in equal patient populations at baseline. Secondary: (1) mean/median overall survival in	see article

Wiley/Cochrane Library

Search period: from inception up to 27 November 2017

Inclusion Criteria: - RCTs, longitudinal retrospective and prospective observational studies and case–control studies
- patients older than 18 years with stages I through IV a histologically proven oesophageal carcinoma [adenocarcinoma (AC) or squamous cell carcinoma (SCC)] treated with curative intent
- Studies comparing definitive chemoradiotherapy (dCRT) with trimodality therapy (TMT) were considered eligible, irrespective of type of surgery and chemoradiotherapy regimen.

Exclusion Criteria: - Case reports
- patients with irresectable disease and patients with Tis or M1b carcinoma
- Studies on adjuvant (chemo)radiotherapy, neoadjuvant

Intervention: definitive chemoradiotherapy (dCRT)

Comparison: trimodality therapy (TMT - neoadjuvant chemoradiotherapy followed by oesophagectomy and lymph node dissection,)

months;
(2) loco-regional recurrence rates;
(3) distant failure rates;
(4) short-term mortality rates in the first 3 months of treatment.

Results: - Of the 35 articles included, two were RCTs and 33 were observational. In total 26,917 patients were included, of whom 17,513 received dCRT and 9404 received TMT.
<u>One-year overall survival</u>
- reported in eight studies
- significantly lower in the dCRT group with a RR of 0.80 (95% CI 0.74–0.88; P<0.00001; I^2=37%)
- One study reported 1-year overall survival rates of 85.9% for dCRT and 97.8% for TMT in matched cohorts
<u>Two-year overall survival</u>
- reported in 14 studies
- significantly lower in the dCRT group with a RR of 0.69 (95% CI 0.57–0.83; P<0.00001; I^2=84%)
- Four studies with equal patient groups at baseline: No statistical significant difference
<u>Three-year overall survival</u>
- reported in 15 studies
- significantly lower in the dCRT group with a RR of 0.76 (95% CI 0.63–0.92; P=0.005; I^2=80%)

chemotherapy or neoadjuvant radiotherapy
- Studies mixing the former groups with TMT

- Five studies with equal patient groups at baseline: No statistical significant difference

Five-year overall survival

- reported in 15 studies
- significantly lower in the dCRT group with a RR of 0.5 (95% CI 0.47–0.71; P<0.00001; I^2=79%)
- Three studies with equal patient groups at baseline: No statistical significant difference

Mean/median overall survival

- mean OS not reported, Sixteen studies reported median OS,
- median OS ranged from 11.8 to 95 months in the dCRT group and from 16.4 to 83 months in the TMT group
- Five studies with equal patient groups at baseline reported median OS: ranging from 14.2 to 57.9 months in the dCRT group and from 17.7 to 59.4 months in the TMT group

Local recurrence

- reported in 18 studies.
- Significantly more was observed in the dCRT group compared to the TMT group with a RR of 2.18 (95%CI 1.79–2.66; P<0.00001; I^2=34%)

Distant failure rate

- reported in 14 studies.
- No difference between dCRT and TMT was observed with a RR of 0.84 (95% CI 0.65–

1.09;P=0.20; I^2=56%)
Short-term mortality (90 days)
- reported in eight studies
- Significantly less was observed in patients treated with dCRT compared to TMT with a RR of 0.20 (95% CI 0.10–0.43;P<0.0001; I^2=0%).

Author's Conclusion: Despite limitations of the available evidence, these meta-analyses comparing survival after dCRT and TMT inresectable oesophageal carcinoma do not show clear survival advantage for the one over the other. Only a non-significant trend towards better survival after TMT was seen assuming comparable groups at baseline. Evidence was mainly based on studies including SCCs. Results are inline with other studies comparing dCRT and TMT in equal patient groups at baseline. Non-operative management of oesophageal carcinoma patients might be part of a personalised and tailored treatment approach in future. However, to date hard evidence proving its non-inferiority compared to operative management is lacking.

Methodical Notes

Funding Sources: no statement

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

Study Quality: - Risk of bias for randomised controlled trials was assessed at study level by DV and checked by CdB, using the Cochrane risk of bias tool for trials
- Risk of bias in cohort studies was assessed at study level using the Cochrane tool for cohort studies.
- Both RCTs had high risk of bias in the "selective reporting" domain since no trial protocols were published. One of the studies did not blind outcome assessment, while one other study did not report on outcome assessment blinding at all. No risk of bias was identified in other domains.
- Risk of bias in the observational studies was high. In 42%, risk of bias in patient selection was high because dCRT patients were older and had more comorbidities, lower performance status and more advanced disease. Only eight studies tried to minimise this difference by matching the cohorts. In addition, 36% of the observational studies did not identify prognostic factors, and 42% did not have similar co-interventions in the two treatment groups, causing major bias.

Heterogeneity: - Homogeneity between included studies was assessed at outcome level using the Higgins I^2 statistic. When I^2 was more than 50%, studies were considered heterogeneous. A random-effect model was used since heterogeneity was expected.
- see results section for further I^2 values

Publication Bias: not assessed

Notes:
evidence level 1: systematic review and meta analysis

Wang, J. et al. Clinical complete response after chemoradiotherapy for carcinoma of thoracic esophagus: Is esophagectomy always necessary? A systematic review and meta-analysis. Thorac Cancer. 9. 1638-1647. 2018

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: systematic review and meta analysis	Population: patients with a cCR (clinical complete response) after concurrent chemoradiotherapy (CRT) in	Primary: two and five-year OS and disease-free survival (DFS) Secondary: none	Castoro et al. 2013, J Gastrointest Surg

Databases: PubMed, the Cochrane Library, and Embase Search period: final date of data retrieval was 30 June 2018. Inclusion Criteria: (i) precision radiotherapy, such as three-dimensional (3D) conformal irradiation and intensity-modulated radiotherapy had been performed; (ii) the original data were detailed, including a curative effect evaluation after CRT; (iii) patients with a cCR were classified into surgery and non-surgery groups (further definitive CRT or active sur-veillance in which patients were subjected to serial clinical investigations after completion of CRT) and relevant contrastive data was provided; (iv) articles included an accurate statistical method, valid data, and clear conclusions; (v) hazard ratios (HRs) and 95% confidence intervals (CI) were provided or could be calculated. Exclusion Criteria: articles that applied 2D	thoracic esophageal carcinoma Intervention: CRT + surgical strategies Comparison: CRT and non-surgical strategies (including further definitive chemoradiotherapy or active surveillance)	Results: four articles were selected for this study, including 648 esophageal carcinoma patients <u>Effects of treatment regimens on overall survival (OS)</u> *Two-year OS* - The results of 3 studies showed that the CRT + surgery group had an advantage over the non-surgery group in two-year OS (HR 2.108, 95% CI 0.981–4.530;P= 0.056) *Five-year OS* - The results of 3 studies showed similar results for CRT + surgery and non-surgery groups (HR 1.361, 95% CI 0.572–3.239; P=0.486) <u>Effects of treatment regimens on disease-free survival (DFS)</u> *Two-year DFS* - The results of 3 studies showed that the CRT + surgery group had an advantage over the non-surgery group (HR 3.186, 95% CI 2.071–4.901;P= 0.000) - *Five-year OS* - The results of 3 studies showed similar results for CRT + surgery and non-surgery groups (HR 1.780, 95% CI 0.866–3.657;P= 0.117) Author's Conclusion: In conclusion, based on the	Piessen et al. 2013, Ann Surg Chao et al. 2013, Ann Surg Oncol Jeong et al 2014, J Surg Oncol

radiotherapy techniques or missed concurrent CRT were excluded	available evidence, additional esophagectomy in patients with cCR after CRT for thoracic locally advanced esophageal carcinoma provided no advantage to OS, while two-year DFS could be improved. Because 95.7% of the sample were esophageal SCC patients, this research conclusion might be more suitable to SCC patients. Thus, more randomized clinical trials are needed to confirm our conclusions.

Methodical Notes

Funding Sources: no statement

COI: No authors report any conflict of interest.

Study Quality: - The case-control study evaluation guideline was applied in order to evaluate the quality of each manuscript from the following aspects: (i) whether the gender, age, and tumor location were clearly stated; (ii) whether the comparability of the two groups was analyzed; and (iii) whether the statistical method was appropriate (e.g. whether the OS or DFS was calculated using the Kaplan–Meier method and log-rank testing had been performed); (iv) whether the test was designed as a prospective randomized control study; and (v) whether the biases in the study were discussed. A score was assigned for each of the five items. A total score of ≥3 indicates reliable quality. Two researchers independently reviewed the literature according to the unified quality standard.
- 1 study scored 3 points, 2 studies scored 4 points, 1 study scored 5 points

Heterogeneity: - A Q test was applied to test the heterogeneity of the results. For P≤0.05, the result was considered to be heterogeneous, and the random effect model was used for statistical consolidation. For P> 0.05, the result was not considered heterogeneous, and the fixed effect model was used.
- none of the articles had publication bias.

Publication Bias: Funnel plots were created to evaluate the risk of publication bias. An asymmetrically shaped funnel indicated the presence of publication bias, and Egger's regression method was conducted to test the publication bias

Notes:
evidence level 1: systematic review and meta-analysis

18 Multimodale Therapie - PET-CT

Inhalt: *2 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
de Gouw, Djjm 2019	1	Systematic review and meta-analysis
Gabrielson, S. 2019	1	subgroupanalysis of a randomized controlled trial

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

de Gouw, Djjm et al. Detecting Pathological Complete Response in Esophageal Cancer after Neoadjuvant Therapy Based on Imaging Techniques: A Diagnostic Systematic Review and Meta-Analysis. J Thorac Oncol. 14. 1156-1171. 2019

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: Systematic review and meta-analysis Databases: Medline, Embase, and Cochrane Library Search period: 01.2000 - 12.2017 Inclusion Criteria: Studies were considered eligible when imaging results of restaging were reported after	Population: 57 studies involving 3660 esophageal cancer patients were included. Imaging techniques used to diagnose ypCR: CT 8, PET-CT 35, EUS 15, MRI 3 studies). In general, studies had a retrospective design and included an uninterrupted series of patients. Intervention: imaging techniques (MRI, CT, PET-CT, EUS) Comparison: Histopathology	Primary: The primary outcome was the accuracy of predicting ypCR after neoadjuvant therapy compared with the final histopathological results after resection. Secondary: Primary Tumor Response, Diagnostic Accuracy: Regional Lymph Node Response, Subgroup and Sensitivity Analyses.	56 studies, see article.

neoadjuvant therapy and before surgery in patients with esophageal cancer.
Only studies in which patients were treated with curative intent, consisting of neoadjuvant chemotherapy and/or radiotherapy followed by esophageal resection
and lymph node dissection, were included. Studies addressing a combination of diagnostic modalities (imaging and nonimaging) were included only if separate data on the imaging test was available.

Exclusion Criteria: Studies without comparison with histopathological or imaging tests that were performed during neoadjuvant treatment were excluded. Other reviews, case reports, conference abstracts, and studies with fewer than 10 patients were excluded. Publications before the year 2000 were excluded to ensure that the review would represent contemporary imaging techniques.

Results: - In total, 57 studies involving 3660 patients included
- CT (eight studies), PET(-CT)(35 studies), EUS (15 studies), and MRI (three studies)
Diagnostic Accuracy: complete response
The pooled sensitivities of CT, PET-CT, EUS, and MRI for detecting ypCR (pathological complete response) were 0.35, 0.62, 0.01 and 0.80, respectively, whereas the pooled specificities were 0.83, 0.73, 0.99,and 0.83, respectively. The positive predictive value in detecting ypCR was 0.47 for CT, 0.41 for PET-CT, not applicable for EUS, and 0.61 for MRI.
- For studies based on PET-CT, a higher specificity was found when only studies with a restaging interval of less than 4 weeks were included (0.86 versus 0.65).

Author's Conclusion: Current imaging modalities such as CT, PET-CT, and EUS seem to be insufficiently accurate to identify complete responders. More accurate diagnostic tests are needed to improve restaging accuracy for patients with esophageal cancer.

Methodical Notes

Funding Sources: not described.

COI: The authors declare no conflicts.

Study Quality: The methodological quality of each study was assessed by the Cochrane Quality Assessment of Diagnostic Accuracy Studies, version 2, model.

Heterogeneity: not investigated.

Publication Bias: not investigated.

Notes:
evidence level 1: systematic review and meta analysis
Publication bias and heterogeneity not investigated.

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

Gabrielson, S. et al. 18F FDG-PET/CT evaluation of histological response after neoadjuvant treatment in patients with cancer of the esophagus or gastroesophageal junction. Acta Radiol. 60. 578-585. 2019

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 1 Study type: subgroupanalysis of a randomized controlled trial Number of Patient: Seventy-nine patients were enrolled and 51 were available for	Intervention: neoadjuvant chemoradiotherapy (NACRT) followed by surgical resection (three cycles of Cisplatin/oxaliplatin-5-FU+40 Gy given in fractions) Comparison: neoadjuvant chemotherapy	Primary: rate of change in SUR (Standardized uptake ratio) Secondary: none Results: The mean time between conclusion of neoadjuvant therapy and follow-up PET/CT was

analysis

Recruitung Phase: 2006–2013

Inclusion Criteria: - histologically confirmed tumors at stage T1–T3,
- any nodal stage and non-distant metastatic SCC or AC of the esophagus or GOJ where there was intent of curative resection.
- patients aged ≤75 years and
- patients who were considered fit for esophagectomy and with performance status, renal and haematological status permitting chemotherapy.
- In order to maintain PET data consistency, only patients treated at our academic center were included in this analysis.

Exclusion Criteria: - who withdrew participation out of personal choice (n=11),
- were not allotted treatment due to human error (n=2),
- had severe adverse effects to neoadjuvant treatment (n=3), had unclear reasons (n=1), were not resected due either to disease progression or co-morbidity (n=10), or due to

(NACT) followed by resection (three cycles of Cisplatin/oxaliplatin-5-FU)

similar in responders (15.7±9.2 days) compared to non-responders (17.9±24.9 days) (P=0.5)
- The mean rate of SUR change (days^{-1}) was –0.048±0.049 and –0.017±0.041 for pooled NACRT and NACT responders and pooled non-responders, respectively (P=0.02)
- The rate of reduction of SUR in histological NACRT responders was statistically significantly higher than that observed in histological non-responders (P=0.02).
- The rate of reduction of SUR in histological NCT responders was not significantly different from that observed in histological non-responders (P=0.49).
- Neoadjuvant treatment with NACRT led to a significantly higher rate of reduction in tumor SUR compared to patients treated with NACT (P=0.04)

Author's Conclusion: In conclusion, this study shows that sequential 18F-FDG PET/CT can discriminate histological responders from non-responders following neoadjuvant therapy with NACRT or NACT. Furthermore, a decrease in the rate of SUR appears to be an accurate predictor of histological response. 18F-FDG PET/CT itself cannot discriminate pCR from non-pCR. Advances in PET technology and a multimodality approach (PET/CT, EUS, endoscopy, genetic analysis, novel biomarkers) are required in order to improve the evaluation of treatment response.

tumor non-avidity at baseline as well at follow-
up (n=1).

Methodical Notes

Funding Sources: The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication ofthis article: This study is part of the NeoRes trial, which was financially supported by the Swedish Society of Medicine, the Swedish Cancer Society, the Cancer Research Foundations of Radiumhemmet, and the Stockholm County Council.

COI: The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Jon Tsai is a medical advisor at SanofiGenzyme. The other authors have no conflict of interests

Randomization: yes, but randomization process not described

Blinding: All PET/CT assessment was performed com-pletely blinded to treatment allocation and other clin-ical data.

Dropout Rate/ITT-Analysis: Analysis was made by intention to treat.

Notes:
evidence level 2: subgroup analysis of a randomized controlled trial

19 Palliative Therapie - Indikation

Inhalt: *6 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Janmaat, V. T. 2017	1	Cochrane systematic review and meta-analysis of randomised controlled trial
Kato, Ken 2019	2	mulitcentre, randomised, open-label, phase 3 trial (ATTRACTION-3; Europe, Asia, USA)
Penniment, M. G. 2018	2	randomised controlled trial
Shah, Manish A 2019	1	phase 2, open-label, interventional, single-arm study
Shitara, Kohei 2018	2	multicentre, randomised, open-label, phase 3 study (worldwide)
van Kleef, J. J. 2019	1	systematic review and meta analysis of phase II/III randomized controlled trials

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

Janmaat, V. T. et al. Palliative chemotherapy and targeted therapies for esophageal and gastroesophageal junction cancer. Cochrane Database Syst Rev. 11. Cd004063. 2017

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: Cochrane systematic review and meta-analysis of randomised controlled trial Databases: 1. Cochrane Central Register of Controlled Trials	Population: People with advanced (T3-T4NxM0 non-resectable; and all TxNxM1), recurrent, or metastatic carcinoma of the esophagus and GE-junction. Intervention: - Chemotherapy or	Primary: overall survival Secondary: progression-free survival Toxicity Quality of life Results: The quantitative synthesis includes 41 studies,	studies included in meta-analysis: Bang 2010; Lancet Bleiberg 1997; European

(CENTRAL; 2017, Issue 9) in the Cochrane Library (searched 19 September 2017) 2. MEDLINE (1950 to 19 September 2017) 3. Embase (1980 to 19 September 2017) 4. Web of Science (1900 to 19 September 2017) 5. Pubmed Publisher (1950 to 19 September 2017) 6. Google Scholar (1592 to 19 September 2017) 7. Clinicaltrials.gov (searched 19 September 2017) 8. WHO International Clinical Trials Registry Platform (ICTRP) (searched 19 September 2017) Search period: from inception to 19 September 2017 Inclusion Criteria: - RCTs with or without blinding - studies involving participants with advanced or non-resectable disease who received	targeted therapy agent(s) plus any control intervention - Chemotherapy encompassed all cytotoxic and anti-neoplastic drug treatment, and targeted therapy encompasses all anti-neoplastic drug treatment targeting a specific protein or small group of proteins. Comparison: - control intervention - We defined 'control arm' as best supportive care (BSC) or treatment with at least one chemotherapy agent whose composition, dose, and schedule were equal in both arms.	Eleven studies in 1347 participants contributed data to the meta-analysis of the main comparison **main analysis: chemotherapy or targeted therapy agent(s) plus control intervention versus control intervention alone in people with esophageal and GE-junction cancer** <u>Overall survival</u> - analysis contained eleven studies in 1347 participants - overall HR in favor of the arm with the additional agent was 0.75 (95%CI 0.68 to 0.84, high-quality evidence), showing an OS benefit - Median OS, weighted for study size, in the arm with the additional agent was 6.7 months versus 5.7 months in the control arm. - Cochrane's Q test for heterogeneity showed a non-significant amount of heterogeneity (I^2= 5%, P=0.40) <u>Progression-free survival</u> - analysis contained five studies in 883 participants - The addition of a targeted therapeutic agent probably leads to an HR of 0.64 (95% CI 0.45 to 0.92, moderate-quality evidence) - Cochrane's Q test for heterogeneity showed a significant amount of heterogeneity (I^2= 79%, P=0.0007) <u>Toxicity</u> - Overall, palliative chemotherapy and/or targeted therapy appears to increase the frequency of	Journal of Cancer Dutton 2014; Lancet Oncology Ford 2014; Lancet Oncology Fuchs 2014; Lancet Huang 2009; Chinese Journal of Integrative Medicine Levard 1998; European Journal of Surgery Lordick 2013; Lancet Oncology Lorenzen 2009; Annals of Oncology Nicolaou 1982; South African

chemotherapy with palliative intent - treatments with systemic intravenous and single oral chemotherapy or targeted therapy, as well as combination regimens in all doses and schedules. Exclusion Criteria: - all non-randomized and quasi-randomized studies - studies including participants receiving chemotherapy for locally advanced cancer in order to assess resectability - combined radiochemotherapy or radio-targeted therapy interventions	treatment-related toxicity of at least grade 3. - Treatment-related deaths were rare in most studies,and there is no clear evidence that treatment-related deaths occur more frequently in the study arms with an additional chemotherapy or targeted therapy agent <u>Quality of life</u> - Overall, the studies reporting quality of life did so in different ways, prohibiting a meta-analyis - quality of life improved in the arms with the additional agent **subanalysis 1: chemotherapy or targeted therapy plus BSC versus BSC** <u>overall survival</u> - Five studies in 750 participants - HR=0.81 (95% CI 0.71 to 0.92, high-quality evidence) in favor of the chemotherapy or targeted therapy arm. - Median OS, weighted for study size, in the chemotherapy arm was 4.7 months versus 4.2 months in the BSC arm - Cochrane's Q test was non-significant (I^2=0%, P=0.56) <u>Progression-free survival</u> - Two studies in 540 participants - overall HR=0.58 (95% CI 0.28 to 1.18, very low-quality evidence) in favor of targeted therapy - Cochrane's Q test showed significant heterogeneity (I^2= 85%, P= 0.01)	Medical Journal Wilke 2014; Lancet Oncology

subanalysis 2: participants who had received previous chemotherapy

Overall survival

- four studies in 769 participants
- overall HR of 0.71(95% CI 0.54 to 0.94, moderate-quality evidence) in favor of the arm with the additional agent
-Median OS, weighted for study size, was 5.1 months in the chemotherapy arm versus 4.4 months in the BSC arm.
- Cochrane's Q test for heterogeneity showed significant heterogeneity (I^2=57%, P = 0.07)

Progression-free survival

- Three studies in 677 participants
- overall HR of 0.51 (95% CI 0.29 to 0.90, low-quality evidence) in favor of the targeted therapy arms
- Cochrane's Q test for heterogeneity showed substantial heterogeneity (I^2= 83%, P < 0.001)

subanalysis 3: chemotherapy agent(s) pluscontrol intervention versus control intervention alone

Overall survival

- Five studies in 358 participants
- overall HR of 0.73 (95% CI 0.63 to 0.85, moderate-quality evidence) in favor of the arm with the additional chemotherapy agent
- Median survival time, weighted for study size, was 6.9 months in the chemotherapy arm versus 5.8 months in

the control arm.
- Cochrane's Q test showed non-significant heterogeneity (I^2= 0%, P=0.50)

subanalysis 4: targeted agent plus control intervention versus control intervention alone

Overall survival
- Six studies with 989 participants
- overall HR in favor of the arm containing a targeted agent was 0.75 (95% CI 0.63 to 0.90, high-quality evidence)
- Median OS in the arm with the additional targeted agent, weighted for study size, was 6.7 months versus 5.7 months in the control arm.
- Cochrane's Q test showed low heterogeneity (I^2= 24%, P=0.25)

Progression-free survival
- Five studies in 883 participants
- overall HR, in favor of the treatment arm that contained a targeted therapy agent, was 0.64 (95% CI 0.45 to 0.92, moderate-quality evidence)
- Median progression-free survival, weighted for study size, was 2.9 months in the arm with the additional targeted therapy agent versus 2.4 months in the control arm
- Cochrane's Q test showed substantial heterogeneity (I^2= 79%, P < 0.001)

Subanalysis 5: chemotherapy or targeted

therapyagent(s) plus control intervention versus controlintervention alone in participants with adenocarcinoma of the esophagus

Overall survival

- Five studies in 538 participants
- For overall survival, we found an HR of 0.66 (95% CI0.54 to 0.81, high-quality evidence) in favor of the experimental arm
- Median OS, weighted for study size, was 7.1 months in the added agent arm versus 6.0 months in the control arm.
- Cochrane's Q test was non-significant (I^2= 0%, P=0.55)

Progression-free survival

- Four studies in 713 participants
- HR of 0.62 (95% CI 0.38 to 1.00, very low-quality evidence) in favor of the experimental arm
- Median OS, weighted for study size, was 1.8 months in the added agent arm versus 1.7 months in the control arm
- Cochrane's Q test was non-significant (I^2= 84%, P < 0.001)

Subanalysis 6: chemotherapy or targeted therapy agent(s) plus control intervention versus control intervention alone in participants with SCC of the esophagus

Overall survival

- Four studies in 268 participants

- HR of 0.76 (95% CI 0.65 to 0.90, high-quality evidence) in favor of the experimental arm
- Median OS, weighted for study size, was 8.0 months in the added agent arm versus 6.5 months in the control arm.
- Cochrane's Q test for heterogeneity was non-significant (I^2= 0%, P=0.95)

<u>progression free survival</u>

- Two studies in 168 participants
- HR of 0.72 (95% CI 0.55 to 0.96, low-quality evidence) in favor of the experimental arm.
- Median OS, weighted for study size, was 1.7 months in the added agent arm versus 1.2 months in the control arm
- Cochrane's Q test for heterogeneity was non-significant (I^2= 0%, P = 0.97)

Author's Conclusion: People who receive more chemotherapeutic or targeted therapeutic agents have an increased overall survival compared to people who receive less. These agents, administered as both first-line or second-line treatments, also led to better overall survival than best supportive care. With the exception of ramucirumab, it remains unclear which other individual agents cause the survival benefit.

Although treatment-associated toxicities of grade 3 or more occurred more frequently in arms with an additional chemotherapy or targeted therapy agent, there is no evidence that palliative chemotherapy and/or targeted therapy decrease quality of life. Based on this meta-analysis, palliative chemotherapy and/or targeted therapy can be considered standard care for esophageal and gastroesophageal junction carcinoma.

Methodical Notes

Funding Sources: Internal sources
- Dept. of Gastroenterology & Hepatology, Erasmus MC / University Medical Center Rotterdam, Netherlands
- Dept. of Public Health, Erasmus MC, University Medical Center Rotterdam, Netherlands
- Biomedical information specialists, Medical Library Erasmus MC, University Medical Center Rotterdam, Netherlands
External sources
- No sources of support supplied

COI: - VTJ: none known
- EWS: none known
- AvdG: none known
- RHJM: none known
- MJB: none known
- MPP: none known
- EJK: none known
- MCWS: none known

Study Quality: - Two review authors (VJ, MS) independently assessed the risk of bias and the quality of the eligible studies according to the Cochrane Handbook for Systematic Reviews of Interventions

- We rated each study as being at low, high, or unclear risk of bias
- We generally considered the analyzed RCTs to be at low risk of bias in most domains. Apart from blinding, the most common methodological weakness in the included studies was the lack of description regarding allocation concealment.
- individual estimates regarding quality of the evidence can be found in the results section

Heterogeneity: - forest plots for heterogeneity by visual inspection.
- To quantify inconsistency across studies, we calculated the I^2 statistic as [(Q−df)/Q] × 100%, where Q is the Chi2 statistic and df its degrees of freedom
- see results section for individual I^2 values

Publication Bias: - funnel plot if enough studies were present (i.e. at least 10).
- for the main analysis, no evidence of publication bias was found

Notes:
evidence level 1: systematic review and meta-analysis

van Kleef, J. J. et al. Quality of life during palliative systemic therapy for oesophagogastric cancer: systematic review and meta-analysis. J Natl Cancer Inst. . . 2019

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: systematic review and meta analysis of phase II/III randomized controlled trials Databases: Medline, EMBASE, and the Cochrane Central	Population: patients with metastatic, unresectable, or recurrent adenocarcinoma of the stomach or esophagus Intervention: comparison of different palliative systemic therapies	Primary: health-related quality of life (HRQoL): cancer-specific QLQ-C30 questionnaire or supplemented with disease-specific EORTC modules, for example, the OES18 for esophageal cancer patients and STO22 for gastric cancer patients. Secondary: functioning and symptom scales, for example, fatigue andphysical functioning.	see article for references

Register ofControlled Trials

Search period: inception to April 2018

Inclusion Criteria: - Phase II and III RCTs
- palliative systemic therapies
- patients with metastatic, unresectable, or recurrent adenocarcinoma of the stomach or esophagus
- provided information regarding planned HRQoL analyses

Exclusion Criteria: Studies using solely self-constructed or nonvalidated measures

Comparison: see intervention

Results: - 43 unique RCTs were included (n=13727); 31 studies investigated HRQoL in the first-line treatment setting (n=9214) and 12 studies beyond first-line treatment setting (n=4513)

<u>Baseline HRQoL</u>

- 13 of 31 (41.9%) first-line therapiy studies reported HRQoL scores at baseline:
- Mean GHS at baseline ranged from 43.0 to 67.9.
- Meta-analysis showed a pooled mean GHS of 54.6 (95% CI=51.9 to 57.3)
- Five of 12 (41.7%) beyond first-line therapy studies reported HRQoL scores at baseline.
- Mean GHS at baseline ranged between 43.6 and 61.5.
- Meta-analysis showed a pooled mean GHS of 57.9 (95% CI=55.7 to 60.1)

<u>Mean HRQoL Scores Over Time</u>

- 16 RCTs investigating first-line treatments with a total of 34 study arms reported on longitudinal HRQoL. 28 study arms showed stable, 5 arms showed improved, and 1 arm showed deteriorated HRQoL over a short period (<18 weeks)
- Mixed-model analysis of follow-up GHS data showed no statistically significant time effect. In addition, no differences in GHS were found between first-line treatments groups; BSC, singlets, doublets and triplets
- 6 RCTs investigating beyond first-line treatments with a total of 14 study arms reported on the course of HRQoL over time.

- 11 arms showed stable, 1 arm showed improved, and 2 arms showed deteriorated HRQoL over a short period (<18 weeks).
- Mixed-model analysis showed no time effect of GHS and stayed within a 10-point difference relative to baseline; No statistically significant treatment-time interaction of BSC vs singlets and doublets was observed

HRQoL Differences Between Treatments

- Of the 37 comparisons made between first-line treatment regi-mens, most studies (n=30) reported similar GHS; six comparisons showed a superior GHS favoring one particular arm.
- Of those six, four arms consisted of the anthracycline-based triplet epirubicine, cisplatin, and 5-fluorouracil (5-FU)(ECF).
- other HRQoL scales showed superior HRQoL in almost one-half of the first-line studies (20 of 37)
- Two first-line studies compared capecitabine and oxaliplatin (CAPOX) with capecitabine (Cap), and both showed superior overall HRQoL in CAPOX-treated patients
- Other doublets compared with singlets did not show this clinically significant result, except for irinotecan and 5-FU/leucovorin (Lv) vs 5-FU/Lv
- Fluoropyrimidine-based doublets (without cisplatin) showed comparable results to cisplatin-based doublets regarding GHS
- comparing first-line anthracycline-based triplets with fluoropyrimidine-based doublets (without cisplatin), one phase III and one phase II trial reported similar outcomes in

terms of HRQoL and OS
- effect of a targeted agent on HRQoL vs BSC was investigated in six RCTs beyond the first-line treatment setting:
- GHS scores were comparable between targeted agents and BSC.
- Patients treated with ramucirumab reported more often (34%) improved or stable GHS than patients treated with BSC (13%). This difference was not statistically significant.
- Two studies investigated the effect of a targeted agent in addition to taxane-monotherapy beyond first-line
- Time to GHS deterioration ≥ 10 points was similar between arms. However, in the RAINBOW trial, ramucirumab plus paclitaxel affected emotional functioning and nausea or vomiting favorably but diarrhea adversely in the TtD analysis.
- Responder analysis also showed favorable outcomes for the ramucirumab plus paclitaxel arm with regard to GHS, physical and role functioning, pain, fatigue, and appetite loss.

Author's Conclusion: In conclusion, patients reported impaired HRQoL, which generally remained stable during systemic therapy. Based on the current evidence, anthracycline-based triplets and fluoropyrimidine-based doublets without cisplatin may be preferable first-line treatment options regarding HRQoL. Taxanes and targeted agents could benefit HRQoL beyond first line com-pared with BSC. Our findings could enable shared decisionmaking during

doctor-patient consultations, where the impact of systemic therapy on survival, side effects, and HRQoL are discussed.

Methodical Notes

Funding Sources: This work was supported by the Dutch Cancer Society grant number UVA 2014–7000.

COI: - Dr van Laarhoven reports grants from the Dutch Cancer Society during the conduct of the study; personal fees from BMS, personal fees from Lilly, personal fees from NordicPharma, grants and nonfinancial support from Bayer, grants from BMS, grants and nonfinancial support from Celgene, grants from Jansen, grants and nonfinancial support from Lilly, grants and nonfinancial support from Nordic Pharma, grants from Philips, and grants from Roche outside this work.
- Dr van Oijen reports grants from Roche, grants from Lilly, grants from Servier, grants from Merck, and grants from Nordic outside this work.
- The other authors declare no competing interests.

Study Quality: - Study quality was assessed by two reviewers using the Cochrane Risk of bias tool (version 5.1.0). Items were scored as unknown, low, or high risk of bias.
- Twenty-eight (65.1%) studies were rated as low risk of bias, and 15 (34.9%) studies were rated as unclear on at least one item.
- The quality of HRQoL: Eleven studies were rated as “probably robust", 27 as “limited,” and five “very limited.”

Heterogeneity: - heterogeneity not assessed

Publication Bias: not assessed

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

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

Kato, Ken et al. Nivolumab versus chemotherapy in patients with advanced oesophageal squamous cell carcinoma refractory or intolerant to previous chemotherapy (ATTRACTION-3): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol. 20. 1506-1517. 2019

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 Study type: mulitcentre, randomised, open-label, phase 3 trial (ATTRACTION-3; Europe, Asia, USA) Number of Patient: 419 patients randomly assigned treatment: 210 to nivolumab and 209 to chemotherapy. Recruitung Phase: Between Jan 7, 2016 and May 25, 2017 Inclusion Criteria: - patients were age 20 years or older with unresectable oesophageal cancer, whose major current or previously resected lesion was in the cervical or thoracic oesophagus (including the oesophagogastric junction) and was pathologically confirmed as squamous or adenosquamous cell carcinoma. - Patients who were refractory or intolerant to fluoropyrimidine-based and platinum-based chemotherapy who had previously received one treatment regimen, were not indicated for a radical resection, and had a life expectancy of at	Intervention: Nivolumab was administered intravenously over 30 min at a dose of 240 mg every 2 weeks (each cycle was 6 weeks) Comparison: Paclitaxel and docetaxel were administered intravenously for at least 60 min; paclitaxel at 100 mg/m² once per week for 6 weeks followed by 1 week off (each cycle was 7 weeks) and docetaxel at 75 mg/m² every 3 weeks (each cycle was 3 weeks)	Primary: overall survival, defined as the time from randomisation until death from any cause. Secondary: - proportion of patients with an investigator-assessed objective response (the percentage of patients whose best overall response was either a complete response or partial response); - best overall response; - progression-free survival (defined as the time from randomisation to the first documented tumour progression or death); - the proportion of patients with disease control (the percentage of patients whose best overall response was assessed as a complete response, partial response, or stable disease); - maximum percentage change from baseline in the sum of the diameters of target lesions; - time to response (the time from randomisation to the first confirmed complete or partial response); - duration of response (the time from the first response date to the date of the first

least 3 months
- at least one measurable or non-measurable lesion per Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1; an Eastern Cooperative Oncology Group ECOG) performance status score of 0 or 1;
- adequate organ function;
- and an ability to provide a fresh or archival tumour sample for the determination of PD-L1 status.
- Baseline laboratory tests required to assess eligibility included white blood cell, neutrophil, and platelet counts; haemoglobin; alanine aminotransferase; aspartate aminotransferase; total bilirubin; and serum creatinine or creatinine clearance

Exclusion Criteria: - Patients with substantial malnutrition, tumour invasion on organs located adjacent to the oesophagus, interstitial lung disease, pulmonary fibrosis, concurrent autoimmune disease, symptomatic brain or meninx metastases, or grade 2 peripheral neuropathy, and patients refractory to taxane therapy were excluded.
- Additionally, patients who previously received nivolumab or other therapeutic antibodies or

documented tumour progression or death)
- health-related quality of life (EuroQol 5D questionnaire (EQ-5D-3L))

Results: <u>overall survival</u>
- median follow-up for overall survival was 10.5 months (IQR 4.5–19.0) in the nivolumab group and 8.0 months (4.6–15.2) in the chemotherapy group.
- At a minimum follow-up time (ie, time from random assignment of the last patient to data cutoff) of 17.6 months, overall survival was significantly improved in the nivolumab group compared with the chemotherapy group (median 10.9 months, 95% CI 9.2–13.3 vs 8.4 months, 7.2–9.9; hazard ratio for death 0.77, 95% CI 0.62–0.96; p=0.019).
<u>secondary outcomes</u>
- 33 (19%, 95% CI 14–26) of 171 patients in the nivolumab group and 34 (22%, 15–29) of 158 patients in the chemotherapy group achieved an objective response
- The HR for progression-free survival with nivolumab versus chemotherapy was 1·08 (0·87–1·34).
- 187 (89%) of 210 patients in the nivolumab group and 176 (84%) of 209 patients in the

systemic anticancer therapies for regulation of T cells, or systemic corticosteroids or immunosuppressants, antineoplastic drugs, or radiotherapy within 28 days before randomisation were excluded.

chemotherapy group had disease progression or died by the time of data cutoff.
- The most common treatment-related adverse events were rash, diarrhoea, and decreased appetite in the nivolumab group; and alopecia, decreased neutrophil count, and decreased white blood cell count in the chemotherapy group
- Serious treatment-related adverse events were reported in 33 (16%) of 209 patients treated with nivolumab (grade 3–4, 20 patients [10%], no grade 5 events), and in 47 (23%) of 208 patients treated with chemotherapy (grade 3–4, 39 patients [19%], two grade 5 events).
- overall significant on-treatment improvement in quality of life for patients given nivolumab compared with those given chemotherapy (calculated for on-treatment data through week 42), in both EQ-5D-3L VAS (least squares [LS] mean 6.9, 95% CI 3.0–10.9; p=0.00069) and utility index (0.076, 0.011–0.142; p=0.02). The mean difference between groups favoured nivolumab at all time points and was clinically meaningful for the VAS at weeks 18 through 30 and for the utility index at weeks 24 through 42.

Author's Conclusion: In summary, nivolumab was associated with a significant improvement in overall survival versus chemotherapy and a favourable safety profile in previously treated patients with advanced oesophageal squamous cell carcinoma. Survival benefit occurred regardless of tumour PD-L1 expression. There were significant, and at times clinically meaningful, improvements in health-related quality of life with nivolumab versus chemotherapy. Nivolumab might represent a new standard second-line treatment option for patients with advanced oesophageal squamous cell carcinoma. A phase 3 study assessing nivolumab-based regimens versus chemotherapy in first-line treatment of patients with oesophageal squamous cell carcinoma is underway (NCT03143153).

Methodical Notes

Funding Sources: This study was supported by ONO Pharmaceutical Company (Osaka, Japan) and Bristol-Myers Squibb (BMS; Princeton, NJ, USA).
The funders of the study had a role in study design, data collection, data analysis, data interpretation, and writing of the clinical study report. All authors had full access to all the data in the study, participated in writing or reviewing the manuscript, and provided final approval for the decision to submit the manuscript for publication.

COI: - KK reports serving as a consultant for ONO Pharmaceutical Company, Oncolys BioPharma, Merck Sharpe & Dohme (MSD) Oncology, and BeiGene; and receiving research funding from ONO Pharmaceutical Company, BeiGene, MSD Oncology, and Shionogi.
- B-CC reports receiving honoraria from ONO Pharmaceutical Company; stock ownership of TheraCanVac; holding patents for Champions Oncology; serving as a consultant for ONO Pharmaceutical Company, Bristol-Myers Squibb (BMS), AstraZeneca, Novartis, Janssen, Yuhan, MSD, Boehringer-Ingelheim, Roche, Pfizer, Eli Lilly, and Takeda; receiving research funding from Novartis, Bayer, AstraZeneca, Mogam Institute, Dong-A ST, Champions Oncology, Janssen, Yuhan, ONO Pharmaceutical Company, Dizal Pharma, and MSD; and receiving honoraria from AstraZeneca, Novartis, Bayer, Mogam Institute, Champions Oncology, Janssen, Yuhan, Dizal Pharma, and MSD.
- MT reports receiving research funding from ONO Pharmaceutical Company; and serving as a speaker for ONO Pharmaceutical Company, BMS, Daiichi Sankyo, and Taiho Pharmaceutical.
- MO reports serving as a speaker for Taiho Pharmaceutical, Chugai Pharma, Covidien, Johnson & Johnson, and Lilly; and receiving research funding from Taiho Pharmaceutical, Nippon Kayaku, Chugai Pharma, Covidien, Johnson & Johnson, Daiichi Sankyo, Yakult Honsha, Lilly Japan, Nihon Medi-Physics, Pfizer, Mochida Pharmaceutical, and Shionogi.
- SK reports receiving research funding from ONO Pharmaceutical Company, Lilly Japan, Taiho Pharmaceutical, and Boehringer Ingelheim, and BMS; and receiving personal fees from Chugai Pharma, Merck Serono, Bayer, Eisai, and Yakult Honsha.
- M-JA reports receiving honoraria from AstraZeneca, Lilly, MSD, and Takeda; serving as a consultant for Alpha Pharmaceuticals; and serving as an advisor with AstraZeneca, Roche, Lilly, MSD, and Takeda.
- YH reports receiving grants from ONO Pharmaceutical Company and BMS.
- YD reports receiving personal fees from ONO Pharmaceutical Company, Taiho Pharmaceutical, Chugai Pharmaceutical, Eli Lilly, MSD, Daiichi Sankyo, Yakult Honsha, Takeda Pharmaceutical, Kaken Pharmaceutical, Abbott Japan, Eisai, Shionogi, Otsuka Pharmaceutical, Ajinomoto Pharmaceutical, Teijin Pharma, Sanofi, Astellas Pharma, Tsumura, AstraZeneca, Asahi Kasei Pharma, Medtronic, Johnson & Johnson, Olympus, and Intuitive Surgical; receiving grants from Taiho Pharmaceutical, Chugai Pharmaceutical, Eli Lilly, MSD, Daiichi Sankyo, Yakult Honsha, Takeda Pharmaceutical, Kaken Pharmaceutical, Abbott Japan, Eisai, Shionogi, Otsuka Pharmaceutical, Ajinomoto Pharmaceutical, Astellas Pharma, Tsumura, AstraZeneca, Johnson & Johnson, Nippon Kayaku, Novartis Pharma, Pfizer Japan, CSL Behring, and Nestle; and receiving conference fees from the Japanese Gastric Cancer Association, the Japan Esophageal Society, and the Japan Surgical Society.
- C-CY reports receiving research funding from ONO Pharmaceutical Company, Eisai, Effective Pharmaceuticals, and Deciphera Pharmaceuticals; receiving honoraria from Lilly, MSD, Amgen, and Eisai; and holding consulting roles with Lilly and MSD.
- S-BK reports receiving researching funding from Novartis, Genzyme, and Dongkook Pharma. C-HH reports receiving honoraria from ONO

Pharmaceutical Company, MSD, and BMS; serving as a consultant for ONO Pharmaceutical Company; receiving research funding from ONO Pharmaceutical Company; serving in a consulting role for Novartis, Lilly, and MSD; and receiving research funding from MSD, AstraZeneca, and Genentech.
- IX reports employment with BMS and ownership of stock in BMS.
- MK reports employment with ONO Pharmaceutical Company and ownership of stock in ONO Pharmaceutical Company.
- YKi reports receiving honoraria from ONO Pharmaceutical Company, Ethicon, Olympus, Taiho Pharmaceutical, Chugai Pharma, Nippon Kayaku, and Asahi Kasei; and receiving research funding from Astellas Pharma, Otsuka, Kyowa Hakko Kirin, Kowa, CSL Behring, Kaken Pharmaceutical, Shionogi, Daiichi Sankyo, Taiho Pharmaceutical, Takeda, Chugai Pharma, Tsumura, Teijin Pharma, Medtronic, Boehringer Ingelheim, Merck Serono, Novartis, Asahi Kasei, Kureha, Sanofi, Sumitomo Dainippon Pharma, Taisho Toyama Pharma, Nippon Kayaku, Lilly, Pfizer, Yakult Honsha, GlaxoSmithKline, Medicon, EA Pharma, Otsuka, ONO Pharmaceutical Company, KCI Licensing, Nihon Pharmaceutical, Mitsubishi Tanabe Pharma Corporation, Eisai, Bayer Yakuhin, Abbot Japan, and Fujifilm Toyama Chemical.
- All other authors declare no competing interests.

Randomization: We randomly assigned patients (1:1) to either nivolumab or investigator's choice of chemotherapy (paclitaxel or docetaxel). Randomisation was done using an interactive web response system with a block size of four and stratified according to geographical region (Japan vs the rest of the world), number of organs with metastases (≤1 vs ≥2), and expression of PD-L1 (<1% vs ≥1%). Investigators registered patients at each site via the web registration system. An authorised vendor used their original internal system to generate the sequentially numbered containers to ensure random allocation, and to assign patients to study treatments. The web registration system ensured that the container sequence was concealed until the treatment allocation was completed. Patients and investigators were not masked to treatment allocation.

Blinding: Patients and investigators were not masked to treatment allocation.

Dropout Rate/ITT-Analysis: - Overall survival and progression-free survival were assessed in the intention-to-treat (ITT) population, which included all randomly assigned patients.
- Objective response, disease control, maximum percentage change from baseline in the sum of the diameters of target lesions, time to response, and duration of response were assessed in all randomly assigned patients who had target lesion measurements at baseline (ie, the

response-evaluable population).
- Safety was assessed in all patients who received at least one dose of the assigned treatment.
- Both descriptive and MMRM analyses of patient-reported outcomes were done for all randomly assigned patients who had an EQ-5D-3L VAS and utility index assessment at baseline and at least one post-baseline assessment including unscheduled or follow-up visits (ie, the patient-reported outcomes population).
- Time to deterioration of health-related quality of life was assessed in the ITT population.

Notes:
Article submitted by hand search.
Evidence level 2: randomised controlled trial

Penniment, M. G. et al. Palliative chemoradiotherapy versus radiotherapy alone for dysphagia in advanced oesophageal cancer: a multicentre randomised controlled trial (TROG 03.01). Lancet Gastroenterol Hepatol. 3. 114-124. 2018

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 Study type: randomised controlled trial Number of Patient: 111 patients were randomly assigned to chemoradiotherapy and 109 patients to radiotherapy. Recruitung Phase: Between July 7, 2003 and March 21, 2012 Inclusion Criteria: Eligible	Intervention: chemoradiotherapy - radiotherapy dose was 35 Gy in 15 fractions over 3 weeks for study participants enrolled in Australia and New Zealand and 30 Gy in ten fractions over 2 weeks for participants enrolled in Canada and the UK. - Chemotherapy consisted of intravenous cisplatin (either 80 mg/m² on day 1 or 20 mg/m² per day on days 1–4 at the clinician's discretion) with intravenous fluorouracil 800 mg/m² per day on days 1–4 of radiotherapy (continuous infusion). Patients received dexamethasone and a 5-HT3 receptor antagonist before cisplatin and were prehydrated as per institutional protocols. Comparison: radiotherapy alone	Primary: dysphagia relief, defined as improvement of at least one point on the Mellow scale at 9 weeks (±2 weeks) that was maintained at the next review 4 weeks later (ie,at 13 weeks ±2 weeks) Secondary: - dysphagia progression-free survival, defined as a worsening of at least one point on the Mellow scale (from baseline or best response) or malignant stricture requiring intervention. - time to achieve any response in dysphagia (an improvement of at least one point on the Mellow scale after treatment, even if not

patients
- had biopsy-proven oesophageal cancer (excluding Seifert 2 and 3 lesions)
- were deemed unsuitable for, or unable to have, curative treatment after discussion with the local multidisciplinary oncology team.
- had symptomatic dysphagia (grade 1–4 on the Mellow scale),
- had Eastern Cooperative Oncology Group performance status 0–2,
- had adequate haematological and renal function (neutrophil count >1.5×10^9 cells per L, platelet count >100×10^9 cells per L, and calculated creatinine clearance ≥50 mL/min)
- provided written informed consent.

Exclusion Criteria: - prior chemotherapy or chest radiotherapy for oesophageal cancer,

- radiotherapy dose was 35 Gy in 15 fractions over 3 weeks for study participants enrolled in Australia and New Zealand and 30 Gy in ten fractions over 2 weeks for participants enrolled in Canada and the UK.

sustained 4 weeks later)
- time to any complete response (Mellow score 0)
- patient's assessment of dysphagia response
- number of patients receiving secondary treatment (radiotherapy, chemotherapy, or stenting)
- and overall survival

Results: <u>dysphagia relief</u>
50 (45%, 95% CI 36–55) patients in the chemo-radiotherapy group and 38 (35%, 26–44) patients in the radiotherapy group achieved dysphagia relief
- The odds ratio for dysphagia relief in the chemoradiotherapy group compared to the radiotherapy group was estimated to be 1.56 (95% CI 0.87–2.78; p=0.14).
- When adjusted for stratification variables (M stage and pretreatment dysphagia), the odds ratio for dysphagia relief for chemoradiotherapy versus radiotherapy was estimated to be 1.64 (0.91–2.97; p=0.10).
-Complete dysphagia relief was noted in 32 (29%) patients in the chemoradiotherapy group and in 26 (24%) patients in the radiotherapy group (p=0.44)

- other active malignancies,
- tracheo-oesophageal fistula or stent in situ,
- pregnancy, lactation or inadequate contraception,
- age younger than 18 years

- The median time from start of radiotherapy to any relief was 9.1 weeks (IQR 8.6–9.7) in the chemoradiotherapy group and 9.0 weeks (8.3–9.6) for radiotherapy (p=0·46). The median duration of any relief was 3.4 months (IQR 1.3–5.7)for chemoradiotherapy and 2.5 months(1.4–5.3) for radiotherapy (p=0.72)
- The median time from start of radiotherapy to complete relief at any assessment was 9.3 weeks (IQR 9.0–12.0) for chemoradiotherapy and 9.2 weeks (8.9–10.1) for radiotherapy (p=0.37)

<u>dysphagia progression-free survival</u>

- Estimated median dysphagia progression-free survival time from randomisation was 4.1 months (95% CI 3.5–4.8) for chemoradiotherapy and 3.4 months (3.1–4.3) for radiotherapy
- The hazard ratio (HR) for chemoradiotherapy versus radiotherapy was estimated to be 0.93 (95% CI 0.71–1.21; p=0.58)

overall survival

- Estimated median overall survival from randomisation was 6.9 months (5.1-8.3) for chemoradiotherapy and 6.7 months (4.9-8.0) for radiotherapy, HR=0.98 (95% CI 0.75–1.29; p=0.88)

<u>Secondary treatments</u>

- were given after failure of trial treatment in 117

patients (55 [51%] of 107 patients in the chemoradiotherapy group and 62 [60%] of 104 patients in the radiotherapy group).
- Oesophageal stenting was used in 23 (21%) patients in the chemoradiotherapy group and 32 (31%) patients in the radiotherapy group, whereas additional palliative chemotherapy was administered to 24 (22%) patients in the chemoradiotherapy group and 33 (32%) patients in the radiotherapy group.
adverse events
- of the 211 patients who commenced radiotherapy, grade 3–4 acute toxicity occurred in 38 (36%) patients in the chemoradiotherapy group and in 17 (16%) patients in the radiotherapy group (p=0.0017). Anaemia, thrombocytopenia, neutropenia, oesophagitis, diarrhoea, nausea and vomiting, and mucositis were significantly worse in patients who had chemoradiotherapy than in patients who had radiotherapy
self-assessment
- 76 patients (39 in the chemoradiotherapy group and 37 in the radiotherapy group) answered a self-assessed dysphagia relief question at 9 weeks (7.1–11.1 weeks)
- Five patients felt their swallowing was worse

(clinical response: no change [three], worse [two]).
- Seven patients reported that their swallowing was about the same as before treatment (clinical response: complete dysphagia relief [two], partial dysphagia relief [five]),
- 64 patients reported that their swallowing was better (clinical response: complete dysphagia relief [37], partial dysphagia relief [21], no change [five], worse [one]).
- The self-assessments were similar between the two treatment arms: 34 patients receiving chemoradiotherapy and 30 patients receiving radiotherapy felt better; three patients receiving chemo-radiotherapy and four patients receiving radiotherapy felt about the same; and two patients receiving chemoradiotherapy and three patients receiving radiotherapy felt worse (p=0.69, trend test)

Author's Conclusion: Palliative chemoradiotherapy showed a modest, but not statistically significant, increase in dysphagia relief compared with radiotherapy alone, with minimal improvement in dysphagia progression-free survival and overall survival with chemoradiotherapy but at a cost of increased

toxicity. A short course of radiotherapy alone should be considered a safe and well tolerated treatment for malignant dysphagia in the palliative setting.

Methodical Notes

Funding Sources: This study was funded by the National Health and Medical Research Council of Australia (291103), Canadian Cancer Society Research Institute, Canadian Cancer Trials Group, Trans Tasman Radiation Oncology Group, and Cancer Australia.
The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

COI: - MGP and SS declare grant funding from NHMRC and Cancer Australia.
- JGS received payments for statistical analysis from the primary trial centre.
- All other authors declare no competing interests

Randomization: Patients were randomly assigned to chemoradiotherapy or radiotherapy alone by telephone or fax to the trial centre at the Royal Adelaide Hospital in Adelaide, SA, Australia. Clinicians, patients, and data managers had no prior knowledge of the treatment arm to which the patients would be assigned. Eligibility was checked and patients were stratified by hospital, dysphagia score (Mellow score 1–4), and presence of metastases before random allocation (1:1) using a computer-generated adaptive biased coin design.

Blinding: no blinding

Dropout Rate/ITT-Analysis: Patients' data were analysed according to their randomised treatment arm (intention-to-treat), except for the exclusion of one patient who was found not to have oesophageal cancer after randomisation. Patients who did not commence any protocol treatment were excluded from the toxicity analyses.

Notes:
evidence level 2: randomised controlled trial

Shah, Manish A et al. Efficacy and Safety of Pembrolizumab for Heavily Pretreated Patients With Advanced, Metastatic Adenocarcinoma or Squamous Cell Carcinoma of the Esophagus: The Phase 2 KEYNOTE-180 Study. JAMA Oncol. 5. 546-550. 2019

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 1 Study type: phase 2, open-label, interventional, single-arm study Number of Patient: 121 Recruitung Phase: 01/2016, 03/2017 Inclusion Criteria: patients with advanced, metastatic esophageal squamous cell carcinoma (ESCC) advanced, metastatic adenocarcinoma of the esophagus and gastroesophageal junction that progressed after 2 or more lines of systemic therapy. Exclusion Criteria: -	Intervention: Pembrolizumab Comparison: no comparison, single arm study.	Primary: Objective response rate (ORR) Secondary: Duration of response (DOR), progression-free survival (PFS), and overall survival (OS). Results: **Patient characteristics:**121 patients (100M, 21W; median age, 65 years [range 33-87 years]), 18 (14.9%) had undergone 3 or more prior therapies, 63 (52.1%) had ESCC, and 58 (47.9%) had tumors positive for programmed death ligand-1 (PD-L1), defined as a combined positive score of 10 or higher assessed by immunohistochemistry. Median duration of follow-up was 5.8 months (range, 0.2-18.3 months). **Results: Primary:** Objective response rate was 9.9% (95%CI, 5.2%- 16.7%) among all patients (12 of 121) with 12 patients having a partial response; 7 of the 12 responses were ongoing at analysis. **Secondary:** Overall survival: The median OS was 5.8 months (95% CI, 4.5-7.2 months), with a 6-month OS rate of 49% (95% CI, 40%-57%) and a 12-month OS rate of 28% (95% CI, 20%-37%). Median duration of response was not reached (range, 1.9-14.4 months). Objective response rate was 14.3%(95%CI, 6.7%-25.4%) among patients with ESCC (9 of 63), 5.2%(95%CI, 1.1%-14.4%)vamong patients with adenocarcinoma (3 of 58),

13.8%(95%CI, 6.1%-25.4%) among patientsvwith PD-L1–positive tumors (8 of 58), and 6.3%(95%CI, 1.8%-15.5%) among patients with PD-L1–negative tumors (4 of 63). Adverse events: Overall, 15 patients (12.4%) had treatment-related grade 3 to 5 adverse events. Only 5 patients (4.1%) discontinued treatment because of adverse events. There was 1 treatment-related death from pneumonitis.

Author's Conclusion: Where effective treatment options are an unmet need, pembrolizumab provided durable antitumor activity with manageable safety in patients with heavily pretreated esophageal cancer. Phase 3 studies evaluating pembrolizumab vs standard therapy for patients with esophageal cancer progressing after first-line therapy or in combination with chemotherapy as first-line therapy for patients with locally advanced unresectable or metastatic esophageal cancer are ongoing.

Methodical Notes

Funding Sources: This study and assistance with medical writing were funded by Merck & Co Inc.

COI: Extensive list: see article.

Randomization: non-randomized

Blinding: open label study

Dropout Rate/ITT-Analysis: 5 patients (4.1%) discontinued treatment because of adverse events. There was 1 treatment-related death from

pneumonitis.

Notes:
Article submitted by handsearch.
Evidence level 3: Non-randomized controlled cohort/follow-up study.

Shitara, Kohei et al. Pembrolizumab versus paclitaxel for previously treated, advanced gastric or gastro-oesophageal junction cancer (KEYNOTE-061): a randomised, open-label, controlled, phase 3 trial. Lancet. 392. 123-133. 2018

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 Study type: multicentre, randomised, open-label, phase 3 study (worldwide) Number of Patient: 592 patients were randomly assigned to pembrolizumab (n=296) or paclitaxel (n=296) Recruitung Phase: between June 4, 2015, and July 26, 2016. Inclusion Criteria: - patients were aged 18 years or older, - had histologically or cytologically confirmed adenocarcinoma of the stomach or gastro-oesophageal junction that was metastatic or locally advanced but unresectable, - had progression as per Response Evaluation	Intervention: pembrolizumab 200 mg every 3 weeks for up to 2 years Comparison: standard-dose paclitaxel.	Primary: overall survival and progression-free survival Secondary: response rate, duration of response, time to progression, safety Results: <u>overall survival</u> Pembrolizumab did not significantly prolong overall survival (HR 0.82, 95% CI 0.66–1.03; onesided p=0.0421). Median overall survival was 9.1 months (95% CI 6.2–10.7) for pembrolizumab and 8.3 months (95% CI 7.6–9.0) for paclitaxel. The estimated proportion of patients surviving at 12 months was 40% (95% CI 33–47) with pembrolizumab and 27% (21–33) with paclitaxel; proportions at 18 months were 26% (95% CI 20–32) and 15% (10–20), respectively. In a posthoc analysis of the treatment difference in overall survival using the weighted logrank test, the onesided pvalue was 0.0009. <u>progression-free survival</u> - HR for progression free survival for pembrolizumab

Criteria in Solid Tumors version 1.1 (RECIST v1.1) after firstline therapy with a platinum and fluoropyrimidine, as well as with trastuzumab in patients with HER2-positive tumours,
- had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1,
- had provided a tumour sample for PDL1 assessment. Initially, patients were enrolled irrespective of PDL1 expression status. After 489 patients were enrolled, the independent data monitoring committee recommended that enrolment be restricted to patients with a PDL1 CPS of 1 or higher on the basis of outcomes in patients with a CPS less than 1.

Exclusion Criteria: squamous cell or undifferentiated histology, previous therapy with any PD1, PDL1, or PDL2 inhibitor, and active autoimmune disease that necessitated systemic treatment.

versus paclitaxel was 1.27 (95% CI 1.03–1.57).
- Median progression free survival was 1.5 months (95% CI 1.4–2.0) for pembrolizumab and 4.1 months (3.1–4.2) for paclitaxel.
- The estimated proportion of patients alive and without disease progression at 12 months was 14% (95% CI 9–19) and 9% (5–14), respectively.

<u>secondary outcomes</u>
- pembrolizumab group: response rate 16% (95% CI 11–22) (paclitaxel group: response rate 14% (95% CI 9–19)
- pembrolizumab did not prolong time to progression compared with paclitaxel

<u>safety</u>
- adverse events were of grade 3–5 severity in 42 (14%) of 294 patients in the pembrolizumab group and 96 (35%) of 276 patients in the paclitaxel group
- most common grade 3–5 adverse events attributed to study treatment were anaemia (seven [2%] of 294 patients) and fatigue (seven [2%]) in the pembrolizumab group and decreased neutrophil count (28 [10%] of 276 patients) and neutropenia (20 [7%]) in the paclitaxel group.

Author's Conclusion: Pembrolizumab did not significantly improve overall survival compared with paclitaxel as second-line therapy for advanced gastric or gastro-oesophageal junction cancer with PD-L1 CPS of 1 or

higher. Pembrolizumab had a better safety profile than paclitaxel. Additional trials of pembrolizumab in gastric and gastro-oesophageal cancer are ongoing.

Methodical Notes

Funding Sources: Merck Sharp & Dohme
- The funder participated in study design, data analysis and interpretation, and manuscript writing. The funder maintained the study database. All authors had full access to the data and had final responsibility for the decision to submit for publication.

COI: - KS reports personal fees outside the submitted work for serving in a consulting or advisory role from Astellas Pharma, Lilly, BristolMyers Squibb, Takeda, Pfizer, and Ono Pharmaceutical; personal fees as honoraria outside the submitted work from Novartis, AbbVie, and Yakult; and grants outside the submitted work from Lilly, Ono Pharmaceutical, Dainippon Sumoitomo Pharma, Daiichi Sankyo, Taiho Pharmaceutical, Chugai Pharma, and MSD.
- YJB reports grants to the institution for clinical trials outside the submitted work from AstraZeneca, Novartis, Genentech/Roche, MSD, Merck Serono, Bayer, GlaxoSmithKline, BristolMyers Squibb, Pfizer, Eli Lilly, Boehringer Ingelheim, MacroGenics, Boston Biomedical, FivePrime, CKD, Ono, Otsuka, Taiho, Takeda, BeiGene, Hanmi, Green Cross, Curis, Daiichi Sankyo, and Astellas and other for serving in a consulting or advisory outside the submitted work from AstraZeneca, Novartis, Genentech/Roche, MSD, Pfizer, Bayer, BristolMyers Squibb, Eli Lilly, Merck Serono, FivePrime, Taiho, Ono, ADC Therapeutics, Green Cross, and Samyang Biopharm.
- MM reports personal fees for advisory boards, lectures, and speakers' bureau outside the submitted work from MSD.
- MHR reports other outside the submitted work for serving in a consultant/advisory role and receiving honorarium from Dae Hwa Pharmaceutical, Eli Lilly, BristolMyers Squibb, ONO Pharmaceutical, and Taiho.
- TO reports personal fees during the conduct of the study for serving as an investigator from Merck & Co.
- CC reports personal fees outside the submitted work for serving as a speaker from MSD, BristolMyers Squibb, Bayer, Boehringer Ingelheim, and Tecnofarma; personal fees outside the submitted work for serving as a principal investigator from MSD, BristolMyers Squibb, Bayer, BoehringerIngelheim, Roche, AstraZeneca, Astellas, and Novartis; personal fees outside the submitted work for serving as a consultant or advisory board member from MSD, BristolMyers Squibb, Bayer, BoehringerIngelheim, Tecnofarma, AstraZeneca, and Lilly; and personal fees outside the submitted work for participating in a sponsored educational program from MSD, BristolMyers Squibb, Boehringer Ingelheim, and Tecnofarma.

- HCC reports grants outside the submitted work from Lilly, GlaxoSmithKline, MSD, MerckSerono, BristolMyers Squibb/Ono, and Taiho; personal fees outside the submitted word for servingon a speakers' bureau from MerckSerono, Lilly, and Foundation Medicine; and personal fees outside the submitted work for serving as a consultant from Taiho, Celltrion, MSD, Lilly, Quintiles, BristolMyers Squibb, and MerckSerono.
- KM reports grants outside the submitted work from Ono Pharmaceutical, MSD, Daiichi Sankyo, Kyowa Hakko Kirin, Shionogi Pharmaceutical, and Gilead Sciences and personal fees outside the submitted work from Chugai Pharmaceutical, Taiho Pharmaceutical, Takeda Pharmaceutical, Merck Serono, Eli Lilly, and Takult Honsha.
- E Goekkurt reports personal fees during the conduct of the study for serving as an investigator from MSD; personal fees outside the submitted work for giving lectures from MSD, Lilly, and Servier; and personal fees outside the submitted work for serving in an advisory role from MSD, BristolMyers Squibb, Lilly, Sanofi, Servier, and Merck.
- RSM reports grants outside the submitted work from Pfizer, Amgen, and Celgene; personal fees outside the submitted work from Clovis, Pfizer, and BristolMyers Squibb; and research funding outside the submitted work from BristolMyers Squibb, Merck,Bayer, and Janssen.
- XC reports personal fees during the conduct of the study for serving as a fulltime employee of Merck Sharp & Dohme,a subsidiary of Merck & Co, Kenilworth, NJ, USA.
- SPK reports personal fees during the conduct of the study for serving as a fulltime employee of Merck Sharp & Dohme, a subsidiary of Merck & Co.
- CM reports personal fees during the conduct of the study for serving as a fulltime employee of Merck Sharp & Dohme, a subsidiary of Merck & Co, Kenilworth, NJ, USA.
- AO reports grants during the conduct of the study from BristolMyers Squibb and personal fees during the conduct of the study from Bristol-Myers Squibb, Ono Pharmaceutical Company, and Chugai.
- CSF reports personal fees outside the submitted work for serving as a consultant from Entrinsic Health, Genentech, Merck & Co, Sanofi, Five Prime Therapeutics, Merrimack, Bayer, Agios, Taiho, Kew, Eli Lilly, and Bain Capital and personal fees outside the submitted work for serving as a board member from CytomX.
- All other authors declare no competing interests.

Randomization: Patients were randomly allocated (1:1) using a central interactive voice response and integrated web response system to receive pembrolizumab 200mg intravenously every 3 weeks or paclitaxel 80mg/m² intravenously on days 1, 8, and 15 of 4 week cycles. The allocation schedule was generated by the system vendor using a computerised random list generator. Enrolment of the first 125 patients was

stratified by geographical region (Europe, Israel, North America, and Australia vs Asia vs rest of world) and ECOG performance status (0 vs 1). Following a protocol amendment, enrolment of the remaining 467 patients was stratified by geographical region (Europe, Israel, North America, and Australia vs Asia vs rest of the world), time to progression on firstline therapy (<6 months vs ≥6 months) and PDL1 CPS (<1 vs ≥1). Treatment was allocated in blocks of four in each stratum.

Blinding: - Patients, treating doctors, the external data monitoring committee and sponsor representatives were not masked to treatment assignment.
- The central radiological reviewers were masked to treatment assignment.

Dropout Rate/ITT-Analysis: - Overall survival, progression free survival, and response rate were analysed in the intention-to-treat population, defined as all patients who were randomly allocated to treatment, irrespective of whether they received the treatment.
- Duration of response was analysed in all patients who had a best response of complete or partial response.
- Safety was assessed in all patients who received at least one dose of study treatment.

Notes:
Article submitted by hand search.
Evidence level 2: randomised controlled study

20 Palliative Therapie - Definition

Inhalt: *6 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Didden, P. 2018	2	randomized controlled trial
Doosti-Irani, A. 2017	1	systematic review and network meta-analysis
Janmaat, V. T. 2017	1	Cochrane systematic review and meta-analysis of randomised controlled trial
Lai, A. 2018	1	systematic review and meta-analysis
Pandit, S. 2019	1	systematic review and meta-analysis
Penniment, M. G. 2018	2	randomised controlled trial

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

Doosti-Irani, A. et al. Complications of stent placement in patients with esophageal cancer: A systematic review and network meta-analysis. PLoS One. 12. e0184784. 2017

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: systematic review and network meta-analysis Databases: Web of Science, Medline, Scopus, Cochrane Library and Embase	Population: patients with esophageal cancer Intervention: palliative treatment interventions Comparison: none	Primary: treatment related death (TRD), bleeding, stent migration, aspiration, severe pain and fistula formation among patients with esophageal Secondary: none Results: <u>Treatment related death</u> - reported in 16 RCTs, which included 1075 patients	Amdal (2013) Radiotherapy and Oncology Conio (2007) American Journal of Gastroenterology Dallal (2001) Gastrointestinal

Search period: until July 2017

Inclusion Criteria: - RCTs that included patients with either histology of esophageal cancer i.e. squamous cell carcinoma and/or adenocarcinoma
- RCTs that had evaluated stent placement or palliative treatments of esophageal cancer

Exclusion Criteria: Cohort studies and non-randomized clinical trials

- The comparisons of treatments for TRD involved four independent sub-networks.
- According to the results of the test for heterogeneity, the I^2 statistic for network A was 15.2%, and for network B, C, and D was zero
- In network A, with the metallic stent as reference, the latex prosthesis increased the risk of TRD. The relative risk (RR) was 3.89 (95% CI: 0.42, 36.33). The RR for thermal ablative therapy compared with the metallic stent was 0.46 (95% CI: 0.04, 5.19).
- In network B, covered Evolution® compared with Ultraflex stent decreased the risk of TRD, RR = 0.70 (95% CI: 0.30, 1.66).
- In network C, SEMS 18 compared to brachytherapy increased the risk of TRD, RR = 5.61, (95% CI: 0.69, 45.80).
- In network D, both the open stent (RR = 3.00, 95% CI: 0.13, 70.23) and 'Ultraflex plus omeprazole' (RR = 2.55, 95% CI: 0.11, 59.49) compared to antireflux stent increased the risk of TRD

<u>bleeding</u>

- reported in 18 RCTs, which included 1374 patients
- Based on the results of the test for heterogeneity, the I^2 statistic for network A, B, C, and D was zero
- In network A, the latex prosthesis and plastic stent increased the risk of bleeding when compared to the metallic stent. The RR for latex prosthesis was 1.62 (95% CI: 0.42, 6.31) and was 2.85 (95% CI: 0.12, 65.93) for the

Endoscopy
De Palma (1996) Gastrointest Endosc
Guo (2008) Radiology
Homs (2004) Lancet (London, England).
Homs (2004) Gastrointestinal Endoscopy
Javed (2012) Journal of Gastrointestinal Cancer
Knyrim (1993) New England Journal of Medicine
O'Donnell (2002) British Journal of Surgery
Power (2007) Diseases of the Esophagus
Sabharwal (2008) Journal of Gastroenterology & Hepatology
Sabharwal (2003) Gut
Shenfine (2009) American Journal of Gastroenterology

plastic stent. On the other hand, thermal ablative therapy (RR = 0.13, 95% CI: 0.01, 2.43) and uncovered stent (RR = 0.27, 95% CI: 0.06, 1.16) decreased the risk of bleeding when compared to the metallic stent. - In network B, the irradiation stent (RR = 1.24, 95% CI: 0.54, 2.83) and CSENACS (RR = 1.24, 95% CI: 0.29, 5.32) increased the risk of bleeding when compared to the conventional stent. - In network C, the covered Evolution® stent decreased the risk of bleeding (RR = 0.07, 95% CI: 0.00, 1.13) when compared to Ultraflex. - In network D, SEMS (RR = 3.00, 95% CI: 0.13, 70.78) and SEMS+BT (RR = 2.86, 95% CI: 0.12, 66.28)increased the risk of bleeding when compared to brachytherapy <u>Stent migration</u> - reported in 19 RCTs involving 1207 patients - In the network A, and B the I^2 statistic was zero, and in the network C the I^2 was 16.1% - In network A, when compared to the Ultraflex stent, the polyflex stent increased the risk of stent migration 2.07 times (95% CI: 1.01, 4.67). The risk of stent migration for covered Evolution® stent, Flamingo stent, and Ultraflex stent plus radiotherapy was lower than the ultraflex stent; however, the 95% CIs involved the null values. - In network B, the risk ratio for the latex prosthesis and plastic stents compared to the metallic stent was 6.82 (95% CI: 0.36, 127.54) and 2.87 (95% CI: 0.87, 10.64),	Vakil (2001) American Journal of Gastroenterology van Heel (2012) Gastrointestinal Endoscopy Wenger (2006) Surgical endoscopy Wenger (2005) European journal of gastroenterology & hepatology White (2015) Journal of Clinical Gastroenterology Zhu (2014) The Lancet Laasch (2002) Radiology Siersema (1998) Gastrointestinal endoscopy Siersema (2001) Gastrointestinal endoscopy Verschuur (2008) The American journal of gastroenterology

respectively.
- In network C, there were no considerable differences between the conventional, Irradiation, open and ultraflex stents plus omeprazole and the Antireflux stent

Aspiration
- reported in 9 RCTs involving 805 esophageal cancer patients, 3 were excluded from network analysis
- The I2 statistic for all networks of this complication was zero
- In terms of ranking, the Polyflex stent (p-score = 0.69), Irradiation stent (p-score = 0.74) and BT (p-score = 0.69) were the better treatments in networks A, B and C

Severe pain
- Severe pain was reported in 14 RCTs
- According to the results of test for heterogeneity, The I^2 statistic for network A, B, C, and D was zero
- The CSENACS (p-score = 0.73), Polyflex stent (p-score = 0.79), Latex prosthesis (p-score = 0.96) and BT (p-score = 0.65) were better treatments in terms of lower risk of severe pain among patients in networks A, B, C and D, respectively.

fistula formation
- Fistula formation was reported in 10 RCTs.
- The I^2 statistic for all networks of this complication was zero
- The Plastic stent (p-score = 0.81), Conventional stent (p-score = 0.72), and SEMS 18 (p-score = 0.62) were better

treatments in terms of lower risk of fistula formation in networks A, B, and C, respectively

Author's Conclusion: Overall, the results of this network meta-analysis showed that thermal ablative therapy, covered Evolution® stents, brachytherapy and antireflux stents are associated with a lower risk of TRD. In terms of lower risk of bleeding, thermal ablative therapy, conventional stent, covered Evolution® stent and brachytherapy were better palliative treatments for patients with esophageal cancer. Based on the lower risk of stent migration, the covered Evolution®, uncovered, and Irradiation stents were better treatments. In terms of lower risk of severe pain as another major complication the CSENACS, polyflex stent, latex prosthesis and brachytherapy were better treatments.

Methodical Notes

Funding Sources: This study supported by Tehran University of Medical Sciences (TUMS). We would like to thank Vic-Chancellor of Research and Technology of TUMS for financial support of this study. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

COI: no statement

Study Quality: - The risk of bias was assessed using Cochrane's tools
- 6 studies were rated as low quality, 11 as intermediate quality and 7 studies as high quality

Heterogeneity: - The statistical heterogeneity was assessed using the Chi^2 test and the heterogeneity across each comparison was quantified

using I^2 statistics
- The results showed no significant heterogeneity in the networks in either of the complications
- see results section for individual I^2 values

Publication Bias: - The publication bias for each complication was assessed visually by the adjusted network funnel plot using Stata 13 (Stata Corp, College Station, TX, USA)
- Based on the adjusted funnel plot there was no evidence of publication bias for the set of studies related to each complication

Notes:
evidence level 1: systematic review

Janmaat, V. T. et al. Palliative chemotherapy and targeted therapies for esophageal and gastroesophageal junction cancer. Cochrane Database Syst Rev. 11. Cd004063. 2017

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: Cochrane systematic review and meta-analysis of randomised controlled trial Databases: 1. Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 9) in the Cochrane Library (searched 19 September 2017) 2. MEDLINE (1950 to 19 September 2017) 3. Embase (1980 to 19	Population: People with advanced (T3-T4NxM0 non-resectable; and all TxNxM1), recurrent, or metastatic carcinoma of the esophagus and GE-junction. Intervention: - Chemotherapy or targeted therapy agent(s) plus any control intervention - Chemotherapy encompassed all cytotoxic and anti-neoplastic drug treatment, and targeted therapy encompasses all anti-neoplastic drug	Primary: overall survival Secondary: progression-free survival Toxicity Quality of life Results: The quantitative synthesis includes 41 studies, Eleven studies in 1347 participants contributed data to the meta-analysis of the main comparison **main analysis: chemotherapy or targeted therapy agent(s) plus control intervention versus control intervention alone in people with esophageal and GE-junction cancer**	studies included in meta-analysis: Bang 2010; Lancet Bleiberg 1997; European Journal of Cancer Dutton 2014; Lancet Oncology Ford 2014;

September 2017) 4. Web of Science (1900 to 19 September 2017) 5. Pubmed Publisher (1950 to 19 September 2017) 6. Google Scholar (1592 to 19 September 2017) 7. Clinicaltrials.gov (searched 19 September 2017) 8. WHO International Clinical Trials Registry Platform (ICTRP) (searched 19 September 2017) Search period: from inception to 19 September 2017 Inclusion Criteria: - RCTs with or without blinding - studies involving participants with advanced or non-resectable disease who received chemotherapy with palliative intent - treatments with systemic intravenous and single oral chemotherapy or targeted therapy, as well as combination	treatment targeting a specific protein or small group of proteins. Comparison: - control intervention - We defined 'control arm' as best supportive care (BSC) or treatment with at least one chemotherapy agent whose composition, dose, and schedule were equal in both arms.	<u>Overall survival</u> - analysis contained eleven studies in 1347 participants - overall HR in favor of the arm with the additional agent was 0.75 (95%CI 0.68 to 0.84, high-quality evidence), showing an OS benefit - Median OS, weighted for study size, in the arm with the additional agent was 6.7 months versus 5.7 months in the control arm. - Cochrane's Q test for heterogeneity showed a non-significant amount of heterogeneity (I^2= 5%, P=0.40) <u>Progression-free survival</u> - analysis contained five studies in 883 participants - The addition of a targeted therapeutic agent probably leads to an HR of 0.64 (95% CI 0.45 to 0.92, moderate-quality evidence) - Cochrane's Q test for heterogeneity showed a significant amount of heterogeneity (I^2= 79%, P=0.0007) <u>Toxicity</u> - Overall, palliative chemotherapy and/or targeted therapy appears to increase the frequency of treatment-related toxicity of at least grade 3. - Treatment-related deaths were rare in most studies,and there is no clear evidence that treatment-related deaths occur more frequently in the study arms with an additional chemotherapy or targeted therapy agent	Lancet Oncology Fuchs 2014; Lancet Huang 2009; Chinese Journal of Integrative Medicine Levard 1998; European Journal of Surgery Lordick 2013; Lancet Oncology Lorenzen 2009; Annals of Oncology Nicolaou 1982; South African Medical Journal Wilke 2014; Lancet Oncology

regimens in all doses and schedules.

Exclusion Criteria: - all non-randomized and quasi-randomized studies
- studies including participants receiving chemotherapy for locally advanced cancer in order to assess resectability
- combined radiochemotherapy or radio-targeted therapy interventions

Quality of life
- Overall, the studies reporting quality of life did so in different ways, prohibiting a meta-analysis
- quality of life improved in the arms with the additional agent

subanalysis 1: chemotherapy or targeted therapy plus BSC versus BSC

overall survival
- Five studies in 750 participants
- HR=0.81 (95% CI 0.71 to 0.92, high-quality evidence) in favor of the chemotherapy or targeted therapy arm.
- Median OS, weighted for study size, in the chemotherapy arm was 4.7 months versus 4.2 months in the BSC arm
- Cochrane's Q test was non-significant (I^2=0%, P=0.56)

Progression-free survival
- Two studies in 540 participants
- overall HR=0.58 (95% CI 0.28 to 1.18, very low-quality evidence) in favor of targeted therapy
- Cochrane's Q test showed significant heterogeneity (I^2= 85%, P= 0.01)

subanalysis 2: participants who had received previous chemotherapy

Overall survival
- four studies in 769 participants
- overall HR of 0.71(95% CI 0.54 to 0.94, moderate-quality evidence) in favor of the arm with the

additional agent
-Median OS, weighted for study size, was 5.1 months in the chemotherapy arm versus 4.4 months in the BSC arm.
- Cochrane's Q test for heterogeneity showed significant heterogeneity (I^2=57%, P = 0.07)
Progression-free survival
- Three studies in 677 participants
- overall HR of 0.51 (95% CI 0.29 to 0.90, low-quality evidence) in favor of the targeted therapy arms
- Cochrane's Q test for heterogeneity showed substantial heterogeneity (I^2= 83%, P < 0.001)
subanalysis 3: chemotherapy agent(s) pluscontrol intervention versus control intervention alone
Overall survival
- Five studies in 358 participants
- overall HR of 0.73 (95% CI 0.63 to 0.85, moderate-quality evidence) in favor of the arm with the additional chemotherapy agent
- Median survival time, weighted for study size, was 6.9 months in the chemotherapy arm versus 5.8 months in the control arm.
- Cochrane's Q test showed non-significant heterogeneity (I^2= 0%, P=0.50)
subanalysis 4: targeted agent plus control intervention versus control intervention alone
Overall survival

- Six studies with 989 participants
- overall HR in favor of the arm containing a targeted agent was 0.75 (95% CI 0.63 to 0.90, high-quality evidence)
- Median OS in the arm with the additional targeted agent, weighted for study size, was 6.7 months versus 5.7 months in the control arm.
- Cochrane's Q test showed low heterogeneity (I^2= 24%, P=0.25)

Progression-free survival

- Five studies in 883 participants
- overall HR, in favor of the treatment arm that contained a targeted therapy agent, was 0.64 (95% CI 0.45 to 0.92, moderate-quality evidence)
- Median progression-free survival, weighted for study size, was 2.9 months in the arm with the additional targeted therapy agent versus 2.4 months in the control arm
- Cochrane's Q test showed substantial heterogeneity (I^2= 79%, P < 0.001)

Subanalysis 5: chemotherapy or targeted therapyagent(s) plus control intervention versus controlintervention alone in participants with adenocarcinoma of the esophagus

Overall survival

- Five studies in 538 participants
- For overall survival, we found an HR of 0.66 (95%

CI0.54 to 0.81, high-quality evidence) in favor of the experimental arm
- Median OS, weighted for study size, was 7.1 months in the added agent arm versus 6.0 months in the control arm.
- Cochrane's Q test was non-significant (I^2= 0%, P=0.55)

Progression-free survival
- Four studies in 713 participants
- HR of 0.62 (95% CI 0.38 to 1.00, very low-quality evidence) in favor of the experimental arm
- Median OS, weighted for study size, was 1.8 months in the added agent arm versus 1.7 months in the control arm
- Cochrane's Q test was non-significant (I^2= 84%, P < 0.001)

Subanalysis 6: chemotherapy or targeted therapy agent(s) plus control intervention versus control intervention alone in participants with SCC of the esophagus

Overall survival
- Four studies in 268 participants
- HR of 0.76 (95% CI 0.65 to 0.90, high-quality evidence) in favor of the experimental arm
- Median OS, weighted for study size, was 8.0 months in the added agent arm versus 6.5 months in the control arm.
- Cochrane's Q test for heterogeneity was non-

significant (I^2= 0%, P=0.95)
progression free survival
- Two studies in 168 participants
- HR of 0.72 (95% CI 0.55 to 0.96, low-quality evidence) in favor of the experimental arm.
- Median OS, weighted for study size, was 1.7 months in the added agent arm versus 1.2 months in the control arm
- Cochrane's Q test for heterogeneity was non-significant (I^2= 0%, P = 0.97)

Author's Conclusion: People who receive more chemotherapeutic or targeted therapeutic agents have an increased overall survival compared to people who receive less. These agents, administered as both first-line or second-line treatments, also led to better overall survival than best supportive care. With the exception of ramucirumab, it remains unclear which other individual agents cause the survival benefit. Although treatment-associated toxicities of grade 3 or more occurred more frequently in arms with an additional chemotherapy or targeted therapy agent, there is no evidence that palliative chemotherapy and/or targeted therapy decrease quality of life. Based on this meta-analysis, palliative chemotherapy and/or

targeted therapy can be considered standard care for esophageal and gastroesophageal junction carcinoma.

Methodical Notes

Funding Sources: Internal sources
- Dept. of Gastroenterology & Hepatology, Erasmus MC / University Medical Center Rotterdam, Netherlands
- Dept. of Public Health, Erasmus MC, University Medical Center Rotterdam, Netherlands
- Biomedical information specialists, Medical Library Erasmus MC, University Medical Center Rotterdam, Netherlands

External sources
- No sources of support supplied

COI: - VTJ: none known
- EWS: none known
- AvdG: none known
- RHJM: none known
- MJB: none known
- MPP: none known
- EJK: none known
- MCWS: none known

Study Quality: - Two review authors (VJ, MS) independently assessed the risk of bias and the quality of the eligible studies according to the Cochrane Handbook for Systematic Reviews of Interventions
- We rated each study as being at low, high, or unclear risk of bias
- We generally considered the analyzed RCTs to be at low risk of bias in most domains. Apart from blinding, the most common methodological weakness in the included studies was the lack of description regarding allocation concealment.
- individual estimates regarding quality of the evidence can be found in the results section

Heterogeneity: - forest plots for heterogeneity by visual inspection.

- To quantify inconsistency across studies, we calculated the I^2 statistic as [(Q−df)/Q] × 100%, where Q is the Chi2 statistic and df its degrees of freedom
- see results section for individual I^2 values

Publication Bias: - funnel plot if enough studies were present (i.e. at least 10).
- for the main analysis, no evidence of publication bias was found

Notes:
evidence level 1: systematic review and meta-analysis

Lai, A. et al. Role of Esophageal Metal Stents Placement and Combination Therapy in Inoperable Esophageal Carcinoma: A Systematic Review and Meta-analysis. Dig Dis Sci. 63. 1025-1034. 2018

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: systematic review and meta-analysis Databases: PubMed and Embase Search period: from inception to January 14, 2016 Inclusion Criteria: Any randomized clinical trial comparing the use of stents to radiotherapy, chemotherapy, or brachytherapy modalities in patients with inoperable esophageal carcinoma regardless of publication status (e.g., abstracts,	Population: patients with inoperable esophageal carcinoma Intervention: - stents combination therapy vs stents alone (5 studies, n = 417), - stents alone vs brachytherapy alone (2 studies, n = 274), - stents + brachytherapy versus brachytherapy alone (1 study, n = 41).	Primary: - changes in dysphagia score - overall survival - quality of life Secondary: any adverse events Results: - eight RCTs enrolling 732 patients were included **Stents Combination Therapy Versus Stents Alone** Dysphagia Score - Of the five studies, four (n=364) reported extractable data on improvements in dysphagia scores - pooled analysis of mean changes in dysphagia	Amdal et al. Radiother Oncol. 2013 Fu et al. Zhonghua Zhong Liu Za Zhi. 2004 Guo et al. Radiology. 2008 Lu et al. Chin J Radiol (China). 2014 Zhu et al.

unpublished studies) were eligible for inclusion Exclusion Criteria: Observational studies and review articles were excluded. Additionally, studies comparing stents with other types of stents were excluded. There was no restriction on comparators, cohort, age, gender, or language of publication.	Stents combination therapy was defined as stents plus radiotherapy, chemotherapy or both. Comparison: see interventions	grade favored stent combination over stent alone (MD= −0.58; 95% CI: -1.21-0.06; p=0.08) with significant heterogeneity detected (p<0.00001; I^2 =90%). - subgroup analysis for mean change in dysphagia scores at different post-op time periods: The pooled analyses for immediate (1 day to 1 week post-op) and short-term (1–2 months post-op) mean change in dysphagia score did not favor either treatment group with no significant heterogeneity, while the pooled analyses for 3-months, 5-months and 7-months mean change in dysphagia score each favored stents combination with no significant heterogeneity <u>Overall Survival</u> - Of the five studies, four (n=357) reported extractable data - The pooled results favored stents combination (HR=0.58; 95% CI 0.44-0.77; p=0.0002) with no significant heterogeneity (p=0.23; I^2=30%). <u>Quality of Life</u> - Javed et al. assessed quality of life (QOL): Both treatment groups found significant improvements in the following parameters measured 1 week after stenting: physical functioning, role functioning, cognitive functioning, emotional functioning, social functioning, and global health.	Lancet Oncol. 2014 Bergquist et al. Dis Esophagus. 2005 Homs et al. Lancet. 2004 Javed et al. J Gastrointest Cancer. 2012

However, after undergoing external beam radiother-apy (EBRT), the experimental group saw significant decline in the same parameters, except for physical functioning.

Adverse Events

- risk of stent migration (2 studies, n=113), aspiration pneumonia (2 studies, n=220) and restenosis (3 studies, n=173) were lower in the stents combination group compared to stents alone
- risk of severe pain (4 studies, n=333), hemorrhage (4 studies, n=333) and fistula formation (2 studies, n=220) were higher in the stents combination group compared to stents alone
- None of the pooled analyses were associated with significant heterogeneity

Stents Alone Versus Brachytherapy Alone

Dysphagia Score

- 2 studies (n=274) reported extractable data
- pooled analysis of mean changes in dysphagia grade favored brachytherapy alone over stent alone (MD=0.15; 95% CI −0.48-0.78; p=0.64) with no significant heterogeneity detected (p=0.09; I^2=66%).
- subgroup analysis for mean chnage dysphagia scores at different post-op time periods: pooled

analysis for 1-month (MD= −0.18; 95% CI −0.39-0.02; p=0.08) and 3-month (MD = −0.04; 95% CI −0.41-0.34; p=0.84) mean change in dysphagia score favored stents alone over brachytherapy alone with no significant heterogeneity while pooled analysis for 6-month mean change in dysphagia score favored brachytherapy alone (MD=0.34; 95% CI −0.60-1.29; p=0.48) with significant heterogeneity (p=0.001; I^2=87%)

Overall Survival

- 2 studies (n=274) reported extractable data
- pooled data did not favor either treatment group (HR=1.05; 95% CI 0.82–1.36; p=0.69) with no significant heterogeneity (p=0.97; I^2=0%).

Quality of Life

- Both Bergquist et al. and Homs et al. assessed QOL using the EORTC QLQ-30 as well as a disease-specific assessment (EORTC QLQ-OG25 or EORTC OES-23)
- Bergquist et al. found the stent group to have scored worse overall compared to the brachytherapy group while Homs et al. found that the brachytherapy group had higher scores compared to the stent group in several parameters over the course of follow-up

Adverse Events

- risk of fistula formation was higher in the stents-

alone vs brachytherapy-alone group (RR=1.86; 95% CI 0.57–6.03; p=0.30) with no significant heterogeneity (p=0.99; I^2=0%).
- risk of hemorrhage was higher in the stents-alone vs brachytherapy-alone groups (RR=2.63; 95% CI 1.03–6.73; p=0.04) with no significant heterogeneity (p=0.98; I^2=0%).
- risk of perforation was lower in the stents-alone vs brachytherapy-alone groups (RR=0.58; 95% CI 0.11–2.95; p=0.66) with no significant heterogeneity (p=0.36; I^2=0%).

Stents + Brachytherapy Versus Brachytherapy Alone

- Amdal et al. reported extractable data
- The combination therapy group saw a favorable mean change in dysphagia grade (MD= −0.93; 95% CI −1.74 to −0.12; p=0.02) but a worse survival curve (HR=1.57; 95% CI 0.77–3.18; p=0.21)
- EORTC QLQ-30 and EORTC QLQ-OG25 revealed that combination therapy group saw significant improvement in dysphagia QoL scores after 3 weeks, and both groups saw improvements after 7 weeks.
- The study also reported three cases aspiration pneumonia, one hemorrhage and one stent migration in the stent+brachytherapy group. No adverse events were reported in brachytherapy-

alone patients.

Author's Conclusion: In conclusion, our findings are consistent with those found by the studies included in the pooled analyses, but also illuminate the lack of event data, especially for adverse events. We report an analysis that favors the addition of brachytherapy, radiotherapy, or chemotherapy with the insertion of metal stents; however, because some procedures are associated with minimal immediate improvements in dysphagia scores or increased risk of adverse events, we recommend that practitioners open a discussion with their patients on treatment options for their disease. Our analy-ses suggest that larger randomized controlled trials should be conducted to assess improvements in dysphagia score, overall survival, quality of life, and adverse events in addition to identifying patient characteristics that could predict longer survival.

Methodical Notes

Funding Sources: no statement

COI: The authors report no conflict of interest and have followed the ethical adherence guidelines.

Study Quality: - Five authors (AL, AK, DB, NL, LS) independently assessed the risk of bias in the included studies using The Cochrane Collaboration's tool. Specifically, for assessment of risk of bias, we graded each component of methodological quality as low, high, or unclear.

- Overall methodological quality of the included studies ranged from moderate to very low.
- Additionally, we evaluated the overall quality of evidence for each outcome according to Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines, which classify evidence as either very low, low, moderate, or high
- The quality of evidence for studies comparing stents combination vs stents alone was also very low
- Of all eight studies, six (75%) reported an explicit method for generation of randomization sequence, five (62.5%) on allocation concealment, two (25%) on blind-ing of participants and personnel, 1 (12.5%) on blinding of outcome assessment. Three studies (37.5%) had low risk of incomplete outcome data, four (50%) for selecting reporting bias, and six (75%) for other biases. Three studies (37.5%) had high risk of incomplete outcome data, as a per-protocol analysis was performed without reporting intention-to-treat results.

Heterogeneity: To evaluate heterogeneity between pooled studies, we calculated $\chi 2$ and I2 statistics [16]. We considered an $I^2 > 50\%$ to indicate substantial heterogeneity or a Chi-square test, with the significance level set at $p < 0.1$ to indicate statistically significant heterogeneity.

Publication Bias: not assessed because of low number of included studies (<10)

Notes:
evidence level 1: systematic review and meta-analysis
- 5 studies were also included in another SR and network meta-analysis (Doosti-Irani, A. et al. 2017)

Pandit, S. et al. Efficacy and safety of standard and anti-reflux self-expanding metal stent: A systematic review and meta-analysis of randomized controlled trials. World J Gastrointest Endosc. 11. 271-280. 2019

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: systematic review and meta-analysis Databases: PubMed, CINAHL, and Cochrane	Population: adult patients with esophageal cancer with stent crossing the EGJ and cardia Intervention: Anti-reflux stents (ARS)	Primary: improvement in dysphagia, GER scores, which were reported as standardized mean difference (SMD) with 95% CI. Secondary: The risk of stent migration, bleeding and obstruction were reported as OR with 95% CI.	Coron et al, 2016, Endosc Int Open Kaduthodil et al, 2011, Cardiovasc Intervent Radiol Blomberg et al,

Library Search period: inception to 2018 Inclusion Criteria: (1) RCTs; (2) Age > 18 years old; (3) Esophageal cancer with stent crossing the EGJ and cardia; (4) Comparison between SS and ARS; (5) Reported improvement in clinical outcome and complications Exclusion Criteria: (1) Foreign language without English version; (2) Study that included stents for benign esophageal stricture; (3) Stents placed by radiologists; (4) Prior history of stent placement	Comparison: standard stent (SS)	Results: - A total of 395 patients were included in the study, ARS (192 patients) and SS (203 patients) <u>primary outcomes</u> - Eight studies were included in the meta-analysis, however, only four studies reported primary outcome as GER and dysphagia, before and after stent placement. - Compared to the SS, the ARS showed a trend towards reduction in the dysphagia score but it did not reach a statistical significance [SMD: -0.33 (-0.71, 0.05); P=0.09, I^2: 37%]. - there was no statistical difference in the GER scores between the two types of stents [SMD: -0.17 (-0.78, 0.45); P=0.008, I^2: 74%] <u>secondary outcomes</u> - Out of five studies which reported stent migration, three studies showed stent migration is more likely with SS. However, pooled results showed there was no significant statistical difference between SS and ARS in terms of risk of stent migration (OR=1.37, 95%CI: 0.66-2.83) - Five studies reported stent related bleeding but one of them did not provide adequate statistical data to calculate OR. Pooled results from four studies showed no statistical difference in bleeding risk using either SS or ARS (OR=1.43, 95%CI: 0.40-5.13) - Four studies reported data on stent occlusion. SS had more cases of stent occlusion; however, pooled data suggested no statistical difference between SS and ARS (OR=1.66, 95%CI: 0.60-4.60)	2010, Scand J Gastroenterol Sabharwal et al, 2008, J Gastroenterol Hepatol Power et al, 2007, Dis Esophagus Wenger et al, 2006, Surg Endosc Shim et al, 2005, Endoscopy Homs et al, 2004, Gastrointest Endosc

Author's Conclusion: In conclusion, both traditional standard open stent and anti-reflux stent with valve are comparable in terms of their efficacy and safety for the palliative treatment of obstructive esophageal and gastroesophageal junction malignancies. Authors believe both SS and ARS could be used in clinical practice as per the availability of clinical expertise, cost, and patient preference with informed decision.

Methodical Notes

Funding Sources: no statement

COI: The authors have no conflicting financial interests to disclose.

Study Quality: - Quality assessment of each study according to the guideline by QUADAS-2
- Concern for biases regarding patient selection, randomization, index test, reference standard was overall low except for flow of patients through the study and timing of index tests, and reference standard.

Heterogeneity: - heterogeneity was assessed
- see results section for calculated I^2 values

Publication Bias: By utilizing Revman Manager funnel, plots were created for outcome gastroesophageal reflux disease and outcome dysphagia. No significant publication bias was found among studies evaluated.

Notes:
evidence level 1: systematic review and meta-analysis

OXFORD (2011) Appraisal Sheet: RCT: *2 Bewertung(en)*

Didden, P. et al. Fully vs. partially covered selfexpandable metal stent for palliation of malignant esophageal strictures: a randomized trial (the COPAC study). Endoscopy. 50. 961?971. 2018

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 Study type: randomized controlled trial Number of Patient: 98 incurable patients with dysphagia Recruitung Phase: Between August 2012 and April 2016 Inclusion Criteria: a dysphagia score of at least 2 caused by a malignant stricture of the esophagus or cardia, no curative treatment options, informed consent given, and age≥18 years. Exclusion Criteria: previous treatment with a SEMS, a tumor located within 2cm of the upper esophageal sphincter, an esophagopulmonary fistula, and inability to undergo upper gastrointestinal endoscopy or to fill out questionnaires	Intervention: partially covered self-expandable metal stent (PC-SEMS) Comparison: fully covered self-expandable metal stent (FC-SEMS)	Primary: recurrent obstruction, defined as reoccurrence of dysphagia Secondary: technical success of SEMS placement, clinical success, adverse event rate and HRQoL Results: <u>Recurrent obstruction</u> - Recurrent obstruction due to SEMS dysfunction developed in 20 out of 97 patients (21%), occurring after a median of 60 days (range 3–184 days). This rate was similar in both groups, occurring in 19% and 22% (P=0.65) after FC-SEMS and PC-SEMS placement, respectively. - Obstructive tumor/tissue growth was seen in five patients (10%) after FC-SEMS placement due to overgrowth (n=4) and ingrowth through the covering of the proximal flare (n=1), and in 7 patients (14%) after PC-SEMS insertion due to ingrowth through the uncovered meshes (n=3),overgrowth (n=1), and both (n=3). - No difference was seen in SEMS migration, occurring in four patients (8%) and three patients (6%) in the FC-SEMS and PC-SEMS groups, respectively. In addition, time free of recurrent obstruction was similar between the two treatment groups (HR 1.05, 95%CI 0.43–2.56;P=0.91, PC-SEMS as reference)

Technical and clinical outcome
- Endoscopic insertion of the SEMS was technically successful in 95 of the 97 patients (98%), 100% in the FC-SEMS group and 96% in the PC-SEMS group (P=0.50)
- Clinical success was reported in 83% after FC-SEMS placement and 88% after PC-SEMS placement (P=0.54).

Adverse events
- the number of SEMS-related adverse events was similar between the two groups. In the FC-SEMS group, 24 adverse events occurred in 19 patients (40%), including 21 major and 3 minor events. In the PC-SEMS group, 31 adverse events were encountered in 24 patients (49%), including 27 major and 4 minor events.
- most common major adverse events were severe retrosternal pain (20%), pneumonia (13%), and hemorrhage (9%), all of which were equally distributed between the two treatment groups.

Health-related quality of life
- No differences in effect over time were found between the two SEMS types for all scales of the EORTC QLQ-C30, including global health status, functional, and symptom scales
- With respect to the EORTC QLQ-OES18, the only significant difference (P=0.04) detected over time was dry mouth (in favor of PC-SEMS)

Author's Conclusion: In conclusion, we have demonstrated

that, in patients with malignant dysphagia, FC-SEMSs do not decrease the recurrent obstruction rate compared with PC-SEMSs. The incidence of major adverse events in this study was higher in women and in patients with proximal strictures. Whether this is related to the specific design of the WallFlex SEMSs remains to be established and warrants further research.

Methodical Notes

Funding Sources: no statement

COI: - Manon C. W. Spaander has received funding for reserach from Scientific.
- Marco J. Bruno is a consultant and lecturer for Boston Scientificand Cook Medical

Randomization: After giving informed consent, patients from all five medicalcenters were centrally randomized using computer-generatedlists. Patients were stratified byhospital. The allocated interventions were sealed in sequentially numbered identical opaque envelopes

Blinding: Neither the endoscopist nor the patient were blinded to the outcome of the randomization.

Dropout Rate/ITT-Analysis: - We performed an intention-to-treat analysis with follow-up data from randomization until 6 months after treatment or until an endpoint had been reached. Patients who did not receive an intervention (SEMS) were excluded from the analysis.
- One patient, who was allocated to an FC-SEMS, was excluded from the analysis because the SEMS could not be inserted
- A total of 97 patients weretherefore included in the final analysis, 48 patients in the FC-SEMS group and 49 patients in the PC-SEMS group

Notes:
evidence level 2: randomised controlled trial

Penniment, M. G. et al. Palliative chemoradiotherapy versus radiotherapy alone for dysphagia in advanced oesophageal cancer: a multicentre randomised controlled trial (TROG 03.01). Lancet Gastroenterol Hepatol. 3. 114-124. 2018

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 Study type: randomised controlled trial Number of Patient: 111 patients were randomly assigned to chemoradiotherapy and 109 patients to radiotherapy. Recruitung Phase: Between July 7, 2003 and March 21, 2012 Inclusion Criteria: Eligible patients - had biopsy-proven oesophageal cancer (excluding Seifert 2 and 3 lesions) - were deemed unsuitable for, or unable to have, curative treatment after discussion with the local multidisciplinary oncology team. - had symptomatic dysphagia (grade 1–4 on the Mellow scale), - had Eastern Cooperative	Intervention: chemoradiotherapy - radiotherapy dose was 35 Gy in 15 fractions over 3 weeks for study participants enrolled in Australia and New Zealand and 30 Gy in ten fractions over 2 weeks for participants enrolled in Canada and the UK. - Chemotherapy consisted of intravenous cisplatin (either 80 mg/m² on day 1 or 20 mg/m² per day on days 1–4 at the clinician's discretion) with intravenous fluorouracil 800 mg/m² per day on days 1–4 of radiotherapy (continuous infusion). Patients received dexamethasone and a 5-HT3 receptor antagonist before cisplatin and were prehydrated as per institutional protocols. Comparison: radiotherapy alone - radiotherapy dose was 35 Gy in 15 fractions over 3 weeks for study participants enrolled in Australia and New Zealand and 30 Gy in ten fractions over 2 weeks for participants enrolled in Canada and the UK.	Primary: dysphagia relief, defined as improvement of at least one point on the Mellow scale at 9 weeks (±2 weeks) that was maintained at the next review 4 weeks later (ie,at 13 weeks ±2 weeks) Secondary: - dysphagia progression-free survival, defined as a worsening of at least one point on the Mellow scale (from baseline or best response) or malignant stricture requiring intervention. - time to achieve any response in dysphagia (an improvement of at least one point on the Mellow scale after treatment, even if not sustained 4 weeks later) - time to any complete response (Mellow score 0) - patient's assessment of dysphagia response - number of patients receiving secondary treatment (radiotherapy, chemotherapy, or stenting) - and overall survival Results: <u>dysphagia relief</u> 50 (45%, 95% CI 36–55) patients in the chemo-radiotherapy group and 38 (35%, 26–44) patients

Oncology Group performance status 0–2,
- had adequate haematological and renal function (neutrophil count >1.5×10^9 cells per L, platelet count >100×10^9 cells per L, and calculated creatinine clearance ≥50 mL/min)
- provided written informed consent.

Exclusion Criteria: - prior chemotherapy or chest radiotherapy for oesophageal cancer,
- other active malignancies,
- tracheo-oesophageal fistula or stent in situ,
- pregnancy, lactation or inadequate contraception,
- age younger than 18 years

in the radiotherapy group achieved dysphagia relief
- The odds ratio for dysphagia relief in the chemoradiotherapy group compared to the radiotherapy group was estimated to be 1.56 (95% CI 0.87–2.78; p=0.14).
- When adjusted for stratification variables (M stage and pretreatment dysphagia), the odds ratio for dysphagia relief for chemoradiotherapy versus radiotherapy was estimated to be 1.64 (0.91–2.97; p=0.10).
-Complete dysphagia relief was noted in 32 (29%) patients in the chemoradiotherapy group and in 26 (24%) patients in the radiotherapy group (p=0.44)
- The median time from start of radiotherapy to any relief was 9.1 weeks (IQR 8.6–9.7) in the chemoradiotherapy group and 9.0 weeks (8.3–9.6) for radiotherapy (p=0·46). The median duration of any relief was 3.4 months (IQR 1.3–5.7)for chemoradiotherapy and 2.5 months(1.4–5.3) for radiotherapy (p=0.72)
- The median time from start of radiotherapy to complete relief at any assessment was 9.3 weeks (IQR 9.0–12.0) for chemoradiotherapy and 9.2 weeks (8.9–10.1) for radiotherapy (p=0.37)
<u>dysphagia progression-free survival</u>

- Estimated median dysphagia progression-free survival time from randomisation was 4.1 months (95% CI 3.5–4.8) for chemoradiotherapy and 3.4 months (3.1–4.3) for radiotherapy
- The hazard ratio (HR) for chemoradiotherapy versus radiotherapy was estimated to be 0.93 (95% CI 0.71–1.21; p=0.58)

overall survival

- Estimated median overall survival from randomisation was 6.9 months (5.1-8.3) for chemoradiotherapy and 6.7 months (4.9-8.0) for radiotherapy, HR=0.98 (95% CI 0.75–1.29; p=0.88)

<u>Secondary treatments</u>

- were given after failure of trial treatment in 117 patients (55 [51%] of 107 patients in the chemoradiotherapy group and 62 [60%] of 104 patients in the radiotherapy group).
- Oesophageal stenting was used in 23 (21%) patients in the chemoradiotherapy group and 32 (31%) patients in the radiotherapy group, whereas additional palliative chemotherapy was administered to 24 (22%) patients in the chemoradiotherapy group and 33 (32%) patients in the radiotherapy group.

adverse events

- of the 211 patients who commenced

radiotherapy, grade 3–4 acute toxicity occurred in 38 (36%) patients in the chemoradiotherapy group and in 17 (16%) patients in the radiotherapy group (p=0.0017). Anaemia, thrombocytopenia, neutropenia, oesophagitis, diarrhoea, nausea and vomiting, and mucositis were significantly worse in patients who had chemoradiotherapy than in patients who had radiotherapy

self-assessment

- 76 patients (39 in the chemoradiotherapy group and 37 in the radiotherapy group) answered a self-assessed dysphagia relief question at 9 weeks (7.1–11.1 weeks)
- Five patients felt their swallowing was worse (clinical response: no change [three], worse [two]).
- Seven patients reported that their swallowing was about the same as before treatment (clinical response: complete dysphagia relief [two], partial dysphagia relief [five]),
- 64 patients reported that their swallowing was better (clinical response: complete dysphagia relief [37], partial dysphagia relief [21], no change [five], worse [one]).
- The self-assessments were similar between the two treatment arms: 34 patients receiving

chemoradiotherapy and 30 patients receiving radiotherapy felt better; three patients receiving chemo-radiotherapy and four patients receiving radiotherapy felt about the same; and two patients receiving chemoradiotherapy and three patients receiving radiotherapy felt worse (p=0.69, trend test)

Author's Conclusion: Palliative chemoradiotherapy showed a modest, but not statistically significant, increase in dysphagia relief compared with radiotherapy alone, with minimal improvement in dysphagia progression-free survival and overall survival with chemoradiotherapy but at a cost of increased toxicity. A short course of radiotherapy alone should be considered a safe and well tolerated treatment for malignant dysphagia in the palliative setting.

Methodical Notes

Funding Sources: This study was funded by the National Health and Medical Research Council of Australia (291103), Canadian Cancer Society Research Institute, Canadian Cancer Trials Group, Trans Tasman Radiation Oncology Group, and Cancer Australia.
The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

COI: - MGP and SS declare grant funding from NHMRC and Cancer Australia.
- JGS received payments for statistical analysis from the primary trial centre.

- All other authors declare no competing interests

Randomization: Patients were randomly assigned to chemoradiotherapy or radiotherapy alone by telephone or fax to the trial centre at the Royal Adelaide Hospital in Adelaide, SA, Australia. Clinicians, patients, and data managers had no prior knowledge of the treatment arm to which the patients would be assigned. Eligibility was checked and patients were stratified by hospital, dysphagia score (Mellow score 1–4), and presence of metastases before random allocation (1:1) using a computer-generated adaptive biased coin design.

Blinding: no blinding

Dropout Rate/ITT-Analysis: Patients' data were analysed according to their randomised treatment arm (intention-to-treat), except for the exclusion of one patient who was found not to have oesophageal cancer after randomisation. Patients who did not commence any protocol treatment were excluded from the toxicity analyses.

Notes:
evidence level 2: randomised controlled trial

Schlüsselfrage:

21 Palliative Therapie - Radiotherapie

Inhalt: *3 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Doosti-Irani, A. 2017	1	systematic review and network meta-analysis
Lai, A. 2018	1	systematic review and meta-analysis
Penniment, M. G. 2018	2	randomised controlled trial

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

Doosti-Irani, A. et al. Complications of stent placement in patients with esophageal cancer: A systematic review and network meta-analysis. PLoS One. 12. e0184784. 2017

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: systematic review and network meta-analysis Databases: Web of Science, Medline, Scopus, Cochrane Library and Embase Search period: until July 2017	Population: patients with esophageal cancer Intervention: palliative treatment interventions Comparison: none	Primary: treatment related death (TRD), bleeding, stent migration, aspiration, severe pain and fistula formation among patients with esophageal Secondary: none Results: <u>Treatment related death</u> - reported in 16 RCTs, which included 1075 patients - The comparisons of treatments for TRD involved four independent sub-networks.	Amdal (2013) Radiotherapy and Oncology Conio (2007) American Journal of Gastroenterology Dallal (2001) Gastrointestinal Endoscopy De Palma (1996)

Inclusion Criteria: - RCTs that included patients with either histology of esophageal cancer i.e. squamous cell carcinoma and/or adenocarcinoma - RCTs that had evaluated stent placement or palliative treatments of esophageal cancer Exclusion Criteria: Cohort studies and non-randomized clinical trials	- According to the results of the test for heterogeneity, the I^2 statistic for network A was 15.2%, and for network B, C, and D was zero - In network A, with the metallic stent as reference, the latex prosthesis increased the risk of TRD. The relative risk (RR) was 3.89 (95% CI: 0.42, 36.33). The RR for thermal ablative therapy compared with the metallic stent was 0.46 (95% CI: 0.04, 5.19). - In network B, covered Evolution® compared with Ultraflex stent decreased the risk of TRD, RR = 0.70 (95% CI: 0.30, 1.66). - In network C, SEMS 18 compared to brachytherapy increased the risk of TRD, RR = 5.61, (95% CI: 0.69, 45.80). - In network D, both the open stent (RR = 3.00, 95% CI: 0.13, 70.23) and 'Ultraflex plus omeprazole' (RR = 2.55, 95% CI: 0.11, 59.49) compared to antireflux stent increased the risk of TRD <u>bleeding</u> - reported in 18 RCTs, which included 1374 patients - Based on the results of the test for heterogeneity, the I^2 statistic for network A, B, C, and D was zero - In network A, the latex prosthesis and plastic stent increased the risk of bleeding when compared to the metallic stent. The RR for latex prosthesis was 1.62 (95% CI: 0.42, 6.31) and was 2.85 (95% CI: 0.12, 65.93) for the plastic stent. On the other hand, thermal ablative therapy (RR = 0.13, 95% CI: 0.01, 2.43) and uncovered stent (RR =	Gastrointest Endosc Guo (2008) Radiology Homs (2004) Lancet (London, England). Homs (2004) Gastrointestinal Endoscopy Javed (2012) Journal of Gastrointestinal Cancer Knyrim (1993) New England Journal of Medicine O'Donnell (2002) British Journal of Surgery Power (2007) Diseases of the Esophagus Sabharwal (2008) Journal of Gastroenterology & Hepatology Sabharwal (2003) Gut Shenfine (2009) American Journal of Gastroenterology Vakil (2001) American Journal of

0.27, 95% CI: 0.06, 1.16) decreased the risk of bleeding when compared to the metallic stent. - In network B, the irradiation stent (RR = 1.24, 95% CI: 0.54, 2.83) and CSENACS (RR = 1.24, 95% CI: 0.29, 5.32) increased the risk of bleeding when compared to the conventional stent. - In network C, the covered Evolution® stent decreased the risk of bleeding (RR = 0.07, 95% CI: 0.00, 1.13) when compared to Ultraflex. - In network D, SEMS (RR = 3.00, 95% CI: 0.13, 70.78) and SEMS+BT (RR = 2.86, 95% CI: 0.12, 66.28)increased the risk of bleeding when compared to brachytherapy	Gastroenterology van Heel (2012) Gastrointestinal Endoscopy Wenger (2006) Surgical endoscopy Wenger (2005) European journal of gastroenterology & hepatology White (2015) Journal of Clinical Gastroenterology
<u>Stent migration</u> - reported in 19 RCTs involving 1207 patients - In the network A, and B the I^2 statistic was zero, and in the network C the I^2 was 16.1% - In network A, when compared to the Ultraflex stent, the polyflex stent increased the risk of stent migration 2.07 times (95% CI: 1.01, 4.67). The risk of stent migration for covered Evolution® stent, Flamingo stent, and Ultraflex stent plus radiotherapy was lower than the ultraflex stent; however, the 95% CIs involved the null values. - In network B, the risk ratio for the latex prosthesis and plastic stents compared to the metallic stent was 6.82 (95% CI: 0.36, 127.54) and 2.87 (95% CI: 0.87, 10.64), respectively. - In network C, there were no considerable differences	Zhu (2014) The Lancet Laasch (2002) Radiology Siersema (1998) Gastrointestinal endoscopy Siersema (2001) Gastrointestinal endoscopy Verschuur (2008) The American journal of gastroenterology

between the conventional, Irradiation, open and ultraflex stents plus omeprazole and the Antireflux stent

Aspiration

- reported in 9 RCTs involving 805 esophageal cancer patients, 3 were excluded from network analysis
- The I2 statistic for all networks of this complication was zero
- In terms of ranking, the Polyflex stent (p-score = 0.69), Irradiation stent (p-score = 0.74) and BT (p-score = 0.69) were the better treatments in networks A, B and C

Severe pain

- Severe pain was reported in 14 RCTs
- According to the results of test for heterogeneity, The I^2 statistic for network A, B, C, and D was zero
- The CSENACS (p-score = 0.73), Polyflex stent (p-score = 0.79), Latex prosthesis (p-score = 0.96) and BT (p-score = 0.65) were better treatments in terms of lower risk of severe pain among patients in networks A, B, C and D, respectively.

fistula formation

- Fistula formation was reported in 10 RCTs.
- The I^2 statistic for all networks of this complication was zero
- The Plastic stent (p-score = 0.81), Conventional stent (p-score = 0.72), and SEMS 18 (p-score = 0.62) were better treatments in terms of lower risk of fistula formation in networks A, B, and C, respectively

Author's Conclusion: Overall, the results of this network meta-analysis showed that thermal ablative therapy, covered Evolution® stents, brachytherapy and antireflux stents are associated with a lower risk of TRD. In terms of lower risk of bleeding, thermal ablative therapy, conventional stent, covered Evolution® stent and brachytherapy were better palliative treatments for patients with esophageal cancer. Based on the lower risk of stent migration, the covered Evolution®, uncovered, and Irradiation stents were better treatments. In terms of lower risk of severe pain as another major complication the CSENACS, polyflex stent, latex prosthesis and brachytherapy were better treatments.

Methodical Notes

Funding Sources: This study supported by Tehran University of Medical Sciences (TUMS). We would like to thank Vic-Chancellor of Research and Technology of TUMS for financial support of this study. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

COI: no statement

Study Quality: - The risk of bias was assessed using Cochrane's tools
- 6 studies were rated as low quality, 11 as intermediate quality and 7 studies as high quality

Heterogeneity: - The statistical heterogeneity was assessed using the Chi^2 test and the heterogeneity across each comparison was quantified using I^2 statistics
- The results showed no significant heterogeneity in the networks in either of the complications

- see results section for individual I^2 values

Publication Bias: - The publication bias for each complication was assessed visually by the adjusted network funnel plot using Stata 13 (Stata Corp, College Station, TX, USA)
- Based on the adjusted funnel plot there was no evidence of publication bias for the set of studies related to each complication

Notes:
evidence level 1: systematic review

Lai, A. et al. Role of Esophageal Metal Stents Placement and Combination Therapy in Inoperable Esophageal Carcinoma: A Systematic Review and Meta-analysis. Dig Dis Sci. 63. 1025-1034. 2018

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: systematic review and meta-analysis Databases: PubMed and Embase Search period: from inception to January 14, 2016 Inclusion Criteria: Any randomized clinical trial comparing the use of stents to radiotherapy, chemotherapy, or brachytherapy modalities in patients with inoperable esophageal carcinoma regardless of publication status (e.g., abstracts,	Population: patients with inoperable esophageal carcinoma Intervention: - stents combination therapy vs stents alone (5 studies, n = 417), - stents alone vs brachytherapy alone (2 studies, n = 274), - stents + brachytherapy versus brachytherapy alone (1 study, n = 41).	Primary: - changes in dysphagia score - overall survival - quality of life Secondary: any adverse events Results: - eight RCTs enrolling 732 patients were included **Stents Combination Therapy Versus Stents Alone** <u>Dysphagia Score</u> - Of the five studies, four (n=364) reported extractable data on improvements in dysphagia scores - pooled analysis of mean changes in dysphagia	Amdal et al. Radiother Oncol. 2013 Fu et al. Zhonghua Zhong Liu Za Zhi. 2004 Guo et al. Radiology. 2008 Lu et al. Chin J Radiol (China). 2014 Zhu et al.

unpublished studies) were eligible for inclusion Exclusion Criteria: Observational studies and review articles were excluded. Additionally, studies comparing stents with other types of stents were excluded. There was no restriction on comparators, cohort, age, gender, or language of publication.	Stents combination therapy was defined as stents plus radiotherapy, chemotherapy or both. Comparison: see interventions	grade favored stent combination over stent alone (MD= −0.58; 95% CI: -1.21-0.06; p=0.08) with significant heterogeneity detected (p<0.00001; I^2 =90%). - subgroup analysis for mean change in dysphagia scores at different post-op time periods: The pooled analyses for immediate (1 day to 1 week post-op) and short-term (1–2 months post-op) mean change in dysphagia score did not favor either treatment group with no significant heterogeneity, while the pooled analyses for 3-months, 5-months and 7-months mean change in dysphagia score each favored stents combination with no significant heterogeneity <u>Overall Survival</u> - Of the five studies, four (n=357) reported extractable data - The pooled results favored stents combination (HR=0.58; 95% CI 0.44-0.77; p=0.0002) with no significant heterogeneity (p=0.23; I^2=30%). <u>Quality of Life</u> - Javed et al. assessed quality of life (QOL): Both treatment groups found significant improvements in the following parameters measured 1 week after stenting: physical functioning, role functioning, cognitive functioning, emotional functioning, social functioning, and global health.	Lancet Oncol. 2014 Bergquist et al. Dis Esophagus. 2005 Homs et al. Lancet. 2004 Javed et al. J Gastrointest Cancer. 2012

However, after undergoing external beam radiother-apy (EBRT), the experimental group saw significant decline in the same parameters, except for physical functioning.

Adverse Events

- risk of stent migration (2 studies, n=113), aspiration pneumonia (2 studies, n=220) and restenosis (3 studies, n=173) were lower in the stents combination group compared to stents alone
- risk of severe pain (4 studies, n=333), hemorrhage (4 studies, n=333) and fistula formation (2 studies, n=220) were higher in the stents combination group compared to stents alone
- None of the pooled analyses were associated with significant heterogeneity

Stents Alone Versus Brachytherapy Alone

Dysphagia Score

- 2 studies (n=274) reported extractable data
- pooled analysis of mean changes in dysphagia grade favored brachytherapy alone over stent alone (MD=0.15; 95% CI −0.48-0.78; p=0.64) with no significant heterogeneity detected (p=0.09; I^2=66%).
- subgroup analysis for mean chnage dysphagia scores at different post-op time periods: pooled

analysis for 1-month (MD= −0.18; 95% CI −0.39-0.02; p=0.08) and 3-month (MD = −0.04; 95% CI −0.41-0.34; p=0.84) mean change in dysphagia score favored stents alone over brachytherapy alone with no significant heterogeneity while pooled analysis for 6-month mean change in dysphagia score favored brachytherapy alone (MD=0.34; 95% CI −0.60-1.29; p=0.48) with significant heterogeneity (p=0.001; I^2=87%)

Overall Survival

- 2 studies (n=274) reported extractable data
- pooled data did not favor either treatment group (HR=1.05; 95% CI 0.82–1.36; p=0.69) with no significant heterogeneity (p=0.97; I^2=0%).

Quality of Life

- Both Bergquist et al. and Homs et al. assessed QOL using the EORTC QLQ-30 as well as a disease-specific assessment (EORTC QLQ-OG25 or EORTC OES-23)
- Bergquist et al. found the stent group to have scored worse overall compared to the brachytherapy group while Homs et al. found that the brachytherapy group had higher scores compared to the stent group in several parameters over the course of follow-up

Adverse Events

- risk of fistula formation was higher in the stents-

alone vs brachytherapy-alone group (RR=1.86; 95% CI 0.57–6.03; p=0.30) with no significant heterogeneity (p=0.99; I^2=0%).
- risk of hemorrhage was higher in the stents-alone vs brachytherapy-alone groups (RR=2.63; 95% CI 1.03–6.73; p=0.04) with no significant heterogeneity (p=0.98; I^2=0%).
- risk of perforation was lower in the stents-alone vs brachytherapy-alone groups (RR=0.58; 95% CI 0.11–2.95; p=0.66) with no significant heterogeneity (p=0.36; I^2=0%).

Stents + Brachytherapy Versus Brachytherapy Alone

- Amdal et al. reported extractable data
- The combination therapy group saw a favorable mean change in dysphagia grade (MD= −0.93; 95% CI −1.74 to −0.12; p=0.02) but a worse survival curve (HR=1.57; 95% CI 0.77–3.18; p=0.21)
- EORTC QLQ-30 and EORTC QLQ-OG25 revealed that combination therapy group saw significant improvement in dysphagia QoL scores after 3 weeks, and both groups saw improvements after 7 weeks.
- The study also reported three cases aspiration pneumonia, one hemorrhage and one stent migration in the stent+brachytherapy group. No adverse events were reported in brachytherapy-

alone patients.

Author's Conclusion: In conclusion, our findings are consistent with those found by the studies included in the pooled analyses, but also illuminate the lack of event data, especially for adverse events. We report an analysis that favors the addition of brachytherapy, radiotherapy, or chemotherapy with the insertion of metal stents; however, because some procedures are associated with minimal immediate improvements in dysphagia scores or increased risk of adverse events, we recommend that practitioners open a discussion with their patients on treatment options for their disease. Our analyses suggest that larger randomized controlled trials should be conducted to assess improvements in dysphagia score, overall survival, quality of life, and adverse events in addition to identifying patient characteristics that could predict longer survival.

Methodical Notes

Funding Sources: no statement

COI: The authors report no conflict of interest and have followed the ethical adherence guidelines.

Study Quality: - Five authors (AL, AK, DB, NL, LS) independently assessed the risk of bias in the included studies using The Cochrane

Collaboration's tool. Specifically, for assessment of risk of bias, we graded each component of methodological quality as low, high, or unclear.
- Overall methodological quality of the included studies ranged from moderate to very low.
- Additionally, we evaluated the overall quality of evidence for each outcome according to Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines, which classify evidence as either very low, low, moderate, or high
- The quality of evidence for studies comparing stents combination vs stents alone was also very low
- Of all eight studies, six (75%) reported an explicit method for generation of randomization sequence, five (62.5%) on allocation concealment, two (25%) on blind-ing of participants and personnel, 1 (12.5%) on blinding of outcome assessment. Three studies (37.5%) had low risk of incomplete outcome data, four (50%) for selecting reporting bias, and six (75%) for other biases. Three studies (37.5%) had high risk of incomplete outcome data, as a per-protocol analysis was performed without reporting intention-to-treat results.

Heterogeneity: To evaluate heterogeneity between pooled studies, we calculated χ2 and I2 statistics [16]. We considered an $I^2 > 50\%$ to indicate substantial heterogeneity or a Chi-square test, with the significance level set at $p < 0.1$ to indicate statistically significant heterogeneity.

Publication Bias: not assessed because of low number of included studies (<10)

Notes:
evidence level 1: systematic review and meta-analysis
- 5 studies were also included in another SR and network meta-analysis (Doosti-Irani, A. et al. 2017)

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

Penniment, M. G. et al. Palliative chemoradiotherapy versus radiotherapy alone for dysphagia in advanced oesophageal cancer: a multicentre randomised controlled trial (TROG 03.01). Lancet Gastroenterol Hepatol. 3. 114-124. 2018

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2	Intervention: chemoradiotherapy - radiotherapy dose was 35 Gy in 15 fractions over 3 weeks	Primary: dysphagia relief, defined as improvement of at least one point on the

Study type: randomised controlled trial Number of Patient: 111 patients were randomly assigned to chemoradiotherapy and 109 patients to radiotherapy. Recruitung Phase: Between July 7, 2003 and March 21, 2012 Inclusion Criteria: Eligible patients - had biopsy-proven oesophageal cancer (excluding Seifert 2 and 3 lesions) - were deemed unsuitable for, or unable to have, curative treatment after discussion with the local multidisciplinary oncology team. - had symptomatic dysphagia (grade 1–4 on the Mellow scale), - had Eastern Cooperative Oncology Group performance status 0–2, - had adequate haematological	for study participants enrolled in Australia and New Zealand and 30 Gy in ten fractions over 2 weeks for participants enrolled in Canada and the UK. - Chemotherapy consisted of intravenous cisplatin (either 80 mg/m² on day 1 or 20 mg/m² per day on days 1–4 at the clinician's discretion) with intravenous fluorouracil 800 mg/m² per day on days 1–4 of radiotherapy (continuous infusion). Patients received dexamethasone and a 5-HT3 receptor antagonist before cisplatin and were prehydrated as per institutional protocols. Comparison: radiotherapy alone - radiotherapy dose was 35 Gy in 15 fractions over 3 weeks for study participants enrolled in Australia and New Zealand and 30 Gy in ten fractions over 2 weeks for participants enrolled in Canada and the UK.	Mellow scale at 9 weeks (±2 weeks) that was maintained at the next review 4 weeks later (ie,at 13 weeks ±2 weeks) Secondary: - dysphagia progression-free survival, defined as a worsening of at least one point on the Mellow scale (from baseline or best response) or malignant stricture requiring intervention. - time to achieve any response in dysphagia (an improvement of at least one point on the Mellow scale after treatment, even if not sustained 4 weeks later) - time to any complete response (Mellow score 0) - patient's assessment of dysphagia response - number of patients receiving secondary treatment (radiotherapy, chemotherapy, or stenting) - and overall survival Results: <u>dysphagia relief</u> 50 (45%, 95% CI 36–55) patients in the chemo-radiotherapy group and 38 (35%, 26–44) patients in the radiotherapy group achieved dysphagia relief - The odds ratio for dysphagia relief in the

and renal function (neutrophil count >1.5×10^9 cells per L, platelet count >100×10^9 cells per L, and calculated creatinine clearance ≥50 mL/min)
- provided written informed consent.

Exclusion Criteria: - prior chemotherapy or chest radiotherapy for oesophageal cancer,
- other active malignancies,
- tracheo-oesophageal fistula or stent in situ,
- pregnancy, lactation or inadequate contraception,
- age younger than 18 years

chemoradiotherapy group compared to the radiotherapy group was estimated to be 1.56 (95% CI 0.87–2.78; p=0.14).
- When adjusted for stratification variables (M stage and pretreatment dysphagia), the odds ratio for dysphagia relief for chemoradiotherapy versus radiotherapy was estimated to be 1.64 (0.91–2.97; p=0.10).
-Complete dysphagia relief was noted in 32 (29%) patients in the chemoradiotherapy group and in 26 (24%) patients in the radiotherapy group (p=0.44)
- The median time from start of radiotherapy to any relief was 9.1 weeks (IQR 8.6–9.7) in the chemoradiotherapy group and 9.0 weeks (8.3–9.6) for radiotherapy (p=0·46). The median duration of any relief was 3.4 months (IQR 1.3–5.7)for chemoradiotherapy and 2.5 months(1.4–5.3) for radiotherapy (p=0.72)
- The median time from start of radiotherapy to complete relief at any assessment was 9.3 weeks (IQR 9.0–12.0) for chemoradiotherapy and 9.2 weeks (8.9–10.1) for radiotherapy (p=0.37)
<u>dysphagia progression-free survival</u>
- Estimated median dysphagia progression-free survival time from randomisation was 4.1 months (95% CI 3.5–4.8) for chemoradiotherapy

and 3.4 months (3.1–4.3) for radiotherapy
- The hazard ratio (HR) for chemoradiotherapy versus radiotherapy was estimated to be 0.93 (95% CI 0.71–1.21; p=0.58)
overall survival
- Estimated median overall survival from randomisation was 6.9 months (5.1-8.3) for chemoradiotherapy and 6.7 months (4.9-8.0) for radiotherapy, HR=0.98 (95% CI 0.75–1.29; p=0.88)
Secondary treatments
- were given after failure of trial treatment in 117 patients (55 [51%] of 107 patients in the chemoradiotherapy group and 62 [60%] of 104 patients in the radiotherapy group).
- Oesophageal stenting was used in 23 (21%) patients in the chemoradiotherapy group and 32 (31%) patients in the radiotherapy group, whereas additional palliative chemotherapy was administered to 24 (22%) patients in the chemoradiotherapy group and 33 (32%) patients in the radiotherapy group.
adverse events
- of the 211 patients who commenced radiotherapy, grade 3–4 acute toxicity occurred in 38 (36%) patients in the chemoradiotherapy group and in 17 (16%) patients in the

radiotherapy group (p=0.0017). Anaemia, thrombocytopenia, neutropenia, oesophagitis, diarrhoea, nausea and vomiting, and mucositis were significantly worse in patients who had chemoradiotherapy than in patients who had radiotherapy

self-assessment

- 76 patients (39 in the chemoradiotherapy group and 37 in the radiotherapy group) answered a self-assessed dysphagia relief question at 9 weeks (7.1–11.1 weeks)
- Five patients felt their swallowing was worse (clinical response: no change [three], worse [two]).
- Seven patients reported that their swallowing was about the same as before treatment (clinical response: complete dysphagia relief [two], partial dysphagia relief [five]),
- 64 patients reported that their swallowing was better (clinical response: complete dysphagia relief [37], partial dysphagia relief [21], no change [five], worse [one]).
- The self-assessments were similar between the two treatment arms: 34 patients receiving chemoradiotherapy and 30 patients receiving radiotherapy felt better; three patients receiving chemo-radiotherapy and four patients receiving

radiotherapy felt about the same; and two patients receiving chemoradiotherapy and three patients receiving radiotherapy felt worse (p=0.69, trend test)

Author's Conclusion: Palliative chemoradiotherapy showed a modest, but not statistically significant, increase in dysphagia relief compared with radiotherapy alone, with minimal improvement in dysphagia progression-free survival and overall survival with chemoradiotherapy but at a cost of increased toxicity. A short course of radiotherapy alone should be considered a safe and well tolerated treatment for malignant dysphagia in the palliative setting.

Methodical Notes

Funding Sources: This study was funded by the National Health and Medical Research Council of Australia (291103), Canadian Cancer Society Research Institute, Canadian Cancer Trials Group, Trans Tasman Radiation Oncology Group, and Cancer Australia.
The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

COI: - MGP and SS declare grant funding from NHMRC and Cancer Australia.
- JGS received payments for statistical analysis from the primary trial centre.
- All other authors declare no competing interests

Randomization: Patients were randomly assigned to chemoradiotherapy or radiotherapy alone by telephone or fax to the trial centre at the

Royal Adelaide Hospital in Adelaide, SA, Australia. Clinicians, patients, and data managers had no prior knowledge of the treatment arm to which the patients would be assigned. Eligibility was checked and patients were stratified by hospital, dysphagia score (Mellow score 1–4), and presence of metastases before random allocation (1:1) using a computer-generated adaptive biased coin design.

Blinding: no blinding

Dropout Rate/ITT-Analysis: Patients' data were analysed according to their randomised treatment arm (intention-to-treat), except for the exclusion of one patient who was found not to have oesophageal cancer after randomisation. Patients who did not commence any protocol treatment were excluded from the toxicity analyses.

Notes:
evidence level 2: randomised controlled trial

22 Palliative Therapie - Stent und Radio bzw. Radiochemotherapie

Inhalt: *10 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Ahmed, O 2019	1	systematic review
Bakheet, Nader 2019	4	retrospective observational study (Case-series, South Korea)
Helminen, Olli 2019	4	retrospective observational study (Finland and Sweden)
Järvinen, Tommi 2017	4	retrospective, observational study (Finland)
Kjaer, D W 2017	4	retrospective observational study (Denmark)
Lancellotta, V. 2019	2	systematic review
Medeiros, V. S. 2017	4	Retrospective cohort study
Reijm, A. N. 2019	4	Retrospective cohort study.
Sigounas, Dimitrios E 2017	4	Single centre, retrospective cohort study.
Wlodarczyk, J. R. 2018	4	Retrospective cohort study.

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

Ahmed, O et al. Use of esophageal stents to relieve dysphagia during neoadjuvant therapy prior to esophageal resection: a systematic review. Dis. Esophagus. . . 2019

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1	Population: patients with an esophageal cancer diagnosis	Primary: dysphagia	Langer et al. 2010, Ann Surg Oncol

Study type: systematic review Databases: - Embase, Medline, PubMed, PubMed Central and Cochrane library - bibliographies of selected articles - review of the 'related citations' in PubMed Search period: up to and inclusive of November 2018 Inclusion Criteria: - Studies involving patients with an esophageal cancer diagnosis undergoing metallic or plastic esophageal stent insertion preintervention as compared with standard care - Original publication (reviews, opinions, letters, protocols and conference proceedings excluded) - Reported outcome measures on at least one of: morbidity, mortality, readmission/reintervention rates, oncologic outcomes Exclusion Criteria: - case reports, review articles and studies reporting on the	undergoing stent insertion prior to resection with curative intent Intervention: self-expanding metallic stents (SEMS) or self-expanding plastic stents (SEPS) Comparison: standard care	Secondary: oncological outcomes, survival Results: 9 studies included in analysis with a total of 465 patients - Esophageal stents were inserted in all patients with a post procedural morbidity rate ranging from 3–55%. <u>dysphagia/nutrition</u> - Six studies reported on patient dysphagia and swallowing status prior to and after esophageal stent insertion - significant improvement in mean dysphagia grades from 2.88 to 0.66 (P<0.01) in the immediate post stent period. - Albumin levels dropped from a mean value of 3.7 g/dL to 3.5 g/dL post stent insertion but failed to achieve statistical significance (P=0.43). - mean weight loss of 4.3 kg post stent insertion, however, there was no significant difference on statistical analysis (P=0.64). surgery - Of 352 stented patients, 117 were suitable for a potential curative resection. The most common reason for not proceeding to surgery was disease progression <u>Oncological outcomes</u> - Surgical margin status was assessed in 3 papers.	Lopes et al. 2010, Dis Esophagus Brown et al. 2011, J Am Coll Surg Pellen et al. 2011, Dis Esophagus Mariette et al. 2015, J Am Coll Surg Francis et al. 2016, Int J Radiat Oncol∗Biol∗Phys Min et al 2017, PloS One Smith et al. 2017, Dig Dis Sci Lu et al. 2018, Oncologist

efficacy of biodegradable stenting where the outcomes of metallic and plastic stenting could not be separated
- Studies focussing on palliative stenting in esophageal malignancy, postoperative patients or patients with recurrent disease were also excluded
- Patients not suitable for operative resection
- Recurrent esophageal cancer
- Papers where data was unavailable or uninterpretable and authors uncontactable
- Papers in languages other than English
- Nonhuman studies

The rate of margin positivity (R1 or R2) was 29%, 20% and 0% in these studies.

Survival data

- Overall survival data were available for 4 studies (median OS: range 10–96 months)
- Survival was significantly superior in a comparative gastrostomy group in one study (P=0.007) and a control group of nonstented patients in the remaining 3 studies (P=0.026,).
- Three-year survival was significantly reduced ina SEMS group of 38 patients when compared to the no stent group (28% vs 44%, P=0.043).

Author's Conclusion: This systematic review has shown that although esophageal stents are associated with improvements in dysphagia during neoadjuvant therapy, they do not improve nutritional markers in the preoperative setting and may be associated with poorer long-term oncological outcomes. Stents should not be routinely used in patients who are being considered for resection with curative intent for esophageal malignancies. Instead nutritional needs can be met using total parenteral nutrition, nasoenteral feeding or percutaneous enteral feeding. Although these have no effect on dysphagia, they may be more likely to meet the

nutritional requirements of patients without the possibility of compromising oncological outcomes. Direct comparison of these strategies would be beneficial in a well-designed randomized controlled trial.

Methodical Notes

Funding Sources: no statement

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

Study Quality: - Study methodological quality was assessed by applying the Methodological Index for Non-Randomized Studies (MINORS)
- Four studies out of nine in this review were conducted prospectively and 3 studies reported on a comparative patient cohort. The 9 studies achieved a median MINORS score of 16 (mean score of 15 for the non-comparative studies and 18 for the comparative analyses).

Heterogeneity: - association of categorical variables (differences for dichotomous variables between groups) was assessed using a chi-square (X2) test.
- results of X2 test not described, but considerable heterogeneity assumed

Publication Bias: not assessed

Notes:
Article submitted by hand search.
evidence level 1: systematic review
- population does not comply with PICO

Lancellotta, V. et al. The role of palliative interventional radiotherapy (brachytherapy) in esophageal cancer: An AIRO (Italian Association of Radiotherapy and Clinical Oncology) systematic review focused on dysphagia-free survival. Brachytherapy. . . 2019

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 2 Study type: systematic review Databases: PubMed, Scopus, and Cochrane library, ClinicalTrials.gov, PROSPERO Search period: Time restriction (1990-2018) as concerns the years of the publication was considered Inclusion Criteria: - full text articles with patients with symptomatic esophageal cancer treated with IRT alone or in combination with other treatment (e.g., external beam radiation therapy, stenting, laser, and so forth) - Time restriction (1990-2018) as concerns the years of the publication was considered Exclusion Criteria: Conference paper, survey, letter, editorial, book chapter, and reviewwere excluded.	Population: patients with symptomatic esophageal cancer treated with IRT alone or in combination with other treatment (e.g., external beam radiation therapy, stenting, laser, and so forth) Intervention: interventional radio-therapy (IRT) Comparison: other treatments (EBRT, PDT, argon plasma coagulation, stent and laser)	Primary: duration of dysphagia relief (dysphagia-free survival, DyFS) Secondary: overall survival and adverse event rates Results: - seven randomized studies including 905 patients, with a median age was 70.5 years - In the IRT group, the median DyFS was 99 days showing a longer duration of palliation compared with all other techniques; the most relevant G3-G4 toxicity was fistula development and stenosis reported, respectively, in 8.3% and 12.2%; the overall median survival was 175.5 days. Author's Conclusion: In conclusion, we provided evidence-based support that IRT is an effective and safe treatment option; therefore, its underuse is no longer justified. IRT is not available in all Italian or European RT departments; hence, a collaboration between radiotherapy centers could be useful to ensure access to all patients who	Homs et al, Lancet 2004 Steyerberg et al, Gastrointest Endosc 2005 Spencer et al, Gut 2002 Sander et al, Gastrointest Endosc 1991 Sur et al, Brachytherapy 2004 Rosenblatt et al, Radiother Oncol 2010 Rupinski et al, Am J Gastroenterol 2011

have the indication to the IRT. Further randomized controlled studies should investigate the optimal radiation dose and number of fractions to obtain the highest dysphagia-free survival rates and the lowest risk of severe adverse events.

Methodical Notes

Funding Sources: no statement

COI: The authors declare no conflicts of interest.

Study Quality: not assessed

Heterogeneity: not assessed

Publication Bias: not assessed

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

NEWCASTLE - OTTAWA Checklist: Case Control: *1 Bewertung(en)*

Järvinen, Tommi et al. Preoperative stenting in oesophageal cancer has no effect on survival: a propensity-matched case-control study. Eur J Cardiothorac Surg. 52. 385-391. 2017

Evidence level	Methodical Notes	Patient characteristics	Interventions

Evidence level: 4 Study type: retrospective, observational study (Finland)	Funding sources: Heart and Lung Centre grant, Helsinki University Hospital, Helsinki, Finland Conflict of Interests: nothing to declare Randomization: none Blinding: none Dropout rates: none	Total no. patients: study population of 174 patients Patient characteristics: January 2006 and January 2014 Inclusion criteria: oesophageal cancer patients undergoing surgery between January 2006 and January 2014 with a cT2 tumour or higher Exclusion criteria: patients with cT1 disease	Interventions: self-expanding covered metallic stent (SEMS) before oesophagectomy for oesophageal cancer Comparison: control group who underwent surgery without SEMS insertion

Article submitted by hand search
evidence level 4: retrospective, observational study

Notes:

Author's conclusion: In conclusion, our study shows that in EC of at least stage T2, SEMS insertion prior to oesophagectomy has no statistically significant effect on OS, recurrence rates or times or complication rates. Preoperative stent insertion may increase overall operative time, but it does not seem to affect the total complication rate, recurrence rate or overall or progression-free survival. Serious early and intraoperative complication subgroups may be affected, but our study is not powered to adequately assess this effect. Therefore, after weighing the potential operative risks and difficulties, stenting seems to be a viable option for securing the nutrition of EC patients in some of the more advanced cases of the disease.

Outcome Measures/results	Primary overall survival (OS) Secondary overall recurrence, postoperative complication rates and operative time.	Results: <u>propensity matching</u> - patients were propensity matched 1:1 in a preoperative SEMS group (n=30) to a control group (n=144 before, n=30 after matching). - Before matching, the standardized differences were significant in age, 3-month weight loss, ECOG performance status, smoking history, cT stage and neoadjuvant

treatment.
- After matching, residual covariate imbalances (d> 0.1) were evident in gender, ECOG performance status, cT stage and histologic type of the tumour. No differences were statistically significant.

Overall survival, progression-free survival and recurrence
- Median OS of the study population was 32.5 months (range: 0–118 months). Median survival in the SEMS insertion group was 28.5 months (0–116 months) and in the control group, 34 months (4–118 months); (P=0.748)
- median PFS was 22 months (0–111 months) vs 27 (4–113 months);(P=0.758). PFS after 2 years of follow-up was 53.3% in the SEMS group and 56.7% in the control group (P= 1.0).
- Median total recurrence rates were 36.7% in the SEMS insertion group versus 43.3% in the control group (P= 0.752)

Postoperative events and operative time
- Differences in complication groups or subgroups were non-significant
- Mean operative times between the groups (436 min vs 375 min) were significantly different (P=0.017).

Complications related to SEMS-insertion
- Two patients suffered oesophageal perforations related to SEMS insertion
- In 10% (n=3) of the SEMS insertion group, the stent had migrated to the stomach during the neoadjuvant treatment

NEWCASTLE - OTTAWA Checklist: Cohort: *7 Bewertung(en)*

Bakheet, Nader et al. Clinical effectiveness and safety of self-expanding metal stent placement following palliative chemotherapy in patients with advanced esophageal cancer. Abdom Radiol (NY). . . 2019

Evidence level	Methodical Notes	Patient characteristics	Interventions

Evidence level: 4 Study type: retrospective observational study (Case-series, South Korea)	Funding sources: This study was supported by a Grant from the Korean Health Technology R&D Project, Ministry of Health and Welfare, Republic of Korea (Grant No. HI15C0484 to H.Y.S.) Conflict of Interests: The authors declare that they have no conflicts of interest. Randomization: none Blinding: none Dropout rates: none	Total no. patients: study population n =105 Recruiting Phase: patients treated between January 2002 (time of development of retrievable esophageal stent) and January 2018. Inclusion criteria: documented unresectable primary esophageal malignancy who had esophageal SEMS placement, with or without receiving prior chemotherapy Exclusion criteria: - Patients who received radio-therapy, concurrent chemoradiotherapy, or who were receiving chemotherapy at the time of SEMS placement	Interventions: self-expanding metal stent (SEMS) only Comparison: self-expanding metal stent (SEMS) after palliative chemotherapy (regimens included platinum-based drugs, such as cisplatin/5-fluorouracil (5-FU), cisplatin/capecitabine, or oxaliplatin/fluoropyrimidine)

Notes:

Article submitted by hand search.
evidence level 4: retrospective observational study

Author's conclusion: In conclusion, prior chemotherapy did not increase the risk of complications following SEMS placement in patients with locally advanced esophageal cancer.

Outcome Measures/results	Primary Technical success clinical improvement (dysphagia score) clinical success (improvement of dysphagia score by 1 point, within 3 days after stenting) Secondary Complications Overall survival Median follow-up	Results: - group A (n=41) received only SEMS as palliative therapy, and group B (n=64) received chemotherapy prior to SEMS placement. <u>Technical and clinical outcomes</u> - SEMS placement was technically successful in all patients and no major complications occurred during the procedure. - The mean dysphagia score improved significantly after SEMS placement in group A (3.15±0.57 to 1.17±0.83; p < 0.001) and group B (3.17±0.80 to 1.14±0.79; p <0.001), with no significant difference in the degree of improvement seen between the groups (p=0.66). - Clinical success was achieved in 39 of 41 patients in group A (95.1%) and 62 of 64 patients in group B (96.8%). <u>Complications</u> - In group A, 10 complications occurred 6–345 days (median 65 days) after SEMS placement. In group B, 24 complications occurred 1–296 days (median 82.5 days) after SEMS placement, No significant difference between the two groups (p=0.094) <u>patient survival</u> - mean SEMS patency was 339 days (95% CI 258.8–419.3) in group A, which was significantly longer than the duration seen in group B (162 days; 95% CI 126.6–198.4), p=0.00 - median and mean overall survival periods were 105 (95% CI 30–180) and 132 days (95% CI 97–167), respectively, in group A, and 126 (95% CI 88–164) and 156 days (95% CI 132–180), respectively, in group B -No significant differences in mean overall survival period between the two groups (p=0.592)

Helminen, Olli et al. Preoperative esophageal stenting and short-term outcomes of surgery for esophageal cancer in a population-based study from Finland and Sweden. Dis. Esophagus. 32. . 2019

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 4 Study type: retrospective observational study (Finland and Sweden)	Funding sources: This study was supported by Finnish State Research Funding (OH), the Instrumentarium Science Foundation (OH), the Sigrid Juselius Foundation (JHK), the Orion Research Foundation (JHK), the Swedish Research Council (JL) and the Swedish Cancer Society (JL), the Finnish Cardiac Society (VK), and the Finnish Cultural Foundation (VK). Conflict of Interests: The authors declare no conflicts of interest Randomization: none Blinding: none Dropout rates: none **Article submitted by hand search.** evidence level 4: retrospective observational study	Total no. patients: 1029 (63.8%) were selected for this study (Finland n=338, Sweden n=691) Recruiting Phase: from January 1, 2007, to October 2, 2014 Inclusion criteria: patients with a confirmed locally advanced esophageal cancer (T≥3 and/orN≥1, M0) Exclusion criteria: not described	Interventions: esophageal stenting prior to esophagectomy Comparison: esophagectomy only
Notes:	Author's conclusion: In conclusion, this population-based study from Finland and Sweden suggests that 30- and 90-day mortality might be increased when preoperative stenting is used in patients with locally advanced esophageal cancer, although the increased point risk estimates were not statistically significant. The results may be used in future meta-analyses.		
Outcome Measures/results	Primary 30- and 90-day mortality	Results: - patients with preoperative esophageal stent: Finland n=49, Sweden n=78; without: Finland n=289, Sweden n=613	

Secondary length of hospital stay and 30- and 90-day readmission rates.		<u>mortality</u> - absolute 30-day mortality rate was 3.9% in patients with a preoperative stent, and 1.6% in those without. The adjusted HR of 30-day mortality was not statistically significantly increased (HR 2.42; 95% CI 0.85–6.92) - absolute 90-day mortality rate was 11.8% in patients with a preoperative stent, and 7.0% in patients without. The adjusted HR of 90-day mortality was not statistically significantly increased (HR 1.68; 95% CI 0.95–2.98) <u>secondary outcomes</u> - median length of hospital stay after esophagec-tomy was 15 days in patients with a preopera-tive esophageal stent, and 16 days in those without (not statistically different) - readmission rate within the first 30 postoperative days was 13.1% in stented patients and 11.4% in patients without a stent (not statistically different) - readmission rates within 90 days of surgery were 33.9% and 32.8%, respectively (not statistically different)

Kjaer, D W et al. A bridging stent to surgery in patients with esophageal and gastroesophageal junction cancer has a dramatic negative impact on patient survival: A retrospective cohort study through data acquired from a prospectively maintained national database. Dis. Esophagus. 30. 1-7. 2017

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 4 Study type: retrospective observational study (Denmark)	Funding sources: no statement Conflict of Interests: no statement	Total no. patients: 273 patients were included for evaluation, 63 in stent group, 210 in control group (no stent)	Interventions: preoperative stenting without neoadjuvant chemotherapy in patients suffering from esophageal and GEJ cancers who later underwent R0 resection (stent group, SG)

	Randomization: none Blinding: none Dropout rates: none	Recruiting Phase: 1st January 2003 and 31st December 2010 Inclusion criteria: - all consecutive patients who underwent an R0 resection for esophageal and GEJ cancer Exclusion criteria: - patients treated with neoadjuvant chemotherapy - TNM-classification was less than pT2N0M0	Comparison: no stenting before surgery (no stent group, NSG)

Article submitted by hand search.
evidence level 4: retrospective observational study

Notes:

Author's conclusion: In conclusion, stenting as a bridge to surgery in patients with obstructing esophageal or GEJ cancer should not be recommended because this therapy results in decreased recurrence-free survival and decreased median survival.

Outcome Measures/results	Primary survival and recurrence free period Secondary none	Results: - The overall 30-day mortality was 2.2% (6/273) in the total patient group, 1.6% (1/63) in the SG and 2.4% (5/210) in the NSG (P=0.706). - overall two-year survival was 43.2% (118/273). The two-year survival was significantly lower in the SG (30.1% vs. 47.1%; P=0.017). - The overall median survival was 20.1 months. The median survival times for the SG and the NSG groups were 11.6 months and 21.3 months with a statistical significant adjusted hazard ratio of 1.78 for having stent (P=0.003) - Data regarding the recurrence of esophageal or GEJ cancer were obtained in 258 of the

		273 patients. Of the 258 patients, a total of 153 suffered recurrence, and there was no difference in recurrence rates between the groups. - The median time for recurrence of esophageal or GEJ cancer was 9.1 months for the SG and 15.2 for the NSG with a hazard ratio of 1.46 for having a stent, but adjusting for the listed variables, having a stent was not a significant hazard (0.076)	

Medeiros, V. S. et al. Adverse events of self-expandable esophageal metallic stents in patients with long-term survival from advanced malignant disease. Gastrointest Endosc. 86. 299-306. 2017

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 4 Study type: Retrospective cohort study	Funding sources: All authors disclosed no financial relationships relevant to this publication. Conflict of Interests: All authors disclosed no financial relationships relevant to this publication. Randomization: - Blinding: - Dropout rates: -	Total no. patients: 63 Recruiting Phase: February 2009-February 2014 Inclusion criteria: Patients submitted to esophageal stent for palliation of malignant strictures or malignant fistulas between February 2009 and February 2014 at the Cancer Institute of the University of São Paulo. Only patients who remained with the stent longer than 6 months were included in the analysis. Exclusion criteria: Patients with benign stenosis or fistula because of anastomotic leakage were excluded.	Interventions: self-expandable esophageal metallic stent implantation Comparison: -
Notes:	**Article submitted by hand search.** Very little information regarding inclusion criteria. Evidence level 4: retrospective follow-up study.		

		Author's conclusion: "AEs are common in patients with long-term esophageal stenting for malignancy. However, AEs were not related to higher mortality rate, and most AEs could be successfully managed by endoscopy. Only performance status was a risk factor for AEs. Our data suggest that metallic stenting is a valid option for the treatment of malignant esophageal conditions, even when survival longer than 6 months is expected."
Outcome Measures/results	Primary Adverse events. Secondary Management of stent dysfunction, Risk factors for AEs	Results: **Patient characteristics:** From February 2009 to February 2014, 250 patients were submitted to esophageal stent insertion and 63 patients were included. Predominantly men (74.6%), mean age was 61.4 years (range, 42-79). Performance status according to the Eastern Cooperative Oncology Group (ECOG) was 0 (n = 10), 1 (n = 26), 2 (n = 18), and 3 (n = 9). The most common cancer was squamous cell carcinoma (80.9%), and most lesions were located in the middle esophagus (53.9%). Regarding stents placed initially, 56 were partially covered (88.8%) and 7 were fully covered. The indication for stent placement was dysphagia because of esophageal malignancy in 49 patients (77.7%), malignant fistula in 8 patients (12.6%), dysphagia associated with fistula in 4 patients (6.3%), and extrinsic compression in 2 patients (3.1%). Clinical success was achieved in all patients. The median stent patency (until death or stent dysfunction) was 7.1 months (standard deviation, ±3.8). Only 4 patients had their stent removed during the follow-up. Mean follow-up time was 10.7 months (range, 6.1-25). At the end of follow-up, 37 patients (58.7%) had a functioning stent and were accepting oral intake. **Results: Primary:** AEAEs occurred in 40 patients (63.5%). 16 patients had more than 1 AE, and 5 patients had recurrence of a previously treated AE. There were a total of 62 AEs, with a mean of 1.5 AEs per patient. Five AEs occurred within 30 days of stenting, 18 occurred between 30 and 180 days, and 39 occurred after 180 days (P = .042). Most AEs (n = 47, 75.8%) were minor and included severe pain (1), severe reflux (1), migration (9), ingrowth/ overgrowth (32), and food impaction (4). There

were 15 major AEs: 13 esophageal fistulas and 2 bleedings. Endoscopic treatment was attempted in 9 of 15 major AEs, with success in 6. Three major AEs were fatal: 2 patients had esophagorespiratory fistulas and died from pulmonary sepsis and 1 died because of tumor bleeding. **Secondary:** Endoscopic management of AEs was successful in 84.5% of cases, with a mean of 1.6 reinterventions per patient. Risk factors for AEs: The univariate analysis revealed that performance status, age, and post-stent radiotherapy presented a trend to higher risk of AEs. The multivariate analysis revealed that only performance status was associated with AEs (P = .025; hazard ratio, 4.1).

Reijm, A. N. et al. Self-expandable metal stent placement for malignant esophageal strictures - changes in clinical outcomes over time. Endoscopy. 51. 18-29. 2019

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 4 Study type: Retrospective cohort study.	Funding sources: not adressed. Conflict of Interests: Prof. Bruno has received personal fees as lecturer and consultant. Reports having received institutional financial support for industry and investigator initiated studies from Boston Scientific, Cook Medical, Pentax Medical and 3M. Prof. Siersema has received research support from Ella-CS, Boston Scientific USA and Cook Medical Ireland. Dr. Spaander has received institutional financial support for investigator initiated studies from Boston Scientific. The remaining authors have no competing interests to report.	Total no. patients: 997 Recruiting Phase: 1994 and 2017 Inclusion criteria: Between 1994 and May 2017 with palliative intent for malignant dysphagia due to an esophageal or cardiac obstruction were included. In addition, patients with a malignant stricture at the anastomosis after esophagectomy with gastric pull-up surgery or with a concomitant fistula were enrolled. Eligible subjects were identified from the esophageal stent database of the Department of Gastroenterology and Hepatology of the Erasmus University Medical	Interventions: Endoscopic SEMS placement: Comparison: -

	Randomization: - Blinding: - Dropout rates: 6 patients were excluded because they were lost to follow-up, leaving 997 patients for the analysis.	Center (Rotterdam, The Netherlands) which serves a tertiary referral center. Endoscopy registries and clinical studies were also reviewed. Exclusion criteria: Patients who received a self-expandable plastic stent were excluded.

Article submitted by hand search.
Evidence level 4: retrospective follow-up/cohort study.

Notes:

Author's conclusion: Despite the introduction of novel esophageal SEMS designs, recurrent dysphagia has not declined over the years. Stent-related complications have increased in recent years, which seems to be mainly associated with more frequent use of chemoradiotherapy prior to SEMS placement.

Outcome Measures/results	Primary Clinical efficacy and safety of esophageal SEMS placement in terms of recurrent dysphagia and other SEMS-related adverse events and to assess shifts in their occurrence over time. Secondary Risk factors for recurrent dysphagia and SEMS-related adverse events, technical success rate, improvement of dysphagia, and survival.	Results: **Patient characteristics**: A SEMS was inserted in 1003 patients. Six patients were excluded because they were lost to follow-up, leaving 997 patients for analysis. All patients had dysphagia≥2 before SEMS placement, including 106 patients with a concomitant fistula. In the last two time periods (TPs), 65% of patients had been pretreated with chemotherapy and/or radiotherapy, compared with 40% in the previous previous periods ($P < 0.01$). In all subjects with prior concomitant chemoradiotherapy, SEMS placement was performed after the treatment had finished. In these patients, SEMS placement was performed for recurrent or residual malignant obstructive disease. The proportion of patients with more distally located disease (i. e. distal esophagus/cardia) seemed to decrease over time, from 64% in TP1 –3 to 55% in TP4–6 ($P < 0.01$). Overall, 11 different

types of SEMS were used, and these were not equally divided among the six TPs. Ultraflex
(Boston Scientific, USA) was most frequently used (354 patients; 35.5%). The median length was 12cm (range 7 – 17). A stent with a regular body diameter (up to 20mm) was used in 92.2% of the SEMS placements. In TP5 and TP6, only regular-diameter SEMSs were used. A partially covered SEMS was inserted in 58.3% of the SEMS placements. In TP4, the proportion of fully covered SEMSs increased to 61.6%.
Results: Primary: Recurrent dysphagia: Recurrence of dysphagia occurred in 309 of 997 patients (31%) and remained stable, although with a trend towards
an increase over time (hazard ratio [HR] 1.02 per 1- year increase; P = 0.05). Migration rate significantly increased over time (HR 1.04 per 1-year increase; P = 0.01).Complications: SEMS-related complications occurred in 461 patients
(46.2 %), with 207 (20.7%) major and 336 (33.7%) minor complications. Prior chemoradiotherapy was significantly associated with major complications (HR 1.69; P < 0.001). Pain was the most common adverse event and showed a significant increase over time (P < 0.01). Factors associated with pain were prior chemoradiotherapy, absence of a fistula, axial and radial forces, and squamous cell carcinoma. Survival: Overall median survival was 92 days (range 1 – 2963). At the end of follow-up, there were 22 patients (2.2 %) who were still alive. Most patients died as a result of tumor progression (n = 903; 90.6%), while 22 patients (2.2%) died because of a stentrelated complication. No significant difference in survival was detected between the six TPs (P = 0.11).

Sigounas, Dimitrios E et al. Argon plasma coagulation compared with stent placement in the palliative treatment of inoperable oesophageal cancer. United European Gastroenterol J. 5. 21-31. 2017

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 4 Study type: Single centre, retrospective cohort study.	Funding sources: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors Conflict of Interests: None declared. Randomization: - Blinding: - Dropout rates: Patients lost to follow-up or with incomplete staging or treatment data were excluded. 24 were excluded due to missing data. The majority of these were lost-to follow-up.	Total no. patients: 228 Recruiting Phase: 01/2000 - 01/2014 Inclusion criteria: All patients who were diagnosed with inoperable oesophageal or oesophago-gastric junction cancer (Siewert type I) between January 2000 and July 2014, and received either argon plasma coagulation APC or self-expandable metal stent SEMS were considered eligible for inclusion in this study. Patients intolerant to the initial chemotherapy treatment, not being able to conclude a cycle of therapy, were also included since a single dose of chemotherapy was not considered as significant to alter the outcome. Exclusion criteria: Patients who received chemotherapy or radiotherapy either before or after SEMS or APC were excluded. Patients lost to follow-up or with incomplete staging or treatment data were or with incomplete staging or treatment data were excluded.	Interventions: argon plasma coagulation APC Comparison: self-expandable metal stent SEMS
Notes:	**Article submitted by handsearch.** Evidence level 4: retrospective cohort study.		

Author's conclusion: "APC is a promising palliation modality in inoperable oesophageal cancer, when patients are not candidates for chemo-radiotherapy. A randomized controlled trial will be needed to confirm those results."

Outcome Measures/results	Primary Survival. Secondary -	Results: **Patient characteristics:** Between January 2000 and July 2014 a total of 388 patients received a diagnosis of inoperable oesophageal cancer and were treated with a palliative modality.160 were excluded because they were initially treated with chemotherapy, radiotherapy or laser. 50 patients (10 in APC group and 40 in SEMS group) were also excluded due to inadequate staging data. 24 patients were also excluded due to inadequate data regarding their treatment. Of the remaining 228 patients, 68 were treated with APC as a primary modality and 160 were treated with SEMS. 6/228 (2.6%) patients still alive at the end of follow-up, 5 of whom were treated with APC and one with SEMS. Patients in APC groups were older and with a higher Charlson comorbidity score. Those differences were statistically significant. **Results: Primary** overall median survival was 257 (IQR: 485, 135) and 102 (188, 41) days in the APC and SEMS group respectively. Patients treated with APC had significantly better median survival (log rank p<0.001). Comparisons between treatment groups for patients belonging to less advanced stages were not performed due to small numbers, especially in SEMS group. The overall median survival of stage III patients was 158 days (IQR: 285, 84). Stage III patients treated with APC had a median survival of 257 days (IQR: 414, 124), while patients treated with SEMS had a median survival of 151 days (IQR: 241, 61). Survival of patients treated with APC was significantly better (log rank p = 0.02). Stage IV patients had an overall median survival of 83 days (IQR: 158, 32). Median survival of the APC group in stage IV disease was 135 days (IQR: 238, 43), while patients treated with SEMS had a median survival of 70 days (IQR: 148, 32). The difference was statistically significant (log rank p = 0.05). Type of treatment was the only statistically significant factor affecting survival, after disease stage stratification (hazard ratio (HR): 1.36, 95% confidence interval (CI): 1.13–1.65 of SEMS over APC, p: 0.002).

Wlodarczyk, J. R. et al. Stenting in Palliation of Unresectable Esophageal Cancer. World J Surg. 42. 3988-3996. 2018

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 4 Study type: Retrospective cohort study.	Funding sources: see COI section Conflict of Interests: Both authors "have no conflicts of interest or financial ties to disclose." Randomization: - Blinding: - Dropout rates: 2/456 (.4%) died from stenting complications, 14/456 (3.0%) were lost to follow-up	Total no. patients: 456 Recruiting Phase: 2008 - 2015 Inclusion criteria: All patients treated in the period 2008–2015 for unresectable or medically inoperable esophageal or (OGJ) cancer, regardless of histological type. Exclusion criteria: Preterminal condition, Karnofsky score B 40%; Patients with mediastinal infiltration causing dysphagia in the course of lung cancer, lymphomas and other malignancies.	Interventions: Esophageal stenting due to unresectability of the tumor or medical inoperability Comparison: -
Notes:	Evidence level 4: Retrospective cohort study. Author's conclusion: "Stenting is an effective procedure in relieving dysphagia in patients with unresectable malignant esophageal stenosis and is associated with low rate of postoperative and long-term complications."		
Outcome Measures/results	Primary safety and efficacy (complications, re-interventions and survival).	Results: *Study characteristics:* Final analysis set included homogenous group of 442 eligible patients with esophageal or OEJ cancer, who underwent esophageal stenting procedure. Patients presented with body weight loss from 4 to 40 kg, dysphagia, cough and cachexia. The mean length of neoplastic	

		infiltration in the esophagus was 5.9 cm (range
Secondary	no description	4–12 cm). In 40 (9.0%) patients, stenting of the upper segment of the esophagus was performed. In 150 (39.3%) patients, stenting was performed in the middle part of the esophagus, in 141 (31.9%)—in the lower thoracic part of the esophagus and in 111 (25.1%)—in the OGJ. 19 (4.3%) patients had primary fistula to the mediastinum or the airway. 15 (3.04%) patients with fistula developed after the stenting procedure. Adjuvant CRT was administered to 201 (45.5%) patients. **Results:** Technical success rate: the technical success rate was 99.4%. Dysphagia relief: After stenting procedure, swallowing improvement was observed in all the patients. The mean dysphagia score improved from 3.0 (range 2–3) before stenting to 1 (range 1–2) after the stenting procedure (p = 0.00001). Minor complications included chest pain (54.5%), delayed complete stent expansion (12.0%), feeling of a foreign body (25.3%), hiccup (1.6%), gastro-esophageal reflux (45.6%) and post-discharge pneumonia (2.5%). A feeling of a foreign body in the esophagus was significantly more common after stenting of the cervical esophagus (p = 0.0001), and hiccup was more common after stenting of the esophagogastric junction (p = 0.02). Major complications included bleeding (1.3%), respiratory insufficiency (0.7%), esophageal perforation (0.9%) and irregular heartburn (2.3%). Late complications: In 18 (4.1%) patients, migration of the stent occurred. Overall procedure-related mortality was 0.4%. The median survival time was 117.8 days (range 2–732)Suvival: Follow-up period ranged between 1 - 732 days. Median survival time was 117.8 days (range 2–732). Median survival time was longer in patients with SCC than with adenocarcinoma: 158 (range 2–732) versus 110 (range 38-221) days (p = 0.06). Median survival time in patients with OAF was 74.5 days (range 41–432). Esophago-airway fistula Esophago-airway fistula (OAF) was found in 34 (7.7%) patients. 19 (4.3%) patients had OAF at presentation, and in 15 patients, it developed after stenting.