Inhaltsverzeichnis der Evidenztabellen

Schlüsselfrage:

AG 1 <u>Risikofaktoren:</u> Wird das Ösophaguskarzinomrisiko (SCC AC) durch einen der folgenden Faktoren beeinflusst?

Citation	Evidence Level	Study Type
Vinogradova, Y. 2013	3b	Series of nested case-control studies
Levi, Z. 2013	2b	Cohort study
Pottegard, A. 2013	3b	population-based case-control study
Cooper, S. 2014	3b	Nested-case control study
Feng, X. S. 2014	2b	Prospective Cohort Study
Alexandre, L. 2014	3b	Case-control study
Hvid-Jensen, F. 2014	3b	Nested case-control study
Masclee, G. M. 2014	2b	dynamic population-based retrospective cohort study
Jia, N. 2014	2b-	Retrospective Cohort Study
Agrawal, S. 2014	3b-	Retrospective case-control study
Lindkvist, B. 2014	2b	Prospective cohort study
Moura, M. A. 2014	3b	case-control study
Cook, M. B. 2015	2b	Prospective Cohort Study
Hazelton, W. D. 2015	2b	Cohort Study
Wienecke, A. 2015	1b-	Cohort Study
Bhat, G. A. 2015	3b	Case-control study
Buckland, G. 2015	1b	prospective cohort study
Chen, T. 2015	3b	population-based case-control study
Rafiq, R. 2016	3b	Case-control study
Sewram, V. 2016	3b	hospital-based Case-Control Study
Thota, P. N. 2016	1b-	Retrospective Cohort Study
Kestens, C. 2016	2b	Retrospective population-based cohort study
Krishnamoorthi, R. 2016	1b	population-based cohort study
Zakaria, D. 2017	2b-	Cohort Study
Nguyen, T. 2017	2b	Retrospective cohort study
Ji, J. 2017	2b	Retrospective cohort study
Busby, J. 2017	3b	Nested case-control study
Cook, M. B. 2017	2b	Cohort study

Evidenztabellen

zurück

Schlüsselfrage:

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

Bewertungsvorlage:

NEWCASTLE - OTTAWA Checklist 4: Cohort

Buckland, G. et al. Healthy lifestyle index and risk of gastric adenocarcinoma in the EPIC cohort study. Int J Cancer. 137. 598-606. 2015			
Evidence level	**Methodical Notes**	**Patient characteristics**	**Interventions**
Evidence level: 1b **Study type:** prospective cohort study	**Funding sources:** SANCO, German Cancer Aid, German Cancer Research Centre, German Federal Ministry of Education and Research, Danish Cancer Society, Dutch Cancer Registry, CIBERESP, The Spanish Ministry of Health, Spanish Regional Governments of Andalusia, Asturias, Basque Country, Murcia; ICO-IDIBELL, Cancer Research UK, Medical Research Council UK, Hellenic Health Foundation, Italian Association for Research on Cancer, Italian National Research Council, Dutch Ministry of Public Health, Welfare and Sports; Dutch Ministry of Health, Dutch Prevention Funds, LK Research Funds, Dutch ZON, WCRF, Swedish Cancer Society, Swedish Scientific Council, Regional Government of Skane, Västerbotten, Sweden; Research Council of Norway, Helga, Associazione Italiana per la Ricerca sul Cancro-AIRC **Conflict of Interests:** not reported **Randomization:** - **Blinding:** - **Dropout rates:** Not relevant, drop out was exclusion criteria	**Total no. patients:** 461 550 participants 662 gastric adenocarcinomas **Recruiting Phase:** aged 25-70 years, recruited between 1992 and 2000 mainly from the general population **Inclusion criteria:** general population of France, Italy, Spain, United Kingdom, The Netherlands, Greece, Germany, Sweden, Denmark, Norway (Not further described) **Exclusion criteria:** for cases: gastric lymphomas, nonadenocarcinoma GC all: incomplete follow-up, missing dietary and lifestyle data, ratio for energy intake *versus* energy expenditure in the top and bottom 1%, missing information for the components used to construct the healthy lifestyle index	**Interventions:** healthy lifestyle index (combining smoking status, alcohol consumption, diet quality evaluated on the basis of adherence to the Mediterranean dietary pattern and body mass index) **Comparison:** -
Notes:	**NOS-rating: 6/8 stars** -part of anthropometric data is based on self-reports (risk of bias) -dietary questionnaire regarding Mediterranean diet for central-/nothern european countries -BMI as a factor to assess obesity/overweight without considering body fat percentage **Author's conclusion:** Results indicate that following a combination of modifiable healthy lifestyle behaviors could dramatically decrease the burden of gastric cancer. These findings are particularly relevant considering the very poor relative survival rate for GC (25% at 5-years), which is reported to be worse for cardia GC (20% at 5-years) compared to non-cardia GC (31% at 5-years). Understanding the impact of combined lifestyle habits on GC risk further underscores the importance of health promotion strategies to eradicate cigarette smoking, reduce overweight/obesity, limit alcohol consumption if consumed and improve diet quality.		
Outcome Measures/results	**Primary** -(Cox proportional hazards regression models and hazard ratios (HR)) associations between healthy lifestyle index and GC **Secondary** -(Population attributable risk (PAR) fractions) proportion of GC cases that could have been avoided, assuming a causal relationship, if all the studied population had been in the healthiest category for all the healthy lifestyle behaviors within the index	**Results:** -Never smoking/quitting more than 10 years previously compared with smokers was associated with decreased risk of overall GC (HR 0.64%, 95% CI 0.54-0.75), noncardia GC (HR 0.67, 95% CI 0.53-0.86) and cardia GC (HR 0.56, 95% CI 0.41-0.75) -Strong inverse association between alcohol intake and overall GC, especially noncardia GC (HR 0.74, 95% CI 0.56-0.97), but no association was observed for cardia GC -High compared with low rMED score (Mediterranean diet) was only significant related to cardia GC (HR 0.61, 95% CI 0.38-0.97) -For BMI a normal compared with non-normal weight was not associated with	

		overall or noncardia GC, but there was a lower, albeit nonsignificant risk of cardia GC -Overall healthy lifestyle index was related to a large significant reduction in GC risk, reaching a 51% (95% CI 30% to 65%) lower risk associated with participants scoring 3 points (following all three healthy behaviors) compared with none. -There was no evidence of effect modification by sex PAR proportion of GCs that could have been avoided if the entire cohort followed the healthiest behaviors in the index, was -18.8% (95% CI 0.2-35.0) for all GC cases -62.4% (95% CI 15.4-90.2)for cardia GC and -10.2% (95% CI 16.4-33.0) for non-cardia GC

Krishnamoorthi, R. et al. Rates and predictors of progression to esophageal carcinoma in a large population-based Barrett's esophagus cohort. Gastrointest Endosc. 84. 40-46.e7. 2016

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 1b **Study type:** population-based cohort study	**Funding sources:** Takeda Pharmaceuticals, Inc. Prasad Iyer and Amitabh Chak are members of the National Cancer Institute–supported Barrett's Esophagus Translational Research Network **Conflict of Interests:** Not reported **Randomization:** N.r. **Blinding:** N.r. **Dropout rates:** N.r.	**Total no. patients:** 9660 **Recruiting Phase:** **Inclusion criteria:** All patients with a diagnosis of BE in the GPRD database between May 1991 and April 2010 **Exclusion criteria:** -Subjects who developed EC within 12 months of the index date -missing data	**Interventions:** Age, gender, overweight, medication (PPI, NSAIDs, statins, insulin, metformin and other anti-diabetic medications (OAD)) **Comparison:** -different ages -female v.s male -Overweight categories (overweight (BMI 25- 29.9), obese-I (BMI 30- 34.9), obese-II (>34.9)) -BE progression ("Progressors" were defined as BE subjects who developed EC 12 months after the index date, "Non-progressors" were defined as BE subjects who did not have a diagnosis of EC in the entire GPRD follow-up) -different days of medication use
Notes:	**NOS-rating: 8/8 star**s **Author's conclusion:** Increasing age, male sex and increasing BMI were found to be risk factors that predicted progression to EC. PPI and statin use were identified as independent factors that protect against progression to EC. These results remained valid with a number of sensitivity analyses. NSAIDs and metformin use showed a trend toward protection against malignant progression. Subjects with high BMI may constitute a group of subjects who could be targeted by suitable chemopreventive agents. Prospective studies are needed to confirm these associations.		
Outcome Measures/results	**Primary** Incidence rates of EC in BE cohort Hazard Ratios of risk of progression to esophageal cancer **Secondary** -	**Results:** -The overall incidence rate of EC in the cohort was 2.23 per 1000 person years of follow-up -Significant association between increasing age, male gender, overweight (BMI 25-29.9), and progression to EC. -On multivariate analysis (adjusting for age, gender, smoking, BMI, hiatal hernia, DM2, PPI, NSAIDs, Statin, Metformin, Insulin, and OAD), increasing age, male gender, and being overweight continued to be independent risk factors predictive of progression to EC. -Obese-I (BMI 30-34.9) patients showed a trend toward significance as a risk factor for predicting progression (p = 0.08). -Increasing hazard ratios for the 3 BMI groups - overweight, Obese-I and Obese-II (HR= 1.63, 1.72 and 2.24) demonstrated a statistically significant trend across the 3 groups (p= 0.034), suggesting increased risk of progression with higher BMI. -Using PDC (Proportion days covered) to determine exposure to medications during the follow-up intervals, PPI use (HR = 0.43, p <0.0001) and statin use (HR = 0.61, p = 0.002) were protective against progression to EC. Once a day versus twice a day PPI use did not appear to influence the protective effect of PPIs	

Thota, P. N. et al. Influence of body mass index on the prevalence and progression of dysplasia in Barrett's esophagus: a retrospective analysis (.). Scand J Gastroenterol. 51. 1288-93. 2016

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 1b- **Study type:** Retrospective Cohort Study	**Funding sources:** not described **Conflict of Interests:** authors report no conflicts of interest **Randomization:** N.r. **Blinding:** N.r. **Dropout rates:** N.r.	**Total no. patients:** 1239 **Recruiting Phase:** -228 (18.4%) → BMI lower 25 -239 (19%) → BMI 25-27.4 -262 (21.1%) → BMI 27.5-29.9 -303 (24.5%) → BMI 30-34.9 -126 (10.2%) → BMI 35-39.9 -86 (6.8%) → BMI ≥ 40 kg/m^2 **Inclusion criteria:** -All patients diagnosed with Barrett's esophagus (BE) at the Cleveland Clinic Digestive Disease Institute from January 2000 - December 2012 -Patients with at least 1 upper endoscopic evidence of BE and confirmed by the presence of intestinal	**Interventions:** -BMI (lower 25, 25-27.4, 27.5-29.9, 30-34.9, 35-39.9 ≥ 40 kg/m^2) **Comparison:** -different BMI levels

		metaplasia on histology. **Exclusion criteria:** -unavailable data regarding BMI within one year of initial endoscopy -patients who did not undergo follow up biopsy or for whom BMI within 1 year of follow up biopsy was unavailable	
Notes:	**NOS-rating: 6/8 stars** -interpretation of results is not consistent with actual results (authors: "high BMI was associated with higher prevalence of dysplasia (*p*= 0.002)") **Author's conclusion:** High BMI was associated with higher prevalence of dysplasia in BE. But once in a surveillance program, higher BMI is not associated with progression of dysplasia in NDBE		
Outcome Measures/results	**Primary** Prevalence of dysplasia in BE (%) **Secondary** Hazard Ratios (HR) of BMI and progression to dysplasia in non-dysplastic barrett's esophagus (NDBE)	**Results:** -Lower BMI groups tended to have lower prevalence of dysplasia while higher BMI groups had higher prevalence of dysplasia (*p*= 0.002) -BMI or BMI change was *not associated* with progression to high-grade dysplasia or esophageal adenocarcinoma in NDBE (*p*= 0.055)	

Wienecke, A. et al. Incident cancers attributable to alcohol consumption in Germany, 2010. Cancer Causes Control. 26. 903-11. 2015

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 1b- **Study type:** Cohort Study	**Funding sources:** Not reported **Conflict of Interests:** The authors declare that they have no conflicts of interest. **Randomization:** n.r. **Blinding:** n.r. **Dropout rates:** n.r.	**Total no. patients:** 2,919 men, 3,007 women (total: 5926) **Recruiting Phase:** average age: 54 SD 11.9 (men) and 55 SD 12.3 (women) **Inclusion criteria:** men and women aged ≥ 35 years of age diagnosed with different cancer types including squamous cell carcinoma (ICD-O-3 morphology codes 8050) of the esophagus (C15) in Germany in the year 2010 **Exclusion criteria:** not reported	**Interventions: alcohol consumption:** -amount in bottles/glasses, frequency per month/week/day → average grams of alcohol consumed per day -moderate drinking (≤3 drinks per day) heavy drinking (at least 3 drinks per day → 3 drinks = more than 24 ml/30 g) **smoking habits:** -smoking status (current smoker: cigarettes/day; ex-smoker: former nr. of cigarettes/day) **Comparison:** Never exposed to tobacco or alcohol

Notes:	NOS-rating: 5/8 stars -For esophageal cancer, simulations could not be conducted, because confidence intervals for the relative risks were not published for the exposure-specific analysis **Author's conclusion:** In Germany, a substantial proportion of cases of common cancers can be attributed to alcohol consumption, even when consumed at moderate levels. Alcohol consumption with concurrent tobacco smoking is especially important for cancers of the UADT. These findings strengthen the rationale for prevention measures that address exposure at all levels.	
Outcome Measures/results	**Primary** Population attributable risk (PAR%) of incident cases by cancer type attributable to alcohol consumption in Germany, 2010 **Secondary** -	**Results:** -PAR was highest for alcohol consumption for esophageal cancer (men: 47.6 %, women: 35.8 %; 2.5th -97.5th percentile) -Regarding estimated prevalence and corresponding population attributable risks for esophageal cancer in Germany by sex and alcohol and tobacco exposure category, highest PARs were found for 15-24 cig/day and 1-24ml/d (8.6% men, 7.9% women) → corresponding Prevalences: 15.7% men, 10.0% women

Cook, M. B. et al. Cancer incidence and mortality risks in a large US Barrett's oesophagus cohort. Gut. . . 2017

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 2b **Study type:** Cohort study	**Funding sources:** This study was supported entirely by the Intramural Research Program of the Division of Cancer Epidemiology and Genetics, Natiional Institutes of Health, Bethesda, MD, USA. No funding or other financial support was received. **Conflict of Interests:** None declared. **Randomization:** N.r. **Blinding:** N.r. **Dropout rates:** N.r.	**Total no. patients:** 8929 **Recruiting Phase:** KPNC (Kaiser Permanente Northern California) **Inclusion criteria:** Patients with BE diagnosed at KPNC at ages 18 years and older during 1995 through 2012 **Exclusion criteria:** - any cancer diagnosis (excluding skin cancer) prior to their BE diagnosis - no diagnosis date associated with a cancer diagnosis - no enrolment information - unknown sex	**Interventions:** Diagnosis of BE (ICD-9: 530.85; 530.2 and SNOMED code M73330) **Comparison:** -

Notes:	**NOS-rating: 6/8 stars** **Author's conclusion:** Patients with BE had a persistent excess risk of oesophageal adenocarcinoma over time, although their absolute excess risks for this cancer, any cancer and overall mortality were modest.	
Outcome Measures/results	**Primary** -cancer incidence (Standardised incidence ratio (SIR)) **Secondary** -Mortality (Standardised mortality	**Results:** Oesophageal adenocarcinoma risk was increasd 24 times in the BE cohort, which translated into an excess absolute risk of 24 cases per 10 000 person years. Although oesophageal adenocarcinoma risk decreased with time since BE diagnosis, oesophageal cancer mortality

	ratio (SMR)) -excess absolute risks as the excess number of cancers per 10 000 BE person-years	did not, indicating that the true risk is stable and persistent with time. -121 oesophagaeal adenocarcinomas diagnosed in the BE cohort (95% CI, SIR 23.86 (19.80-28.51) -crude incidence rates of OA was 2.5 per 1000 person-years (95% CI 2.1 to 3.0) which translates to a crude absolute annual risk of 0.25% (95% CI 0.21% to 0.30%) Oesophageal cancer overall (including squamous cell carcinoma and other oesophageal malignancies) had a slightly lower relative risk (SIR) of 16 compared with the total KPNC population, which decreased further when assessed as a joint outcome of either all oesophageal cancers plus cardia cancers (SIR=8.94) or all oesophageal cancers plus cardia cancers (SIR=14.34) -SIR for OA was much higher for female patients with BE (SIR=59.61) compared with male patients with BE (SIR=21.46) Oesophageal cancer had the highest relative mortality risk with an SMR over 10 for this BE cohort and excess absolute risk of 15 deaths per 10 000 person-years. Risk of OC-death did not vary by time since diagnosis of BE

Cook, M. B. et al. Childhood body mass index in relation to future risk of oesophageal adenocarcinoma. Br J Cancer. 112. 601-7. 2015

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 2b **Study type:** Prospective Cohort Study	**Funding sources:** This study was funded by the Intramural Program of the National Cancer Institute, National Institutes of Health, Department of Health and Human Services and by the European Research Council-European Union's Seventh Framework Programme **Conflict of Interests:** The authors declare no conflict of interest. **Randomization:** Not relevant **Blinding:** Not relevant **Dropout rates:** Not relevant	**Total no. patients:** 255 053 individuals (128 330 males, 126 723 females) **Recruiting Phase:** **Inclusion criteria:** -boys and girls born 1930 to 1971 -registered in Copenhagen School Health Records Register (CSHRR) -BMI and cancer data available at all ages -having personal ID Number **Exclusion criteria:** -emigrated/deseased/lost to follow-up prior to 40 years -Height or BMI measures outlier at all ages	**Interventions:** childhood BMI (z-scores) childhood height (z-scores) **Comparison:** -
Notes:	**NOS rating: 7/8 stars** **Author's conclusion:** Childhood BMI was associated with increased risk of oesoohageal adenocarcinoma in adulthood. Whether childhood BMI is directly related to oesophageal adenocarcinoma, or associated indirectly through increased likelihood of adult obesity cannot be determined from our data. Nevertheless, our findings support lifestyle interventions targeted towards the growing number of overweight and obese children worldwide.		
Outcome Measures/results	**Primary** Relationship between childhood anthropometric variables and risk of oesophageal adenocarcinoma (Cox proportional hazards regression models using age as the underlying time metric with the baseline hazard) **Secondary** -birth cohort in 5-year intervals [Hazard ratios (HR)] -sex [Hazard ratios (HR)]	**Results:** -During more than 5.4 million person-years of follow-up, there were 254 incident oesophageal adenocarcinoma cases (216 males and 38 females). Incidence rates increased with increasing age and with more recent birth cohorts. **Hazard ratios of the associations between per unit increase in childhood BMI z-score and oesophageal adenocarcinoma risk:** -For females and males: HRs increased from 1.14 (0.99-1.31; 95% CI; N=240 435, 241 cases) at 7 years to 1.31 (1.13-1.51; 95% CI; N= 240 913, 241 cases) per BMI z-score at the age of 13 -For females: HRs increased from 1.30 (0.90-1.87; 95% CI;N= 119 398 34 cases) at 7 years to 1.68 (1.15-2.44; 95% CI; 120 581, 36 cases) per BMI z-score at the age of 13 -For males: HRs increased from 1.11 (0.95-1.30; 95% CI, N= 121 037, 207 cases) at 7 years to 1.25 (1.06-1.46; 95% CI; N= 120 332, 205 cases) per BMI z-score at the age of 13 years HRs were not significantly different between the sexes.	

Feng, X. S. et al. Prevalence and age, gender and geographical area distribution of esophageal squamous cell carcinomas in North China from 1985 to 2006. Asian Pac J Cancer Prev. 15. 1981-7. 2014

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 2b **Study type:** Prospective Cohort Study	**Funding sources:** The First Affiliated Hospital of Henan University of Science and Technology Endoscopy Center **Conflict of Interests:** Not reported **Randomization:** N.r. **Blinding:** N.r. **Dropout rates:** N.r.	**Total no. patients:** 4092 **Recruiting Phase:** Patients of The First Affiliated Hospital of Henan University of Science and Technology (North China) **Inclusion criteria:** All the cases of ESCC that were diagnosed by endoscopy and histologically confirmed in the 22 years period from January 1985 to December 2006 **Exclusion criteria:** Patients with only adenocarcinoma of the esophagogastric junction	**Interventions:** Age, Sex, Geographical Area **Comparison:** 10 year age bands (20-29, 30-39, 40-49, 50-59, 60-69, 70-79, 80-89), male vs. female, rural vs. urban area

Notes:	**NOS-rating: 5/8 stars** **Author's conclusion:** In summary, our current study is the first to describe the prevalence and distribution status of ESCC in North China with a novel epidemiological approach. We found the prevalence of ESCC is higher in male and rural area patients though the overall rates decline and the median age of onset increases, which suggested that rural areas and male patients are more urgent need for the public health initiatives aimed at reducing risk factors such as unhealthy lifestyles.	
Outcome Measures/results	**Primary** Prevalence of ESCC Odds Ratio (female:male; rural:urban) **Secondary** -	**Results:** -4092 cases among 74,854 patients -Prevalence among males (5.90%) was higher than that among females (4.91%) (OR: 1,2; 95% CI 1.2-1.3) -Prevalence in rural areas was higher than in urban areas (OR: 2.6; 95% CI 2.4-2.9) -The rural:urban ORs and the 95% CI increased continuously from 2.6 (2.3-3.0) to 2.7 (2.2-3.3) for 4 consecutive periods during the 22 years study period -Onset age of male is later than female, and the onset age for both sexes rise continuously during study period

Hazelton, W. D. et al. The Role of Gastroesophageal Reflux and Other Factors during Progression to Esophageal Adenocarcinoma. Cancer Epidemiol Biomarkers Prev. 24. 1012-23. 2015

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 2b **Study type:** Cohort Study	**Funding sources:** This research was supported by the National Cancer Institute (NCI) and by a Graduate Research Fellowship from the National Science Foundation. **Conflict of Interests:** J.M. Inadomi reports receiving a commercial research grant from Ninepoint [provided equipment for an NIH grant (U01)] and is a consultant/advisory board member for ChemImage (Clinical Advisory Committee). J.H. Rubenstein is a consultant/advisory board member of ORC, International and Analogy Growth Partners. No potential conflicts of interest were disclosed by the other authors. **Randomization:** N.r. **Blinding:** N.r. **Dropout rates:** N.r.	**Total no. patients:** estimation of 100,000 person years **Recruiting Phase:** **Inclusion criteria:** -EAC incidence and population data for all-race men and women by single years for ages 20 to 84 years and calendar years 1975 to 2009 from nine SEER incidence databases -EAC incidence defined using ICD-O-3 histology codes (8140–8141, 8143–8145, 8190–8231, 8260– 8263, 8310, 8401, 8480–8490, 8550–8551, 8570–8574,8576) **Exclusion criteria:** -	**Interventions:** -Symptomatic gastroesophageal reflux disease (sGERD) -Other factors (OF): obesity, eradication of H. pylori, smoking, less frequent or non-symptomatic GERD, proton pump inhibitors (PPI) **Comparison:** -

Notes:	**NOS-rating: 5/8 stars** -Interpretations of results concerning intervention "Other factors" cannot be transferred to single factors (OFs are collection of multiple factors) -sGERD incidence and prevalence data are extracted from two U.S. cohort studies -results rely partly on calculated estimations, not on real data -no statement regarding exclusion criteria **Author's conclusion:** This analysis suggests that premalignant promotion is the most important biologic mechanism driving EAC incidence trends, accounting for 95.0% (95% CI, 88.4%–100.0%) of the increase among men from 1975 to 2009, and 90.1% (95% CI, 84.5%– 97.3%) among women. Individuals with early onset of both BE and sGERD are at highest risk. For extended duration of sGERD (greater than 40 years), the absolute sGERD-associated EAC risk for women approaches one third to one half that of men, depending on age and calendar year, whereas the risk is 10- to 20-fold lower for women than men for individuals who never acquire sGERD. The dominant driver of promotion is OF. Premalignant cell promotion is an important driver of carcinogenesis that causes incidence to increase exponentially with sGERD and OF exposure duration. Thus, prevention and screening should focus on long-duration exposures, including earlyonset sGERD.	
Outcome Measures/results	**Primary** Incidence rates for EAC **Secondary**	**Results:** -Men: 77.8% [95% credibility interval (CI), 64.9%–85.6%] of the incidence trend is attributable to OF, 13.4% (95% CI, 11.4%–17.3%) to sGERD, and 8.8% (95% CI, 4.2%– 13.7%) to sGERD–OF interactions. -Women: 32.6% m(95% CI, 27.0%–39.9%) of the trend is attributable to OF, 13.6% (95% CI, 12.5%–15.9%) to sGERD, and 47.4% (95% CI, 30.7%–64.6%) to interactions. The predicted trends were compared with historical trends for obesity, smoking, and proton pump inhibitor use.

Ji, J. et al. Associations of alcohol use disorders with esophageal and gastric cancers: a population-based study in Sweden. Eur J Cancer Prev. 26. 119-124. 2017

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 2b **Study type:** Retrospective cohort study	**Funding sources:** Swedish Research Council, The Swedish Research Council for Health, Working Life and Social Research, ALF, Swedish Freemasons Foundation, **Conflict of Interests:** There are no conflicts of interest. **Randomization:** -	**Total no. patients: Total no. patients:** - 14 518 patients with esophageal cancer (735 with alcohol use disorders (AUD), 13 783 without) - 73 504 patients with gastric cancer (641 with AUD, 72 863 without) **Recruiting Phase: Swedish registers for AUD's during 1973-2010:** Swedish Hospital Discharge Register and Outpatient Register by ICD-Codes (ICD-9 & ICD-10), the Crime	**Interventions:** alcohol use **Comparison:** no alcohol use

	Blinding: - **Dropout rates:** -	Register for 1973-2010, the Prescription Drug Register for 2005-2010. **Swedish Cancer Registry for identifying cases of esophageal and gastric cancers during study period** **Inclusion criteria:** -esophaegeal cancer (ICD-7 code: 150) -gastric cancer (ICD-7 code: 151) -AUDs (ICD-9: 291A-291F, 291 W, 291X, 303, 305A; ICD-10: F10) **Exclusion criteria:** N.r.	
Notes:	No report of how No-AUD group was constituted **NOS grade: 6/8 stars** **Author's conclusion:** In summary, individuals with AUDs, as a proxy for heavy alcohol drinking, had an increased risk of esophaegaeal cancer, both squamous cell carcinoma and adenocarcinoma. In addition, they had a lower risk of gastric cancer, especially corpus cancer, which may be related to the elimination of H. pylori. However, the underlying mechanisms need to be explored in future studies.		
Outcome Measures/results	**Primary** Incidence of esophageal or gastric cancer (Observed number of cases, standardized incidence ratio) **Secondary** N.r.	**Results:** - Incidence of esophageal cancer is significantly increased among AUDs compared to those without AUD (SIR = 2.24 [95%CI 2.08-2.41]) - Risk of gastric cancer is decreased in AUDs compared to those without AUD (SIR = 0.73 [95%CI 0.68-0.79) - decrease more prominant for corpus cancer in the stomach compared with cardia cancer) - Risk of esophageal cancer is somewhat higher in women (SIR = 3.93 [95% CI 3.17-4.81]compared to men (SIR = 2.11 [95% CI 1.95-2.28]	

Kestens, C. et al. Patients With Barrett's Esophagus and Persistent Low-grade Dysplasia Have an Increased Risk for High-grade Dysplasia and Cancer. Clin Gastroenterol Hepatol. 14. 956-962.e1. 2016

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 2b **Study type:** Retrospective population-based cohort study	**Funding sources:** PALGA foundation **Conflict of Interests:** The authors disclose no conflicts. **Randomization:** N.r. **Blinding:** N.r. **Dropout rates:** N.r.	**Total no. patients:** 1579 **Recruiting Phase:** n=50 no-dsyplasia, n= 14 indefinite for dysplasia, n= 161 Low grade dysplasia, n= 2 high grade dysplasia, n= 4 unknown **Inclusion criteria:** -all histopathology reports (diagnostic codes of BE and LGD) from January 2005 to December 2010, with followup data until July 2014. **Exclusion criteria:** -HGD/EAC in the same set of biopsies during the index LGD diagnosis -a history of HGD/EAC before the index LGD diagnosis -index LGD diagnosis before 200, -cases with no follow-up or follow-up of less than 1 year -Cases of prevalent HGD/EAC, defined as detected within 1 year after the initial LGD diagnosis	**Interventions:** Barrett Esophagus, Low Grade Dysplasia **Comparison:** no confirmed BE or LGD
Notes:	**NOS-rating: 6/8 stars** **Author's conclusion:** We demonstrate that confirmed and persistent LGD identifies a subgroup of patients with an increased risk of malignant progression. In addition, in half of these patients LGD was no longer detected during follow-up, and one-fourth of them exhibited persistent ND BE. Therefore, we believe that endoscopic treatment of LGD BE is indicated in patients with confirmed and persistent LGD. In patients in whom confirmed LGD does not persist, it may well be that a wait and see policy is justified.		
Outcome Measures/results	**Primary** Incidence rate of developing High grade dysplasia or EAC or EAC alone **Secondary** -	**Results:** -Incidence rate in patients with ND BE at the first follow-up endoscopy after an initially confirmed LGD diagnosis was significantly lower 2.32 (95% CI, 1.08–4.40; *p*< .0001) and 1.45 (95% CI, 0.53–3.21; *p* = .007) for HGD/EAC and EAC, respectively than in patients with confirmed and persistent LGD. In addition, patients with 2 consecutive endoscopies showing ND BE after a confirmed LGD diagnosis (29%, n = 46) developed no HGD/EAC during a follow-up of 117 patient-years. -In patients with ND BE after an unconfirmed LGD diagnosis (n = 765) (median follow-up, 4.35 years; IQR, 2.99–5.95), the incidence rate was significantly lower 0.99 (95% CI, 0.70–1.37; P < .001) and 0.38 (95% CI, 0.21–0.63; P < .0001) per 100 person-years, respectively than in patients with unconfirmed persistent LGD diagnosis. -History of no-dysplasia BE did not affect risk of developing HGD/EAC	

Lindkvist, B. et al. Metabolic risk factors for esophageal squamous cell carcinoma and adenocarcinoma: a prospective study of 580,000 subjects within the Me-Can project. BMC Cancer. 14. 103. 2014

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 2b **Study type:** Prospective cohort study	**Funding sources:** World Cancer Research Fund, Wereld Kanker Onderzoek Fonds **Conflict of Interests:** The authors declare that they have no competing of interests. **Randomization:** N.r. **Blinding:** N.r. **Dropout rates:** N.r.	**Total no. patients:** 578 700 **Recruiting Phase:** -289 866 men -288 834 women **Inclusion criteria:** not reported **Exclusion criteria:** -unrealistic or missing baseline data -prevalent cancer diagnosis	**Interventions:** -metabolic factors (BMI, mid blood pressure, smoking habits, blood plasma, serum levels of glucose, total cholesterol, triglycerides) -Metabolic Syndrome score (cluster of metabolic risk factors, including obesity, hypertension, insulin resistance/hyperglycemia and dyslipidemia -BMI Quintiles (Mean, SD: 1= 20.7 (1.5) 2= 23.0 (1.1) 3= 24.7 (1.0) 4= 26.8 (1.0) 5= 31.3 (3.3) **Comparison:** -
Notes:	**NOS-rating: 6/8 stars** -mid blood pressure is not convincing as variable for blood pressure		

	Author's conclusion: High BMI was associated with an increased risk of EAC and a decreased risk of ESCC. An association between high blood pressure and risk of ESCC was observed but alcohol consumption is a potential confounding factor that we were not able to adjust for in the analysis. The Metabolic Syndrome was associated with EAC but not ESCC. However this association was largely driven by the strong association between BMI and EAC. We hypothesize that this association is more likely to be explained by factors directly related to obesity than the metabolic state of the MetS, considering that no other metabolic factor than BMI was associated with EAC.	
Outcome Measures/results	**Primary** Relative risks (RR) for esophageal cancer related to different metabolic risk factors in quintiles **Secondary** -	**Results:** <u>EAC:</u> -Association between BMI and risk of EAC. Highest adjusted RR for EAC were Quintiles 4 (5.19 95% CI 2.00-13.42) and 5 (7.34 95% CI 2.88-18.68) -Mid BP, glucose, cholesterol and triglycerides were not associated with the risk of EAC. -Association between the composite Metabolic Syndrome score and the risk of EAC (RR 1.56 (95% CI 1.19-2.05) per one unit increase of the composite MetS score. <u>ESCC:</u> -Association between BMI and risk of ESCC. Highest adjusted RR for ESCC were Quintiles 2 (0.50 95% CI 0.32-0.79) and 3 (0.76 95% CI 0.51-1.12) -Higher BMI was associated with a decreased risk of ESCC (adjusted RR for top versus bottom quintile of BMI: 0.38, 95% CI 0.23-0.62) -Higher mid BP was associated with an increased risk of ESCC. The adjusted RR for ESCC was 2.60 (95% CI 1.54-4.39) for top versus bottom quintile of mid BP -There was no association between glucose, cholesterol and risk of ESCC -Marginal significant association between triglycerides and risk of ESCC (RR 1.19 (95% CI, 1.01-1.40)

Masclee, G. M. et al. The incidence of Barrett's oesophagus and oesophageal adenocarcinoma in the United Kingdom and The Netherlands is levelling off. Aliment Pharmacol Ther. 39. 1321-30. 2014

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 2b **Study type:** dynamic population-based retrospective cohort study	**Funding sources:** None **Conflict of Interests:** EJK has since completion of this research started working for the medical board of Erasmus University Medical Center. MCJMS is coordinating a research group that has unconditional research grants from Pfizer, Novartis, Lilly, none related to this research **Randomization:** N.r. **Blinding:** N.r. **Dropout rates:** N.r.	**Total no. patients:** 12 312 (all incidents of Barrett's oesophagus cases) **Recruiting Phase:** **Inclusion criteria:** patients aged ≥ 18 years in UK and NL databases **Exclusion criteria:** -Patients with oesophageal or stomach cancer at any time before study entry -Patients with a diagnosis of stomach cancer within 6 months after BO diagnosis	**Interventions:** age, sex **Comparison:** age categories (<40, 40-60, >60), female vs. male
Notes:	**NOS-rating: 8/8 stars** **Author's conclusion:** In conclusion, the incidence rate of Barrett's oesophagus in the UK and the Netherlands has increased substantially in both males and females at the beginning of the millennium but has remained stable since then. Therise in incidence was not explained by an increase in gastroscopies. Around 0.3% of BO patients are diagnosed with oesophageal adenocarcinoma at least 1 year after diagnosis of BO, demonstrating a 1-year risk of 0.09%. The observed current increase in the OAC incidence among BO patients probably reflects the increase in the incidence of BO a decade ago.		
Outcome Measures/results	**Primary** -Incidence Rates (IR) of BO in population of UK and the Netherlands -IR of OAC in BO population of UK and the Netherlands **Secondary** -	**Results:** -From the BO cases, we identified 40 (0.3%) incident OAC cases in the UK and 5 (0.4%) incident OAC cases in the NL. -Forty-five patients in the UK (0.4%) and two patients in the NL (0.1%) were diagnosed with OAC within 1 year of BO diagnosis and were considered prevalent OAC and therefore excluded in the analysis. -Mean age of BO diagnosis in the incident OAC cases was 67.0 years (s.d. 10.3) and mean time from BO diagnosis until OAC diagnosis was 4.2 years (s.d. 2.5). -In the NL, incident OAC cases were diagnosed with BO at a <u>mean age</u> of 63.5 years (s.d. 11.3) and mean time to OAC diagnosis was 3.5 years (s.d. 0.8). -*The overall IR of OAC was 22.6/100 000 PYs in the UK and 80.1/100 000PYs in the NL.* -In 2000, the IR of OAC was 8.9/100 000 PYs and increased 4-fold up to 38.1/100 000 PYs in 2010. -The 1-year risk of OAC after BO diagnosis, excluding OAC cases within 1 year after BO diagnosis, was 0.086% (95% CI: 0.04–0.17) overall, 0.11% (95% CI: 0.05–0.23) for <u>males</u> and 0.06% (95% CI: 0.02–0.24) for <u>females.</u>	

Nguyen, T. et al. The Annual Risk of Esophageal Adenocarcinoma Does Not Decrease Over Time in Patients With Barrett's Esophagus. Am J Gastroenterol. 112. 1049-1055. 2017

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 2b **Study type:** Retrospective	**Funding sources:** "This work is funded in part by National Institutes of Health grant NCI R01 116845, and the Texas Digestive Disease	**Total no. patients:** 28,561 **Recruiting Phase:** 5 Years (2004-2009) **Inclusion criteria:** male patients (mean age: 62 years) with BE (first ICD-9-CM code for BE; BE ICD-9-CM 530.85 combined with	**Interventions:** -- **Comparison:** --

cohort study	Center NIH DK58338. Dr El-Serag is also supported by NIDDK K24-04-107. This research was supported in part with resources at the VA HSR&D Center for Innovations in Quality, Effectiveness and Safety (#CIN 13–413), at the Michael E. DeBakey VA Medical Center, Houston, TX." **Conflict of Interests:** The authors report no competing interests for this publication. **Randomization:** -- **Blinding:** -- **Dropout rates:** --	endoscopy code (43200– 43259, excluding 43246) within 1 year) newly diagnosed during fiscal years (FY) 2004–2009 (10/1/2004 to 9/30/2010). The date of BE diagnosis (the index date for follow-up) was defined as the date of the first ICD-9-CM code for BE. **Exclusion criteria:** female (number to low). BE patients with conditions, diagnosed within 5 years prior to and including the BE index date, that may affect the likelihood of developing EAC or represent prevalent cases of EAC, including: gastroesophageal cancer, gastroesophageal resection, esophageal ablation, and bariatric surgery.	
Notes:	NOS-rating: 7/8 stars **Author's conclusion:** "Persistence of non-neoplastic BE on multiple consecutive endoscopies was not associated with lower EAC risk. These findings argue against discontinuation of endoscopic surveillance in patients with persistent nondysplastic BE after multiple negative endoscopies."		
Outcome Measures/results	**Primary** "The outcome of this study was the development of incident EAC a er the BE index date. We used Poisson regression models to calculate incidence rates, rate ratios, and corresponding 95% confidence intervals (CI) for EAC according to number of successive follow-up endoscopies, number of follow-up years since the index BE diagnosis date (independent of the number of follow-up endoscopies), and calendar year of BE diagnosis (FY 2004–2009)." **Secondary** --	**Results:** E**AC incidence rates"**: Among 28,561 male patients with BE, 406 developed EAC during 140,499 person-years of follow- up (median 4.9 years). EAC incidence rates increased with each additional endoscopy following a previous negative endoscopy (RR per additional endoscopy, 1.43; 95% CI, 1.25–1.64). Compared to the EAC incidence rate at the 1st follow-up EGD, the EAC incidence rate at the 5th follow-up EGD was ninefold higher (adjusted RR, 8.82; 95% CI, 4.90–15.9). EAC incidence was highest at the first year of follow-up (5.34 per 1,000 person-years); however, EAC rates starting from the second follow- up year increased during successive years of follow up. Compared to the EAC incidence rate in the 2nd year of follow-up, the EAC incidence rate was 1.5-fold higher in EGDs conducted ≥5 years after the index BE date (adjusted RR, 1.49; 95% CI, 1.07–2.10). In contrast, we found no significant change in EAC incidence rates by calendar year."	

Jia, N. et al. Younger age of onset and multiple primary lesions associated with esophageal squamous cell carcinoma cases with a positive family history of the cancer suggests genetic predisposition. Chin Med J (Engl). 127. 2779-83. 2014

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 2b- **Study type:** Retrospective Cohort Study	**Funding sources:** Not reported **Conflict of Interests:** Not reported **Randomization:** N.r. **Blinding:** At enrollment, slides made from surgically resected specimens at the time of serial histological examination for the 2524 patients were read blindly by Wang XL again to verify the diagnosis **Dropout rates:** N.r.	**Total no. patients:** 2524 (2542 ESCCs, including multiple primary cancers) **Recruiting Phase:** Patient registration was performed by the Department of Thoracic Surgery of Hebei Tumor Hospital and the Fourth Hospital of Hebei Medical University for the purpose of survival analysis. All patients undergoing surgical resection of ESCC were registered, i.e. entering into the cohort right after operation. **Inclusion criteria:** All patients undergoing surgical resection of ESCC and followed up for more than 15 years (operated before 1989) in Hebei Tumor hospital (China) **Exclusion criteria:**	**Interventions:** -Positive family history of cancer (at least one first-degree or two second-degree relatives of the hospitalized patient diagnosed with ESCC and/or GCA -average onset age of cancer **Comparison:** Negative family history of cancer
Notes:	**NOS-rating: 8/8 stars** -Acquisition of family history data by self-report (risk of bias) -No definition of negative family history of cancer -Unclear how data for gastric cardia adenocarcinoma (GCA) was attained and included in analysis **Author's conclusion:** In conclusion, we found significant differences in age at onset and multiple primary cancers between ESCC patients with or without a positive family history of the cancer. Younger onset age possibly stands for genetic and environmental interaction, but multiple primary cancers represent only genetic predisposition.		
Outcome Measures/results	**Primary** Incidence rates (%) **Secondary** -	**Results:** -Of the 2 542 ESCCs analyzed, 30.13% (766/2 542) were associated with a positive and 69.87% (1 776/2 542) associated with a negative family history of ESCC and/or GCA. -Average onset age of ESCCs associated with a positive family history (n= 766) is 51.38 years old, younger than that of 53.49 years old associated with ESCCs with a negative family history (n= 1 776)	

Levi, Z. et al. Body mass index and socioeconomic status measured in adolescence, country of origin, and the incidence of gastroesophageal adenocarcinoma in a cohort of 1 million men. Cancer. 119. 4086-93. 2013

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 2b- **Study type:** Cohort study	**Funding sources:** No specific funding was disclosed. **Conflict of Interests:** The authors made no disclosures. **Randomization:** - **Blinding:** - **Dropout rates:** N.r.	**Total no. patients:** 1,088,530 **Recruiting Phase:** Israeli male adolescents [16 to 19 years at time of medical examination (for military service) between 1967 and 2005] who were born between 1947 and 1978. **Inclusion criteria:** N.r. **Exclusion criteria:** N.r.	**Interventions:** - Centers for Disease Control and Prevention: BMI lower 85th percentile; BMI greater or equal 85th percentile - WHO: BMI lower 24.9 kg/m^2; greater or equal 25 kg/m^2 - WHO: BMI lower 18.5 kg/m^2; 18.5-24.9 kg/m^2; 25-29.9 kg/m^2 - SES (Socioeconomic status): High, medium, low

			- Country of birth: Israel, West, Africa, Former Soviet Union, Asia - No. of years of education: 12, 11, 10, lower 9 **Comparison:** -
Notes:	**NOS rating: 5/8 stars** - Confusing separation into EAC and GEJAC group, although previously stated that distinction between both groups is difficult outside surgical setting (?) - therefore combination of both group by authors. Resulting unclear validity of results concerning separated and combined groups - Unclear validity of SES grouping into low, medium and high - Unclear validity of BMI results due to confounding variable classifications as dichotomous and ordinal - No reporting on why cohort number is once stated as 1,088,530 and once as 1,088,242 **Author's conclusion:** Overweight during adolescence was found to be substantially associated with the subsequent development of EAC and GEJAC. In addition, although potential confounding by Helicobacter pylori infection status or lifestyle factors was not fully accounted for in the analyses, lower SES as well as immigration from higher-risk countries are countries are important determinants of NCGC.		
Outcome Measures/results	**Primary** Incidence of gastroesophageal cancer, gastroesophageal junction adenoma carcinoma and noncardia gastric cancer **Secondary** - Risk for EAC and GEJAC, NCGC, NCGC intestinal and Mucinous (Multivariable cox proportional Hazard Ratios) - Cumulative Incidence for EAC and GEJAC-group and NCGC	**Results:** -Association between BMI greater or equal 85th percentile during adolescence and future adenocarcinoma of the lower esophagus and gastric cardia -Association between adult obesity (especially abdominal obesity) and an increased risk of EAC and GEJAC -Lower SES and immigration from higher-risk countries (Asia and former Soviet Union) are important determinants of NCGC	

Zakaria, D. et al. Cancers attributable to excess body weight in Canada in 2010. Health Promot Chronic Dis Prev Can. 37. 205-214. 2017			
Evidence level	**Methodical Notes**	**Patient characteristics**	**Interventions**
Evidence level: 2b- **Study type:** Cohort Study	**Funding sources:** N.r. **Conflict of Interests:** The authors declare no conflicts of interest. **Randomization:** N.r. **Blinding:** N.r. **Dropout rates:** N.r.	**Total no. patients:** N.r. **Recruiting Phase:** Canadian adults aged 25+ years in 2010 **Inclusion criteria:** Canadian adults aged 25+ years in 2010 **Exclusion criteria:** N.r.	**Interventions:** BMI (Overweight: 25.00 - 29.99 kg/m2; Obese: 30.00+ kg/m2) **Comparison:** N.r.
Notes:	**NOS-rating: 2/8 stars** BMI data is partly based on self-report (bias), partly on adjusted data on a subsample of respondents who agreed to have their height and weight measured in addition to providing self-reports. Data was pooled later on. No report of duration of overweight/obesity - impact on cancer risk Different sources of cancer case data were merged later on (Canadian Cancer Registry for whole Canada and Statistics Canada's website especially for Quebec) Cancer case counts for Quebec needed to be adjusted for a few cancers not directly available through Statistics Canada's website. No report of how BMI and cancer data were linked. Assumption of no cancer risk for BMI below 25.00 kg/m2 without evidence.Results only applicable on BMI above 25.00 kg/m2 **Author's conclusion:** An estimated 5.7% (1 in 18) of all new cancer cases diagnosed in Canadian adults in 2010 were attributable to high BMI after correcting for bias in self-reported height and weight.		
Outcome Measures/results	**Primary** Not explicitely reported (possibly PAFs of cancer cases, attributable cases and plausible ranges) **Secondary** N.r.	**Results:** 5.7% of all cancer cases, or 9645 cancer cases, diagnosed in Canadian adults in 2010 were attributable to excess body weight. Esophageal adenocarcinoma: Total in whole Canada N= 435; PAF: 41.3 (plausible range: 32.8-51.8) Males in whole Canada N= 380; PAF: 42.2 (34.3-52.6) Females in whole Canada N= 50; PAF: 36.1 (23.6-47.0)	

Evidenztabellen

zurück

Schlüsselfrage:

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

Bewertungsvorlage:

NEWCASTLE - OTTAWA Checklist 3: Case Control

Alexandre, L. et al. Statin use is associated with reduced risk of histologic subtypes of esophageal cancer: a nested case-control analysis. Gastroenterology. 146. 661-8. 2014

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 3b **Study type:** Case-control study	**Funding sources:** The Medical Research Council provided funding for this study under a project license. The funding source had no input regarding the design, conduct, or interpretation of this study. **Conflict of Interests:** The authors disclose no conflicts. **Randomization:** N.r. **Blinding:** Not reported **Dropout rates:** N.r.	**Total no. patients:** 1126 cases, 4192 controls **Patient characteristics:** *EAC:* 581 patients with EAC, 2167 controls *EGJA:* 213 participants with EGJA, 783 controls *ESCC:* 332 participants with ESCC, 1242 controls **Inclusion criteria:** cases: patients with EAC, EGJA, ESCC controls: patients without a history of any cancer; according to sex, year of birth, general practice (socioeconomic staus) **Exclusion criteria:** cases: participants with less than 10 months of statin use in the year before diagnosis	**Interventions:** -Statin prescription -Statin duration (≥ 1 to < 4 years; ≥ 4 to < 6 years; ≥ 6 years) **Comparison:** -No Statin prescription -Statin duration
Notes:	**NOS-rating: 6/8 stars** -There were too few prescriptions of individual statins to allow meaningful analysis **Author's conclusion:** In a nested case-control analysis of a UK population-based cohort, statin use was inversely associated with histologic subtypes of esophageal cancer. Randomized controlled trials are warranted to determine whether statins have chemo-preventive effects in high-risk groups.		
Outcome Measures/results	**Primary** Adjusted Odds Ratios (95% CI) **Secondary**	**Results:** *EAC:* -Regular statin prescription was inversely associated with EAC (OR = 0.58; 95% CI: 0.390.87; *p* = .009) and there was evidence of both a dose-response (*p* for trend = .036) and duration-response (*p* for trend = .005) relationship. *EGJA:* -Regular statin prescription was not significantly associated with EGJA (OR = 0.60; 95% CI: 0.331.11; *p* = .102) (Table 2), however, there was evidence of a doseresponse (*p* for trend = .040) and durationresponse (*p* for trend = .052) with borderline significance. Only high-dosage regular statin prescriptions were significantly inversely associated with EGJA (OR = 0.29; 95% CI: 0.090.92;*p* = .036). *ESCC:* -Regular statin prescription was non-significantly inversely associated with risk of ESCC (OR = 0.61; 95% CI: 0.351.06; *p* = .081) with borderline evidence of a doseresponse (*p* for trend = .057) relationship, and no significant durationresponse (*p* for trend = .249). Statin use for between 1 and 4 years was significantly inversely associated with ESCC (OR = 0.51 95% CI: 0.270.98; *p* = .045).	

Bhat, G. A. et al. Family history of cancer and the risk of squamous cell carcinoma of oesophagus: a case-control study in Kashmir, India. Br J Cancer. 113. 524-32. 2015

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 3b **Study type:** Case-control study	**Funding sources:** This study was financially supported by Extramural grant of Indian Council of Medical Research (ICMR), New Delhi **Conflict of Interests:** The authors declare no conflict of interest **Randomization:** Not relevant **Blinding:** Not relevant **Dropout rates:** Not relevant	**Total no. patients:** 2367 (703 ESCC cases and 1664 controls without ESCC) **Patient characteristics:** SDRs: cousins, uncles, aunts, stepsiblings **Inclusion criteria:** cases: -histopathologically confirmed ESCC -age above 18 years -no personal history of cancer controls: -hospital-based -matched for sex, age (± 5 years), place of residence **Exclusion criteria:** controls: disease with relation to tobacco or alcohol use or affection of dietary habits of the patient (e.g. diabetes)	**Interventions:** -Family History of Cancer [FHC: FDRs= Parents, siblings and children; Second-degree relatives= cousins, uncles, aunts, stepsiblings] **Comparison:** No FHC, FDRs, SCRs
Notes:	NOS-rating: 5/8 stars		

	-possible source of bias regarding self-reported information of family history data **Author's conclusion:** Our results showed that FHC was strongly associated with ESCC risk in Kashmir. It seems both genetic factors and shared environment are involved in this association.		
Outcome Measures/results	**Primary** ESCC risk (Adjusted Odds Ratio) **Secondary** gene polymorphisms (Adjusted Odds Ratio)	**Results:** -A strong increase in ESCC risk was observed in subjects who had FHC (OR=5.8; 95% CI= 4.1-8.3) -The risk was stronger when first-degree relatives (FDRs) had FHC (OR=6.8; 95% CI= 4.6-9.9) -Having a sibling with a cancer showed the strongest association (OR=10.8; 95% CI= 6.0-19.3) -A history of any cancer in the spouse was associated with ESCC risk (OR=4.1; 95% CI= 1.6-20.2) -Having a child with a cancer was not associated with ESCC risk	

Busby, J. et al. The effect of medications which cause inflammation of the gastro-oesophageal tract on cancer risk: a nested case-control study of routine Scottish data. Int J Cancer. 140. 1828-1835. 2017

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 3b **Study type:** Nested case-control study	**Funding sources:** Not reported **Conflict of Interests:** Not reported **Randomization:** N.r. **Blinding:** Not reported **Dropout rates:** Not reported	**Total no. patients:** 3,098 cases, 14 870 controls **Patient characteristics:** Between 1993 and 2011, the PCCIUR collected computerised medical records from around 15% of the Scottish general practice population, and includes details on patient demographics, clinical diagnoses and prescriptions. **Inclusion criteria:** *cases:* patients with a first-time oesophageal (Read code: B10.) or gastric (Read code: B11.) cancer diagnosis after January 1, 1999 and before April 30, 2011. *controls:* matched on age, gender, year of diagnosis and general practice **Exclusion criteria:** -cases and controls with an earlier cancer diagnosis (other than non-melanoma skin cancer) and those with less than three years of exposure prior to index date -prescriptions before January 1, 1996 and those in the year prior to index date	**Interventions:** medication use **Comparison:** never, ever, lower usage, higher usage of medication

Notes:	**NOS-rating: 6/8 stars** **Author's conclusion:** Overall, there is little evidence that the use of biphosphonate, tetracycline or spironolactone is associated with increased risk of gastro-oesophageal cancer. Our findings should reassure GPs and patients that these widely-used medications are safe with respect to gastro-oesophageal cancer risk.	
Outcome Measures/results	**Primary** Odds Ratio (OR) for the association between medication use (Biphosphonate, Tetracycline, Spironolactone) and osesophageal cancer risk **Secondary** -	**Results:** -There was evidence of a 34% increased risk (ORadj = 1.34; 95% CI: 1.03, 1.74) of oesophageal cancer in bisphosphonate users -The association between bisphosphonate use and oesophageal or gastric cancer did not appear to follow a dose–response relationship. -little associations were observed between tetracycline use and oesophageal (ORadj = 1.01; 95% CI: 0.82, 1.25) -little evidence of higher risk for oesophageal cancer alone in spironolactone users, with adjusted odds ratios of 1.04 (95% CI: 0.68, 1.61)

Chen, T. et al. Family history of esophageal cancer increases the risk of esophageal squamous cell carcinoma. Sci Rep. 5. 16038. 2015

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 3b **Study type:** population-based case-control study	**Funding sources:** National Natural Science Foundation of China, Key Projects in the National Science & Technology Pillar Program, Key Scientific and Technological Projects of Shandong Province **Conflict of Interests:** The authors declare no competing financial interests. **Randomization:** random selection of population controls **Blinding:** Not reportet **Dropout rates:** Not relevant	**Total no. patients:** 619 esophageal cancer cases (648 cases of ESCC, 63 cases of esophageal adenocarcinoma, 7 cases of other types of esophageal cancer) 772 controls **Patient characteristics:** local inhabitants aged 40-85 who have lived in Taixing for at least 5 years prior to diagnosis date for cases or interview date for controls -Interviews with study subjects face-to-face using a structured questionnaire, which covers information on demographic characteristics, lifestyles and family history of cancer. **Inclusion criteria:** -cases: ESCC cases in Taixing of Jiangsu Province from 10.2010-03.2012. -controls: population controls which were frequency matched to the cases of ESCC on sex and age (in 5-year groups) **Exclusion criteria:** -incomplete questionnaire information on family history cancer	**Interventions:** Family history of cancer (First-degree relatives, parents, siblings) **Comparison:** no family history of cancer (First-degree relatives, parents, siblings)

Notes:	NOS-rating: 5/8 stars -no mentioning of exclusion criteria of cases, untransparent description of case recruitment -review of section performed only by one study pathologist (risk of bias) **Author's conclusion:** Our results indicate that familial aggregation of ESCC in endemic area is notable. The shared genetic susceptibility and environmental exposures, or possibility their interaction, might contribute to this phenomenon which urges future studies to explore the underlying mechanisms.	
Outcome	**Primary** Risk of ESCC (adjusted Odds Ratio)	**Results:** -excess risks of ESCC increased monotonically with the

Measures/results	**Secondary** -	increasing number of first-degree relatives reportedly afflicted with esophageal cancer -individuals whose both parents were diagnosed with esophageal cancer had an 8-fold excess risk of ESCC, compared with those without any parents affected by esophageal cancer (adjusted OR=7.96, 95% CI: 1.74-36.32) -increasing number of affected siblings did not seem to further increase the relative risks -excess ESCC risks were associated with a positive family history of any cancer (Adjusted OR=1.43, 95% CI:1.13-1.81) or digestive tract cancer (adjusted OR=1.55, 95% CI: 1.23-1.96)

Cooper, S. et al. Risk factors for the development of oesophageal adenocarcinoma in Barrett's oesophagus: a UK primary care retrospective nested case-control study. United European Gastroenterol J. 2. 91-8. 2014

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 3b **Study type:** Nested-case control study	**Funding sources:** 'The Upper GI Blues', CSD Medical Research UK **Conflict of Interests:** The authors declare that there is no conflict of interest. **Randomization:** N.r. **Blinding:** N.r. **Dropout rates:** N.r.	**Total no. patients:** 3749 **Patient characteristics:** BO subjects were identified from The Health Improvement Network (THIN) database. THIN database contains computerized and anonymized longitudinal records from 326 UK general practice (GP) surgeries, covering 5 million patients that are regionally and demographically representative of the UK population **Inclusion criteria:** BO subjects (data record period: 1988-2004) with a minimum of 1 year of follow up, and when applicable, a minimum of 1 year between diagnosis of BO and OC *cases:* Subjects developing OC (oesphageal cancer) *controls:* Subjects who did not develop OC **Exclusion criteria:** Cases proven to be squamous cell carcinoma	**Interventions:** age, gender, smoking, body mass index, medication (aspirin/nonsteroidal anti-inflammatory drugs/proton pump inhibitors, lower oesophageal sphincterrelaxing and asthma drugs) **Comparison:** -male:female -ever smoking: never smoking -high BMI: mid BMI: low BMI -medication quintiles

Notes:	**NOS-rating: 6/8 stars** -It cannot be guaranteed that medication is dispensed or taken by the patient. In some cases (e.g. b-agonist inhalers), multiple devices may be obtained but not used. -overthe-counter medication and drugs prescribed at other institutions will not be recorded. **Author's conclusion:** Progression to OAC from BO is more common among men and with increasing age. There is some evidence of smoking being associated with progression to OAC but this association was not significant on multivariate analysis. LOS-relaxing drugs do not appear to be associated with OAC development once drugs for asthma are excluded. The association of inhaled steroids with OAC development strongly suggests that it is the pathophysiolology of asthma/chronic asthma or the severity of gastro oesophageal reflux necessary to cause asthma, rather the drugs themselves that are associated with progression to OAC.
Outcome Measures/results	**Primary** -Hazard Ratios of risk of developing oesophageal adenocarcinoma from Barrett's oesphagus **Secondary** -	**Results:** -Male gender was associated with progression to OAC (HR 3.06, 95% CI 1.50–6.24, p = 0.002), with 84% of those developing OAC compared with 63% of those remaining with BO. -Increasing age (HR (for each year: 1.03, 95% CI 1.01–1.05, p = 0.005) was associated with developing OAC, with a median age of 67 years (Interquartile range IQR 59–73 years) among those developing OC, compared with a median age of 63 years (IQR 52–72 years) among those who did not progress. -Having smoked doubled the risk for progression to OAC on univariate analysis (HR 2.36, 95% CI 1.13– 4.93, p = 0.023), but there was no significant association when corrected for age and gender (HR 1.99, 95% CI 0.94–4.19, p = 0.07). -There was no association between increasing BMI and progression to OC on univariate and multivariate analyses. -No association was seen when analysed by categorizing BMI 25 kg/m^2, overweight (BMI 25.1–30 kg/m^2), and obese (BMI >30 kg/m^2) -No association was seen between developing OAC and the following drug classes: aspirin, NSAIDs, COX-2 inhibitors, and statins. There was also no association with iron preparations, anticholinergics, ACE-I, calcium-channel antagonists, tricyclic antidepressants, benzodiazepines, or nicorandil -The use of both inhaled steroids (HR 2.11, 95% CI 1.12–3.97, p = 0.021) and steroid and b-agonist combination inhalers (HR 2.54, 95% CI 1.17–5.51, p = 0.018) was associated with progression to OAC on both univariate and multivariate analysis -Increasing number of drugs used for asthma showed an increasing association with progression to OAC (HR 2.91, 95% CI 1.10–7.68, p = 0.031 for the use of all three examined drugs) following correction for age, gender, and smoking status

Hvid-Jensen, F. et al. Proton pump inhibitor use may not prevent high-grade dysplasia and oesophageal adenocarcinoma in Barrett's oesophagus: a nationwide study of 9883 patients. Aliment Pharmacol Ther. 39. 984-91. 2014

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 3b **Study type:** Nested case-control study	**Funding sources:** Institute of Clinical Medicine, Aarhus University Hospital, Denmark **Conflict of Interests:** None **Randomization:** N.r. **Blinding:** N.r. **Dropout rates:** N.r.	**Total no. patients:** 9,883 **Patient characteristics:** **Inclusion criteria:** *all:* All patients with new diagnosis of BO from 1995 to 2009 in Denmark *cases:* Patients with HGD or OAC *controls:* no diagnosis of HGD or OAC before the diagnosis date of the patient, matched according to birth date and date of BO **Exclusion criteria:** -Patients with a diagnosis of HGD or OAC, made before or up to 1 year after the diagnosis of BO	**Interventions:** ever users of PPI (more than 2 prescriptions) **Comparison:** never/rare users of PPI (less than 2 prescriptions)

Notes:	**NOS-rating: 7/8 stars**

	-no data regarding patient's actual compliance to PPI's **Author's conclusion:** No cancer-protective effects from PPI's were seen. In fact, high-adherence and long-term use of PPI were associated with a significantly increased risk of adenocarcinoma or high-grade dysplasia. This could partly be due to confounding by indication or a true negative effect from PPIs. Until the results from future studies hopefully can elucidate the association further, continuous PPI therapy should be directed at symptom control and additional modalities considered as aid or replacement.	
Outcome Measures/results	**Primary** Odds Ratios (ORs) as a measure of the relative risks (RR) of oesophageal adenocarcinoma and high grade dysplasia **Secondary** -	**Results:** -Relative risk of OAC or HGD among BO patients using PPI compared to never/rare users, was 1.1 (95% CI: 0.4–3.3) in former PPI users, 1.9 (95% CI: 0.7–4.9) in ever users and 2.1 (95% CI: 0.8–5.6) in recent users. -Long-term PPI use yielded a relative risk of OAC or HGD of 2.2 (95% CI: 0.7–6.7) in the low-adherence group and 3.4 (95% CI: 1.1–10.5) in high-adherence users.

Moura, M. A. et al. The magnitude of the association between smoking and the risk of developing cancer in Brazil: a multicenter study. BMJ Open. 4. e003736. 2014

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 3b **Study type:** case-control 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 **Randomization:** N.r. **Blinding:** N.r. **Dropout rates:** N.r.	**Total no. patients:** 231 102 **Patient characteristics:** 204 131 cancer cases, 26 971 controls **Inclusion criteria:** -patients with initial diagnosis of 30 different cancer types including oesophageal cancer, diagnosed between 1998 and 2011 and seen in 168 reference centres for cancer treatment, in 24 Brazilian states -controls: patients with non-melanoma skin cancer **Exclusion criteria:** -patients younger than 18 years and older than 100 years -patients with no information on gender and smoking	**Interventions:** gender, smoking **Comparison:** female vs. male, smoking yes vs. no

Notes:	**NOS-rating: 5/8 stars** **Author's conclusion:** This study confirms a high risk of developing cancer of the hypopharynx, bronchi and lung, larynx, oropharynx and oral cavity, *oesophagus* and bladder cancer among smokers and establishes the AF attributable to smoking in the development of different types of cancer in Brazil.	
Outcome Measures/results	**Primary** Odds Ratio (OR) of association of risk between tobacco consumption and cancer development **Secondary** Attributable Fractions (AF) referring to cancer sites for both genders	**Results:** -Tobacco was classified as a strong risk factor for cancers of the oesophagus (adjusted OR = 4.0 (95% CI 3.7-4.2)) -THE AF results referring to cancer sites for both genders was 58.7% for oesophageal cancer

Pottegard, A. et al. Use of benzodiazepines or benzodiazepine related drugs and the risk of cancer: a population-based case-control study. Br J Clin Pharmacol. 75. 1356-64. 2013

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 3b **Study type:** population-based case-control study	**Funding sources:** Not reported. **Conflict of Interests:** All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare MA and JH have participated in research projects funded by Nycomed, the manufacturer of nitrazepam, and Pfizer, the manufacturer of Halcion (triazolam) and Tafil (alprazolam), with grants paid to institutions where they have been employed. JH has personally received fees for teaching from Nycomed. AP and SF declare no conflicts of interest. **Randomization:** N.r. **Blinding:** N.r. **Dropout rates:** N.r.	**Total no. patients:** 149 360 cases, 1 194 729 controls **Patient characteristics:** Patients registered in The Danish Cancer Registry **Inclusion criteria:** -All Danish residents alive on January 2002 -Lived in Denmark continuously from 1995 to the index date -No history of any cancer (except non-melanoma skin cancer) prior to the index date **Exclusion criteria:** -Persons who redeemed a prescription for any anxiolytic, hypnotic or sedative (ATC-codes, N05B and N05C) during the first 2 running years of the prescription database, i.e. 1995 and 1996	**Interventions:** Ever use and long term use of BZRD (cumulative amount of BZRD equal to/greater than 500 DDD within a period of 5 to 1 year prior to the index date) BZRD: Benzodiazepines or benzodiazepine related drugs **Comparison:** No use of BZRD

Notes:	**NOS-rating: 7/8 stars** **Author's conclusion:** In conclusion, our findings do not support a carcinogenic effect of BZRD. Most ORs were close to unity, except a few that seemingly can be explained by lifestyle confounding. We also found that the recently reported excess of cancers among BZRD users can be explained entirely by a flawed design. For other reasons than carcinogenesis, however, use of BZRD should generally be avoided, or reserved for short term use in select patient groups.	
Outcome Measures/results	**Primary** Odds Ratio (OR) for cancer associated with use of BZRD **Secondary** -	**Results:** Association between long term exposure to BZRD and oesophageal cancer risk: Adjusted OR = 1.43 (95% CI: 1.01 - 2.02)

Sewram, V. et al. Tobacco and alcohol as risk factors for oesophageal cancer in a high incidence area in South Africa. Cancer Epidemiol. 41. 113-21. 2016

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 3b **Study type:** hospital-based Case-Control Study	**Funding sources:** South African Medical Research Council, The Rockefeller Foundation, Cancer Council NSW and UICC are	**Total no. patients:** 670 cases; 1188 controls **Patient characteristics:** **Inclusion criteria:** CASES -All patients with	**Interventions:** Tobacco use (Smoking status: never vs. ever; Commercial cigarettes: never vs. ever; No. of cigarettes per day: Never vs. 1-4; Hand-rolled cigarettes: Never vs. ever; No. of hand-rolled cigarettes per day: Never vs. 1-3, 4-6, 7+; Pipe: Never vs. ever; No. of pipes per day: Never vs. 1-3, 4-6, 7+; Total Tobacco (grams per day/All smokers): Never vs. 1-7, 7.1-14, 14.5) Alcohol consumption (Alcohol consumption: Never vs. ever; Maize beer (consumption per week: Never, ≤ 1 day, 2-4 days, 5-7 days); Quantity of

	acknowledged for their financial support of this study. **Conflict of Interests:** The authors declare that they have no conflict of interest. **Randomization:** N.r. **Blinding:** N.r. **Dropout rates:** N.r.	incident histopathologically, radiologically or endoscopically confirmed squamous cell carcinoma of the oesophagus between November 2001 and February 2003, South Africa -sufficient good physical and mental health -Patients lived in the Eastern Cape Province for at least 5 years prior to diagnosis CONTROLS -diseases/conditions not related to smoking, alcohol consumption or diet **Exclusion criteria:** -	Maize beer per week (Litres): Never, ≤ 1 vs. 1.01-3, 3.01+; Sorghum beer: Never vs. ≤ 1 day, 2-4 days, 5-7 days; Quantity Sorghum beer peer week (Litres): Never vs. ≤ 1, 1.1-3, >3; Commercial beer: Never vs. ≤ 1 day, 1.01-2, >2; Home-made spirits: Never vs. ever; Commercial spirits: Never vs. ≤ 1 day, 2-4 days, 5-7 days; Quantity commercial spirits consumed per week (Litres): Never vs. 0.025-0.1, 0.11+; Wine: Never vs. ≤ 1 day, 2+ days; Quantity wine consumed per week (Litres): Never vs. 0.1-1, >1 **Comparison:** see "interventions"
Notes:	**NOS-rating: 4/8 stars** -interview was not blinded to case/control status (risk of bias) **Author's conclusion:** Our study shows that 58% and 48% of oesophageal cancers were attributed to smoking and alcohol consumption respectively, therefore a substantial health benefit could be expected by efforts to reduce the prevalence of smoking and drinking. Recent data suggest that only after at least 10 years of abstaining from drinking does the risk of oesophageal cancer return to being within the risk levels for abstainers and that stopping smoking for 5 years cuts the risk by 50%. After 10 or more years since stopping both habits the relative risk is about one-tenth of that of current smokers and drinkers, but local data on this effect are unavailable.		
Outcome Measures/results	**Primary** Adjusted Odds Ratio (OR) for risk of developing oesophageal cancer **Secondary** Population attributable fractions (PAFs)	**Results:** Tobacco use: -Males: ever smokers (70%) had 4-fold increased odds compared to never smokers (OR = 4.11, 95% CI 2.55–6.65). -Females: ever smokers had approximately 3.5-fold increased odds (OR = 3.45, 95% CI 2.47–4.82) compared with nonsmokers. -Male commercial smokers: 78% indicated smoking commercial cigarettes with ever smokers having almost 40% greater odds of developing OC (OR = 1.39, 95% CI 1.01–1.92). -Males smoking hand-rolled cigarettes (70%) and pipe smoking (64%): Those reporting having smoked 7 or more hand-rolled cigarettes per day had 4.4-times greater odds of developing OC (OR = 4.40, 95% CI 2.35–8.24), whilst those smoking 7 or more pipes per day had a 7.72 times increased odds compared to non-smokers (95% CI 3.99–14.92). -Amongst the female smokers, 43% indicated having smoked commercial cigarettes. Females having smoked 7 or more hand-rolled cigarettes per day had 3-times greater odds of developing OC (OR = 3.14, 95% CI 1.09–9.07), whilst those smoking 7 or more pipes per day had almost 6-fold increased odds compared to nonsmokers (OR = 5.63, 95% CI 2.05–15.43). -Males and females smoking more than 14 g of tobacco per day had approximately 6-times greater odds of developing OC compared to non-smokers (Male OR = 6.27, 95% CI 3.74–10.52, female OR = 5.60, 95% CI 3.23–9.73). *Alcohol use:* -Male ever drinkers had a 3.5-fold increased odds of OC (OR = 3.48, 95% CI 1.99–6.06) and females had 2-fold increased odds (OR = 2.23, 95% CI 1.60–3.11) compared to nondrinkers. -Males and females consuming maize beer 2–4 days per week had 4-fold increased odds compared to non-drinkers (males OR = 4.04, 95% CI 2.19–7.46; females OR = 4.29, 95% CI 2.49–7.37) -Risk increased with the quantity of each beverage type consumed with ORs ranging between 4.00 and 5.50 for the highest quantity category, the exception being for females consuming more than 1 litre of wine per week who had 7 times greater odds of developing OC (OR = 7.10, 95% CI 3.39–14.87). -Total ethanol consumption (representing the sum of the averages of grams of ethanol from each of beer, spirits and wine) was positively associated with OC risk with male drinkers consuming more than 52.8 g per day having almost 5-times the odds of developing OC (OR = 4.72, 95% CI 2.64–8.41) than non-drinkers. -Female drinkers, 5-fold increased odds was observed for those consuming more than 52.8 g of ethanol per day (OR = 5.24, 95% CI 3.34–8.23). -Lower estimated ORs were observed for lower alcohol consumption. *Joint effects:* -Those using more than 14 g of tobacco/day and consuming more than 371 g ethanol/week had 8.45-fold increased odds of developing oesophageal cancer (95% CI 5.51–12.96) compared to those who are both non-smokers and non-drinkers. *PAFs:* -The attributed fraction for both exposures (alcohol and tobacco) combined was 64%

Vinogradova, Y. et al. Exposure to bisphosphonates and risk of gastrointestinal cancers: series of nested case-control studies with QResearch and CPRD data. Bmj. 346. f114. 2013			
Evidence level	**Methodical Notes**	**Patient characteristics**	**Interventions**
Evidence level: 3b **Study type:** Series of nested case-control studies	**Funding sources:** This work was funded by the division of primary care of University of Nottingham. **Conflict of Interests:** All authors have completed the Unified Competing Interest from www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any additional organisation for the submitted work. **Randomization:** Not relevant **Blinding:** Not relevant **Dropout rates:** Not relevant	**Total no. patients:** QResearch database: 5364 cases, 25 101 controls CPRD database: 5132 cases, 24 053 controls Total: 59 650 **Patient characteristics:** Patients aged over or equal 50 with a diagnosis of primary gastrointestinal cancer in 1997-2011, each matched with up to five controls by age, sex, practice and calendar year **Inclusion criteria:** -open cohort for patients aged over or equal 50 years and registered with the practice at some time during the study period (January 1997 to July 2011) -gastrointestinal cancers (oesophageal, gastric colorectal) -at least two years of data before their index date to ensure the completeness of records **Exclusion criteria:** -patients aged lower 50 years -cases and controls with prescriptions for bisphosohonates licensed for any malignancies before the index date. -patients with Paget's disease	**Interventions:** exposure to biphosphonates (alendronate, etidronate, ibandronate, risedronate) **Comparison:** No exposure to biphosphonates (alendronate, etidronate, ibandronate, risedronate)
Notes:	NOS-rating: 5/8 stars -selection of cases was based on the first record of a cancer while the exact origin site might have been determined only later -no data available on adherence to treatment **Author's conclusion:** In this series of population based case-control studies in two large primary care databases, exposure to biphosphonates was not associated with an increased risk of common gastrointestinal cancers.		
Outcome Measures/results	**Primary** Odds ratios for incident gastrointestinal cancers (colorectal, oesophageal, gastric) and use of biphosphonates, adjusted for smoking status, ethnicity, comorbidities, and use of other drugs. **Secondary** -	**Results:** -5135 cases of oesophageal cancer cases were identified from QResearch and CPRD. -Overall biphosphonate use was not associated with risk of oesophageal in either database. Adjusted odds ratio (95% CI) for QResearch and CPRD were 0.97 (95% CI; 0.79-1.18) and 1.18 (95% CI; 0.97-1.43) for oesophageal cancer -There were no significant associations for individual types of bisphosphonate	

Agrawal, S. et al. Metformin use and the risk of esophageal cancer in Barrett esophagus. South Med J. 107. 774-9. 2014			
Evidence level	**Methodical Notes**	**Patient characteristics**	**Interventions**
Evidence level: 3b- **Study type:** Retrospective case-control study	**Funding sources:** The authors have no financial relationships to disclose **Conflict of Interests:** The authors have no conflicts of interest to report **Randomization:** n.r. **Blinding:** n.r. **Dropout rates:** n.r.	**Total no. patients:** 583 **Patient characteristics:** Veterans (Military veteran's hospital) 115 EAC, 468 BE, 98% men, 96% white **Inclusion criteria:** All patients at Military veteran's hospital (U.S.) with diagnoses of BE and EAC between 1992 and 2012 **Exclusion criteria:** All patients with histological diagnosis of esophageal squamous cell carcinoma	**Interventions:** medication (metformin, statin, aspirin, proton pump inhibitor), age, BMI, alcohol use, **Comparison:** no use of medication, BMI categories (<25.00, 25-29.99, ≥30), no alcohol use
Notes:	**NOS-rating: 5/8 stars** <u>-no association analysis was conducted concerning metformin use and risk of EAC</u> -no collection of data regarding duration and dosage of metformin use -risk of recall bias due to data collection via chart review -participants not representative of average population: very specific cases and controls regarding demographic data (98% men, 96% white) **Author's conclusion:** The three independent variables that predicted progression of Barrett esophagus to esophageal adenocarcinoma in our study were older age, smoking and diabetes mellitus. Statin use showed protective effect against development of esophageal adenocarcinoma. Metformin use did not demonstrate any statistically significant protective effect.		
Outcome Measures/results	**Primary** Odds Ratios (OR) of risk of developing EAC **Secondary** -	**Results:** -No significant difference in metformin use in patients with EAC and BE -Age (OR 1.04; 95% CI 1.02-1.07), smoking (OR 2.27; 95% CI 1.28-4.02), diabetes mellitus (OR 2.15; 95% CI 1.27-3.64) were significant risk factors for the development of EAC -Statin use was protective against the development of cancer (OR 0.46; 95% CI 0.28-0.75)	

Rafiq, R. et al. Secondhand Smoking and the Risk of Esophageal Squamous Cell Carcinoma in a High Incidence Region, Kashmir, India: A Case-control-observational Study. Medicine (Baltimore). 95. e2340. 2016			
Evidence level	**Methodical Notes**	**Patient characteristics**	**Interventions**
Evidence level: 3b- **Study type:** Case-control	**Funding sources:** This study was supported by Extramural Grant of Indian Council of Medical Research (ICMR), New Delhi. Rumaisa Rafiq	**Total no. patients:** 703 ESCC patients, 1664 controls **Patient characteristics:** **Inclusion criteria:** *-cases:* ESCC patients from Regional Cancer Centre and Department of Radiation Oncology of Sher-i-Kashmir	**Interventions:** weekly exposure to secondhand smoking

study	was supported by Department of Science and Technology (DST), New Delhi **Conflict of Interests:** The authors have no conflicts of interest to disclose **Randomization:** N.r. **Blinding:** Not reported **Dropout rates:** N.r.	Institute of Medical Sciences (SKIMS) from September 2008 to January 2012 -*controls:* SKIMS, Government Medical College Hospital, and 10 district hospitals of Kashmir. Matched for cases regarding sex, age, and district of residence. **Exclusion criteria:** -cases: without history of previous cancer -controls:Disease for which they had been admitted did not have a strong association with tobacco or alcohol consumption	**Comparison:** no (never) exposure to secondhand smoking
Notes:	**NOS-rating: 5/8 stars** -unclear if interviews were blinded to case/control status -control group consisted of patients when disease for which they had been admitted did not have a strong association with tobacco/alcohol consumption → ESCC patients not explicitly excluded -in group of tobacco consumers, patients who *chew* tobacco were also included (cultural specificity) **Author's conclusion:** Our findings indicate increased risk of ESCC due to SHS exposure in dose-dependent manner. Our results may help to increase the awareness about harms of SHS, particularly in developing populations where tobacco use is on rise and ESCC incidence is high. However, more studies with a larger sample size are required before making any conclusion on the association between SHS and ESCC risk.		
Outcome Measures/results	**Primary** Odds Ratios (95% CI) for risk of ESCC development **Secondary**	**Results:** -Secondhand smoking (SHS) in the unadjusted model increased ESCC risk (OR = 1.64; 95% CI, 1.14– 2.36); however, the association was attenuated and the 95% CI included unity (OR = 1.23; 95% CI, 0.72–2.11) in the models adjusted for tobacco smoking and chewing and other potential confounding factors.The OR (95% CI) for the association between weekly exposure to secondhand smoke for >14 h and ESCC risk, compared to no exposure, was (OR = 1.91; 95% CI, 0.75–4.89) -When analysis was limited to never tobacco users (never smokers and never chewers) the OR (95% CI) for the association between SHS and ESCC risk, in adjusted model, was (OR = 1.32; 95% CI, 0.43–4.02) (Table 2). The OR increased with a higher exposure (OR = 2.69; 95% CI, 0.75– 20.65) for SHS >14 h a week versus no exposure	

Inhaltsverzeichnis der Evidenztabellen

Schlüsselfrage:

AG 2 <u>Diagnostik:</u> Stellenwert endoskopischer Spezialuntersuchungen (z.B. Chromoendoskopie, NBI, Zoom etc.) (Primärdiagnostik)

Citation	Evidence Level	Study Type
Qumseya, B. J. 2013	2a	Syst REview, Meta Analysis, 14 studies (11 RCTs) (n=843)
Sharma, P. 2013	1b	RCT - cross over within 3-8 weeks
Canto, M. I. 2014	1a	RCT
Gupta, A. 2014	2a	Systematic REview, Meta Analysis, 8 studies, n= 345 patients, n=3080 lesions
Fugazza, A. 2016	2a	Systematic REview, Meta Analysis, 102 studies (prospective, retrospective clinical studies)n=6943, 16 countries.
Chung, C. S. 2016	2a	Systematic review and meta-analysis (n= 4918 patients from 16 prospective and randomized trials)
Coletta, M. 2016	2a	Meta Analysis, 13 prospective studies (n= 1690)

Evidenztabellen

zurück

Schlüsselfrage:

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

Bewertungsvorlage:

OXFORD Appraisal Sheet 1: Systematic Reviews

Chung, C. S. et al. Image-enhanced endoscopy for detection of second primary neoplasm in patients with esophageal and head and neck cancer: A systematic review and meta-analysis. Head Neck. 38 Suppl 1. E2343-9. 2016

Evidence level/Study Types	Population	Outcomes/Results	Literature References	Methodical Notes
Evidence level: 2a **Study type:** Systematic review and meta-analysis (n= 4918 patients from 16 prospective and randomized trials) **Databases:** PubMed and Cochrane Library **Search period:** January 1, 1990, to May 1, 2014. **Inclusion Criteria:** (1) studies on humans and in the English language; (2) randomized controlled trials, prospective studies, or cohort studies; (3) outcome measurement, including sensitivity, specificity, or accuracy; (4) availability of adequate data for analysis. **Exclusion Criteria:** Studies of Barrett's esophagus, adenocarcinoma, Studies without raw data Studies primarily designed as case reports, reviews, or retrospective studies	**Intervention:** Patients with esophageal (n=2205) and head and neck (n=1781) cancer. Image-enhanced endoscopy for detection of second primary neoplasm. **Comparison:** White-light imaging (WLI), narrow band imaging (NBI), and Lugol chromoendoscopy	**Primary:** detection of second primary neoplasm **Secondary:** --- **Results:** WLI, NBI, and Lugol chromoendoscopy pooled sensitivity 0.53 (95% CI = 0.48–0.59; chi-square = 30.00; p = .0016; I^2 = 63.3%), 0.87 (95% CI = 0.83–0.90; chi-square = 113.02; p < .0001; I^2 = 90.3%), 0.88 (95% CI = 0.85–0.91; chisquare = 15.61; p = .0484; I^2 = 48.7%), pooled specificity 0.99 (95% CI = 0.98–0.99; chisquare = 108.59; p < .0001; I^2 = 89.9%), 0.95 (95% CI = 0.94–0.96, chi-square = 138.11; p < .0001; I^2 =92.0%), 0.63 (95% CI = 0.61–0.66, chi-square = 105.01; p < .0001; I^2 = 92.4%). the areas under the receiver-operating characteristic (ROC) curve were 66%, 97%, and 82%. NBI endoscopy has the most highly accurate diagnostic performance for detection of second primary neoplasms in high-risk patients. Lugol chromoendoscopy was never used in evaluation of a head and neck second primary neoplasm. The sensitivity of NBI in screening the esophagus (0.97%; 95% CI = 0.95–0.99) was superior to head and neck second primary neoplasms (0.61%; 95% CI = 0.51–0.70). **Author's Conclusion:** In this systematic review and meta-analysis of 16 studies consisting of 4918 patients with esophageal cancers, head and neck cancers, and high-risk endoscopy for the detection of second primary neoplasm. Our result highlights the high diagnostic performance of NBI endoscopy and proposes routine surveillance for second primary neoplasms in high-risk populations.	Morimoto M, Nishiyama K, Nakamura S, et al. Jpn J Clin Oncol 2010; Chung CS, Liao LJ, Lo WC, et al. BMC Gastroenterol 2013; Yokoyama A, Ichimasa K, Ishiguro T, et al. Dig Endosc 2012. Watanabe A, Taniguchi M, Tsujie H, et al. Otolaryngol Head Neck Surg 2008; Wang CH, Lee YC, Wang CP, et al. Dig Endosc 2014; Tincani AJ, Brandalise N, Altemani A, et al. Head Neck 2000; Takenaka R, Kawahara Y, Okada H, et al. Am J Gastroenterol 2009; Shiozaki H, Tahara H, Kobayashi K, et al. Cancer 1990; Nonaka S, Saito Y, Oda I, Kozu T, Saito D. J Gastroenterol Hepatol 2010; Muto M, Minashi K, Yano T, et al. J Clin Oncol 2010; Moschler O, Spahn TW, Middelberg–Bisping C, et al. Digestion 2006; Lee YC, Wang CP, Chen CC, et al. Gastrointest	**Funding Sources:** --- **COI:** --- **Study Quality:** Risk of bias in Quality Assessment of Diagnostic Accuracy Studies-2 was low. **Heterogeneity:** See Results **Publication Bias:** --- **Notes:**

			Endosc 2009; Lee CT, Chang CY, Lee YC, et al. Endoscopy 2010; Katada C, Tanabe S, Koizumi W, et al. Endoscopy 2010; Katada C, Muto M, Nakayama M, et al. Laryngoscope 2012; Ishihara R, Takeuchi Y, Chatani R, et al. Dis Esophagus 2010; Ide E, Maluf–Filho F, Chaves DM, Matuguma SE, Sakai P. World J Gastroenterol 2011; Hori K, Okada H, Kawahara Y, et al. Am J Gastroenterol 2011; Hashimoto CL, Iriya K, Baba ER, et al. Am J Gastroenterol 2005; Fukuhara T, Hiyama T, Tanaka S, et al. J Clin Gastroenterol 2010; Dubuc J, Legoux JL, Winnock M, et al. Endoscopy 2006; Boller D, Spieler P, Schoenegg R, et al. Surg Endosc 2009;	

Coletta, M. et al. Acetic acid chromoendoscopy for the diagnosis of early neoplasia and specialized intestinal metaplasia in Barrett's esophagus: a meta-analysis. Gastrointest Endosc. 83. 57-67 e1. 2016

Evidence level/Study Types	Population	Outcomes/Results	Literature References	Methodical Notes
Evidence level: 2a **Study type:** Meta Analysis, 13 prospective studies (n= 1690) **Databases:** Ovid MEDLINE, Ovid Embase,Web of Science **Search period:** up to March 2014 **Inclusion Criteria:** (1) included adult patients 18 years of age or older, (2) reported data on the diagnostic accuracy of AAC with or without magnification (index test) for the detection of HGD/EC or SIM, (3) used histopathological assessment as the reference standard, (4) described the endoscopic and mucosal patterns of the assessed areas, or (5) performed real-time assessment of lesions or post hoc characterization of digital images or videos **Exclusion Criteria:** (1) there was no description	**Intervention:** Acetic acid chromoendoscopy for diagnosis **Comparison:** Histopathology	**Primary:** diagnostic accuracy in HGD/EC **Secondary:** Diagnostic accuracy in SIM **Results:** 1. HGD/EC 9 studies, n=1379. Sensitivity 0.92 (95% CI,0.83-0.97). Specificity 0.96 (95% CI, 0.85-0.99) LR+ 25.0 (95% CI, 5.9-105.3). LR- 0.08 (95% CI, 0.04-0.18) 2. SIM 8 studies, n=516. Sensitivity 0.96 (95% CI, 0.83-0.99). Specificity 0.69 (95% CI, 0.54-0.81) LR+ 3.0 (95% CI, 2.0-4.7), LR- 0.06 (95% CI, 0.01-0.26) **Author's Conclusion:** AAC has	Bhandari et al, 2012, Dis Esophagus Ferguson et al, 2006, Am J Gastroenterol Fortun et al,2006, Aliment Pharmacol Ther Guelrud et al,2001, Gastrointest Endosc Hoffman et al,2006,Gastrointest Endosc Hoffman et al,2014, Gastrointest Endosc Longcroft-Wheaton	**Funding Sources:** Dr Sami is funded by an Olympus Core National Endoscopy Research Fellowship grant (RB4803), Core charity, United Kingdom. **COI:** All other authors disclosed no financial relationships relevant to this

of lesion characterization or endoscopic technique; (2) other imaging techniques in combination with AAC were used, namely, methylene blue, indigo carmine,narrow-band imaging, iScan, and Fuji Intelligence Chromoendoscopy;or (3) there were insufficient data		an overall high diagnostic accuracy for detecting HGD/EC in patients with BE. For SIM characterization, AAC sensitivity is very high but has poor specificity, suggesting that histological confirmation is necessary when AAC is positive.	et al, 2010, Clin Gastroenterol Hepatol Mayinger et al, 2006, Scand J Gastroenterol Pohl et al, 2007, Endoscopy Pohl et al, 2010, Am J Gastroenterol Reaud et al, 2006, Gastroenterol Clin Biol Vazquez-Iglesias et al, 2007, J Gastroenterol Hepatol Yagi et al, 2006, Dig Endosc	publication. **Study Quality:** Prospective Studies **Heterogeneity:** No significant sources of heterogeneity **Publication Bias:** no info **Notes:**

Fugazza, A. et al. Confocal Laser Endomicroscopy in Gastrointestinal and Pancreatobiliary Diseases: A Systematic Review and Meta-Analysis. Biomed Res Int. 2016. 4638683. 2016

Evidence level/Study Types	Population	Outcomes/Results	Literature References	Methodical Notes
Evidence level: 2a **Study type:** Systematic REview, Meta Analysis, 102 studies (prospective, retrospective clinical studies)n=6943, 16 countries. **Databases:** MEDLINE, EMBASE, Scopus, and Cochrane Oral Health Group Specialized Register **Search period:** Until January 2015. **Inclusion Criteria:** The search was restricted to studies that were performed in humans and that were published in English. Prospective and retrospective clinical studies were both eligible for inclusion, and there were no limits based on trial duration. **Exclusion Criteria:** Review articles, case reports, commentaries, editorials, letters, and conference abstracts were not considered. Likewise, ex vivo studies were excluded.	**Intervention:** Evaluate the applicability and diagnostic yield of CLE in patients with gastrointestinal and pancreatobiliary diseases. **Comparison:** histopathological diagnosis	**Primary:** sensitivity,specificity, accuracy of CLE **Secondary:** none **Results:** Esophagus surveillance and evaluation of suspicious lesions, Barrett's esophagus "per biopsy" meta-analysis of 7 studies. Pooled sensitivity of 58% (CI95%: 52%–63%; I2: 95.2%), specificity of 90% (CI95%: 89%–91%; I2: 96.9%), Pooled positive likelihood ratio (LR) of 11.57 (CI95%: 5.38–24.89; I2: 93.7%), pooled negative LR of 0.23 (CI95%: 0.08–0.64; I2: 98%).Theare a under the curve was 0.9758. "per patient" meta-analysis based on 4 studies. Pooled sensitivity of 79% (CI95%: 65%–90%; I2 : 58.5%), specificity of 90%(CI95%: 85%–94%; I2: 82.9%), Pooled positive LR of 8.04 (CI95%: 2.28–28.3; I2: 83.5%), negative LR of 0.24 (CI95%: 0.08–0.69; I2: 55.4%). The area under the curve was 0.926. Stomach and Duodenum. Detection of polyps and neoplastic lesions "per patient" meta-analysis for 3 of the included studies. Pooled sensitivity of 85% (CI95%: 78%–91%; I2: 52.3%), specificity of 99% (CI95%: 98%-99%; I2: 92.9%), Pooled positive LR of 16.49 (CI95%: 1.48–183.19; I2: 96%), negative LR of 0.16 (CI95%: 0.08–0.35; I2: 57.4%). The area under the curve was 0.929. The estimated diagnostic accuracy of CLE ranged from 85% to 98.8%. Gastritis and gastric metaplasia, "per biopsy" metaanalysis 6 studies were included. Pooled sensitivity of 94% (CI95%: 92%–96%; I2: 54.8%), specificity of 95% (CI95%: 92%–97%; I2: 55.6%), Pooled positive LR of 17.66 (CI95%: 9.04–34.51; I2: 63.8%), negative LR of 0.07 (CI95%: 0.04–0.12; I2: 47.4%). The area under the curve was 0.9832. Helicobacter Pylori-related gastritis A meta-analysis of two studies Pooled sensitivity of 86% (CI95%: 76%–93%; I2: 0%), specificity of 93% (CI95%: 87%–97%; I2: 2.6%), Pooled positive LR of 11.28 (CI95%: 5.4–23.57; I2: 15.5%), negative LR of 0.16 (CI95%: 0.09–0.27; I2: 0%). Assessing celiac disease (intraepithelial lymphocytes and villous atrophy) A meta-analysis performed on 3 studies. Pooled Sensitivity of 84% (CI95%: 72%–92%; I2: 71.3%), specificity of 94% (CI95%: 85%–99%; I2: 66.4%), Pooled positive LR of 9.9 (CI95%: 2.12–46.35; I2: 53.9%), negative LR of 0.15 (CI95%: 0.04–0.52; I2: 45.2%). The area under the curve was 0.9691. Colon Dysplasia and neoplasia in IBD patients A meta-analysis of 4 studies. "per lesion" sensitivity of 80% (CI95%: 61%–92%; I2: 84.5%), pooled specificity of 93% (CI95%: 9%–96%; I2: 86.3%), positive LR of 8.76 (CI95%: 1.78–44.23; I2: 71.7%),	102 studies	**Funding Sources:** no info **COI:** None of the authors have a conflict of interests to disclose in relation to the present systematic review. **Study Quality:** Based on the GRADE system, the overall quality of the evidence included in our analysis was judgedas low(10 studieshadavery low levelofquality; 59 were low; 31 weremoderate; and 2 were high). **Heterogeneity:** no info **Publication Bias:** 6 RCTS high risk, 17 studies high risk **Notes:**

		negative LR of 0.25 (CI95%: 0.01–7.44; I2: 96.2%).The area under the curve was 0.9630. Colorectal neoplasms and polyps A meta-analysis of 7 studies. "per lesion" sensitivity of 83% (CI95%: 79%–87%; I2: 88.8%), pooled specificity of 90% (CI95%: 87%–92%; I2: 94.8%), Pooled positive LR of 6.65 (CI95%: 2.8–15.8; I2: 90.3%), negative LR of 0.17 (CI95%: 0.07–0.43; I2: 92%). The area under the curve was 0.9430. Biliary Duct diagnosis of common biliary duct lesions. Meta-analysis of 8 studies Pooled sensitivity of 90% (CI95%: 86%–94%; I2: 1.6%), specificity of 72% (CI95%: 65%–79%; I2: 0%), Pooled positive LR of 3.21 (CI95%: 2.55–4.11; I2: 0%), negative LR of 0.15 (CI95%: 0.10–0.23; I2: 0%).The area under the curve was 0.8578. Pancreas Pancreatic lesions A meta-analysis of two studies. Pooled sensitivity of 68% (CI95%: 55%–80%; I2: 79.8%), specificity of 90% (CI95%: 74%– 98%; I2: 82.4%), Pooled positive LR of 6.72 (CI95%: 0.94–47.89; I2: 52%), negative LR of 0.30 (CI95%: 0.10–0.84; I2: 60.6%). **Author's Conclusion:** In gastrointestinal and pancreatobiliary diseases, endoscopyassociated new technologies should offer the possibility to make clear diagnosis when routine procedures make it difficultly be cost-effective with clear impact on the choice of endoscopy versus surgical therapies for macroscopic lesions and achieve early detection of malignancies in those individuals with very high risk of cancer development. CLE is one of these new technologies able to address the challenge. The overall sensitivity, specificity, accuracy, and predictive values of CLE are favorable and were often found to be superior in comparison with standard endoscopy plus histopathology. However, the widespread use of CLE remains limited by its low availability, high costs, and need for trained personnel. Moreover, there is a need for further clinical trials, including medicoeconomic evaluations, to assess the applicability and implementation of CLE in routine clinical practice, as currently very few such studies exist.		

Gupta, A. et al. Utility of confocal laser endomicroscopy in identifying high-grade dysplasia and adenocarcinoma in Barrett's esophagus: a systematic review and meta-analysis. Eur J Gastroenterol Hepatol. 26. 369-77. 2014

Evidence level/Study Types	Population	Outcomes/Results	Literature References	Methodical Notes
Evidence level: 2a **Study type:** Systematic REview, Meta Analysis, 8 studies, n= 345 patients, n=3080 lesions **Databases:** Medline, Cochrane Central Register **Search period:** 1946 to May 2013 **Inclusion Criteria:** Studies carried out in humans and published in the English literature Prospective studies that compared the accuracy of CLE with standard four-quadrant biopsies for the detection of HGD and EAC in Barrett's esophagus. **Exclusion Criteria:** Case reports, review papers,consensus letters, abstracts, studies that included patients with squamous cell carcinoma	**Intervention:** Confocal laser endomicroscopy in identifying high-grade dysplasia and adenocarcinoma in Barrett's esophagus **Comparison:** standard four-quadrant biopsies	**Primary:** diagnostic accuracy of the CLE-based targeted biopsies in detecting HGD/adenocarcinoma **Secondary:** ---- **Results:** Per-lesion' analysis (7 studies) for the diagnosis of HGD/adenocarcinoma yielded a pooled sensitivity and specificity of 68% (95% CI of 64–73%, I^2 statistic of 96.1%)and 88% (95% CI of 87–89%, I^2 statistic of 95.6%), respectively. The pooled positive and negative likelihood ratios were 6.56 (95% CI of 3.61–11.90, I^2 statistic of 89%) and 0.24 (95% CI of 0.09–0.63, I^2 statistic of 98%),respectively. Similar numbers were calculated on the basis of 'per-patient' basis (4 studies), which showed a pooled sensitivity and specificity of 86% (95% CI of 74–94%, I^2 statistic of 54%) and 83% (95% CI of 77–88%, I^2 statistic of 90.9%), respectively. The pooled positive and negative likelihood ratios were 5.61 (95% CI of 2.00–15.69, I^2 statistic of 80.5%) and 0.21 (95% CI of 0.08–0.59, I^2 statistic of 55.8%), respectively. **Author's Conclusion:** Our systematic review and meta-analyses suggest that CLE with targeted biopsies has good diagnostic	Kiesslich R, Gossner L, Goetz M, et al. Clin Gastroenterol Hepatol 2006; Gaddam S, Mathur SC, Singh M, et al. Am J Gastroenterol 2011; Dunbar KB, Okolo P, Montgomery E, Canto MI. Gastrointest Endosc 2009; Pohl H, Rosch T, Vieth M, Koch M, et al. Gut 2008; Sharma P, Meining AR, Coron E, et al.Gastrointest Endosc 2011; Wallace MB,	**Funding Sources:** --- **COI:** There are no conflicts of interest **Study Quality:** Oxford RoB table: low risk **Heterogeneity:** High , see results **Publication Bias:** ---- **Notes:**

		accuracy for detecting HGD/EAC. However, because of its relatively low sensitivity and positive LR, it may not replace the standard of care at this time. The overall prevalence of HGD/EAC in the studies included was much higher than what would be seen in clinical practice and these results should be interpreted with caution. Further studies are needed before CLE can surpass random biopsies for the diagnosis of dysplasia in Barrett's esophagus.	Sharma P, Lightdale C, et al.Gastrointest Endosc 2010; Jayasekera C, Taylor A, Desmond P, Macrae F, Williams R. Endoscopy 2012; Bajbouj M, Vieth M, Rosch T, Miehlke S, et al. Endoscopy 2010;	

Qumseya, B. J. et al. Advanced imaging technologies increase detection of dysplasia and neoplasia in patients with Barrett's esophagus: a meta-analysis and systematic review. Clin Gastroenterol Hepatol. 11. 1562-70 e1-2. 2013

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

			Digestive and Liver Disease. 2006; Sharma P, Hawes RH, Bansal A, et al. Gut. 2012	

Evidenztabellen

zurück

Schlüsselfrage:

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

Bewertungsvorlage:

OXFORD Appraisal Sheet 2: RCT

Sharma, P. et al. Standard endoscopy with random biopsies versus narrow band imaging targeted biopsies in Barrett's oesophagus: a prospective, international, randomised controlled trial. Gut. 62. 15-21. 2013

Population	Intervention	Outcomes/Results	Methodical Notes
Evidence level: 1b **Study type:** RCT - cross over within 3-8 weeks **Number of Patient:** 123 **Recruitung Phase:** October 2005 to April 2009 **Inclusion Criteria:** over the age of 18 **Exclusion Criteria:** erosive oesophagitis or grossly visible nodules or lesions (>5 mm)within the BO segment suggestive of invasive OAC or contraindications to oesophageal biopsies such as anticoagulation or varices	**Intervention:** White light endoscopy with random biopsies **Comparison:** Narrow band imaging (NBI)targeted biopsies	**Primary:** Proportion of patients with biopsy-confirmed IM **Secondary:** proportion of patients with dysplasia/cancer, proportion of areas with dysplasia and/or cancer and number of biopsies obtained using each procedure **Results: Overall detection** Both HD-WLE and NBI detected 104/113 (92%) patients with IM, but NBI required fewer biopsies per patient (3.6 vs 7.6, p < 0.0001). **Detection of dysplasia** NBI detected a higher proportion of areas with dysplasia (30% vs 21%, p = 0.01). During examination with NBI, all areas of high-grade dysplasia and cancer had an irregular mucosal or vascular pattern. **Detection of subtle visible lesions** There was no statistically significant difference in the proportion of dysplastic visible lesions identified by NBI compared with HD-WLE (5/11 vs 6/22, p = 0.44). **Characteristics of NBI surface patterns** Of the 143 ridged/villous mucosal pattern areas, IM was detected in 56% and 17% had LGD. Of the 33 circular mucosal pattern areas, IM was detected in 70% and 9% had LGD. HGD and OAC were only found in areas containing an irregular mucosal pattern. **Utility of NBI biopsies** Targeted detection of intestinal metaplasia NBI targeted biopsies detected 99/113 (87.6%) patients with IM compared with 104/113 (92%) in the HD-WLE group (p = 0.36). HD-WLE (targeted and random biopsies) had a sensitivity, specificity,negative predictive value (NPV) and positive predictive value (PPV) for the detection of patients with IM of 92%, 100%, 53% and 100%. NBI (targeted biopsies only) had a sensitivity, specificity, NPV and PPV for the detection of patients with IM of 87.6%, 100%, 41.7% and 100%. Targeted detection of dysplasia Comparison of these NBI targeted biopsies alone with both targeted and random biopsies for HD-WLE showed that NBI did not detect more patients with higher grades of neoplasia.HD-WLE (targeted and random biopsies) had a sensitivity, specificity, NPV and PPV for the detection of patients with dysplasia of 63.6%, 100%, 77.3% and 100%. NBI (targeted biopsies only) had a sensitivity, specificity,NPV and PPV for the detection of patients with dysplasia of 52.7%, 100%, 72.3% and 100%. **Author's Conclusion:** NBI targeted biopsies can have the same IM detection rate as an HD-WLE examination with the Seattle protocol while requiring fewer biopsies. In addition, NBI targeted biopsies can detect more areas with dysplasia. Regular appearing NBI surface patterns did not harbour high-grade dysplasia/cancer, suggesting that biopsies could be avoided in these areas.	**Funding Sources:** This study was funded through an ASGE research award and an investigator initiated grant from Olympus America. **COI:** PS has received previous grants/research support from Olympus America Inc, BARRX Medical Inc and Takeda Pharmaceutical Company Ltd. RHH serves as a consultant for Olympus America. PF serves as a consultant for Boston Scientific and Torax Medical. He has received grant/research support from Olympus Medical Systems and royalties from Elsevier. AR has received previous grant/research support from Olympus America. JJB has received previous grant/research support from BARRX Medical, Cook Medical, Olympus and Astra Zeneca. All other authors have no conflicts of interest to declare. **Randomization:** Patients were randomised in a 1:1 ratio using a computergenerated list of random numbers and administered by study coordinators in sealed opaque envelopes that were opened after patient enrolment and immediately before the first study procedure. **Blinding:** The performing endoscopists kept blinded to the patient's previous endoscopy and biopsy results **Dropout Rate/ITT-Analysis:** per protocol no info about drop outs **Notes:** registered at clinicaltrials.gov (NCT00576498), correct sample size calculation

Canto, M. I. et al. In vivo endomicroscopy improves detection of Barrett's esophagus-related neoplasia: a multicenter international randomized controlled trial (with video). Gastrointest Endosc. 79. 211-21. 2014

Population	Intervention	Outcomes/Results	Methodical Notes
Evidence level: 1b **Study type:** RCT **Number of Patient:** 192 **Recruitung Phase:** February 2010 to December 2011 **Inclusion Criteria:** adult patients undergoing outpatient endoscopy for either routine surveillance of Barrett's esophagus (BE) (surveillance group) or suspected or biopsy-proven unlocalized BE-associated HGD and/or early intramucosal ECA (neoplasia group) referred for confirmation	**Intervention:** high definition white light endoscopy alone (HDWLE) with random biopsy (RB) **Comparison:** HDWLE+ endoscope-based confocal laser endomicroscopy(eCLE)+targeted biopsy(TB)	**Primary:** Diagnostic yield **Secondary:** performance characteristics, clinical impact **Results:** Diagnostic Yield per biopsy analysis The addition of eCLE to HDWLE endoscopy decreased the number of mucosal biopsies obtained during endoscopy and led to a 4.8-fold reduction in the total number of biopsies obtained and an overall decrease in the median number of biopsies obtained per patient (2 for HDWLE+eCLE vs 4 for HDWLE alone, p < .0001, Wilcoxon rank sum test) by allowing TB of abnormal BE mucosa. The reduction in median biopsy number was from 6 to 3 in the neoplasia group (p = 0.0001)and 3 to1 in the	**Funding Sources:** **COI:** --- **Randomization:** 1:1 allocation using a centralized computer-generated permuted block randomization stratified by study site and by procedure indication

of diagnosis and/or endoscopic therapy **Exclusion Criteria:** patients with BE ha 1cm and > 10 cm, known ECA, advanced BE lesions 2 cm or more in size, Paris classification of 0-Ip (polypoid), 0-Is (protruding sessile), 0-IIa (flat elevated), or 0-IIb (flat), 4) any Paris 0-IIc (superficial shallow depressed) or 0-III (excavated) lesion, esophageal strictures or altered anatomy preventing passage of the endomicroscope, allergy to fluorescein or history of any severe anaphylactic reaction, active gastrointestinal bleeding, coagulopathy orc chronic anticoagulation, pregnancy, contraindications to endoscopy due to medical instability.		surveillance group (p < 0.0001)comparing HDWLE and HDWLE + eCLE. With comparable sampling of neoplastic BE (41 in HDWLE+eCLE versus 40 in HDWLE-alone) and fewer biopsies of non-neoplastic BE, there was a higher diagnostic yield for neoplasia obtained using HDWLE+eCLE+TB approach (yield 40/119 or 34%) compared to HDWLE+RB (yield 41/580 or 7%, p < 0.0001). The difference in diagnostic yield was seen mainly in the neoplasia group (45% with eCLE versus 9% for HDWLE alone, p=0.004). The diagnostic yield was higher in the surveillance group (12% versus 5%) but this did not reach statistical significance. per patient analyis. the addition of eCLE to HDWLE led to a 2.7-fold higher diagnostic yield for neoplasia (6/98 or 22% vs. 21/94 or 6%, p=.002). This difference between HDWLE+eCLE+TB and HDWLE+RB was found primarily in patients with neoplasia (12/24 or 75% vs. 5/23 or 22%, p=.0004). Performance Characteristics per biopsy basis The sensitivity of the HDWLE+eCLE+TB for the in vivo detection of BE neoplasia was higher than HDWLE+RB (86% versus 10%, respectively, p < 0.0001) with comparable overall accuracy (92% versus 93%, p=0.45), despite lower specificity. per patient analysis the addition of eCLE imaging to HDWLE increased the sensitivity of neoplasia detection from 40% to 95% (p < 0.0001) and increased the NPV from 90% to 98% (p=0.005), with comparable accuracy. Clinical Impact Of the 94 patients in the HDWLE+eCLE group, 32 (34%) had a correct change in dysplasia grade after eCLE when compared to initial HDWLE endoscopic findings. **Author's Conclusion:** Real time eCLE and targeted biopsy after HDWLE can improve the diagnostic yield and accuracy for neoplasia and significantly impact in vivo decision-making by altering the diagnosis and guiding therapy. In summary, the addition of in vivo imaging with eCLE to HDWLE is associated with improved targeting of neoplasia, decrease in unnecessary mucosal biopsies, and significant change in diagnosis and management plan in BE patients. The approach of real time CLE diagnosis and imaging-guided therapy represents a potential paradigm shift in BE surveillance. Research studies are needed to address training in CLE, comparative effectiveness studies of advanced endoscopic imaging techniques, the role of imaging-guided therapy, and advances in CLE devices and contrast agents.	(surveillance or suspected neoplasia) based on review of the endoscopic and pathology records **Blinding:** single blind: biopsy specimens were blindly interpreted by 2 expert gastrointestinal pathologists **Dropout Rate/ITT-Analysis:** n=20 (9,43%) **Notes:** This trial was registered on Clinicaltrials.gov (registration number NCT004876, no sample size calculation

Inhaltsverzeichnis der Evidenztabellen

Schlüsselfrage:

AG 2 <u>Erweiterte Diagnostik:</u> Stellenwert des endoskopischen Ultraschalls EUS

Evidenztabellen

zurück

Schlüsselfrage:

AG 2 *Erweiterte Diagnostik: Stellenwert des endoskopischen Ultraschalls EUS*

Bewertungsvorlage:

OXFORD Appraisal Sheet 1: Systematic Reviews

Luo, L. N. et al. Endoscopic Ultrasound for Preoperative Esophageal Squamous Cell Carcinoma: a Meta-Analysis. PLoS One. 11. e0158373. 2016

Evidence level/Study Types	Population	Outcomes/Results	Literature References	Methodical Notes
Evidence level: 2a **Study type:** Meta Analysis, 44 studies (n=2280) **Databases:** PubMed, Cochrane Library, Web of Science,Embase and Google Scholar **Search period:** - October 2015 **Inclusion Criteria:** If the EUS results of preoperative patients with ESCC were confirmed by final pathological staging of surgery, endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD). **Exclusion Criteria:** Reviews, abstracts, editorials or letters, case reports and non-English publications.	**Intervention:** Endoscopic Ultrasound **Comparison:** Pathological staging	**Primary:** The overall T-staging diagnostic accuracy of EUS **Secondary:** Diagnostic accuracies of EUS and CT in T-staging **Results:** The overall T-staging diagnostic accuracy of EUS was 79% (95%CI: 77 to 80), and for the overall N-staging the diagnostic accuracy of EUS was 71% (95%CI: 69 to 73). The pooled sensitivity and specificity of T1 were 77% (95%CI: 73 to 80) and 95% (95%CI: 94 to 96). Among the T1 patients, EUS had a pooled sensitivity in differentiating T1a and T1b of 84% (95%CI: 80 to 88) and 83% (95%CI: 80 to 86), and a specificity of 91% (95%CI: 88 to 94) and 89% (95%CI: 86 to 92). For the T2 stage, EUS had a pooled sensitivity of 66% (95%CI: 61 to 70) and a specificity of 88% (95%CI: 86 to 89). For T3 staging cancer, EUS had a pooled sensitivity of 87% (95%CI: 85 to 89) and a pooled specificity of 87% (95%CI: 84 to 89) To stage T4, EUS had a pooled sensitivity of 84% (95%CI: 79 to 89) and a specificity of 96% (95%CI: 95 to 97). The diagnostic accuracies of EUS and CT in T-staging were 77% (95%CI: 73% to 81%) and 59% (95%CI: 54 to 64). **Author's Conclusion:** EUS has good diagnostic accuracy for staging ESCC, which has better performance in T1 sub-staging (T1a and T1b) and advanced disease (T4).	Lee G, Hoseok I, Kim SJ, Jeong YJ, Kim IJ, Pak K, et al. Journal of Nuclear Medicine [Internet]. 2014 Choi J, Kim SG, Kim JS, Jung HC, Song IS. Surgical endoscopy. 2010; Binmoeller KF, Seifert H, Seitz U, Izbicki JR, Kida M, Soehendra N. Ultrasonic esophagoprobe for TNM staging of highly stenosing esophageal carcinoma. Gastrointestinal endoscopy. 1995; 41(6):547–52. Epub 1995/06/01. PMID: 7672546. Catalano MF, Alcocer E, Chak A, Nguyen CC, Raijman I, Geenen JE, et al. Gastrointestinal endoscopy. 1999; Catalano MF, Sivak MV Jr., Rice T, Gragg LA, Van Dam J. Gastrointestinal endoscopy. 1994; Gheorghe C, Stanescu C, Gheorghe L, Bancila I, Herlea V, Becheanu G, et al. Journal of gastrointestinal and liver diseases: JGLD. 2006; Goda K, Tajiri H, Ikegami M, Yoshida Y, Yoshimura N, Kato M, et al. Diseases of the esophagus: official journal of the International Society for Diseases of the Esophagus / ISDE. 2009; Grimm H, Binmoeller KF, Hamper K, Koch J, Henne-Bruns D, Soehendra N. Endoscopy. 1993; Hasegawa N, Niwa Y, Arisawa T, Hase S, Goto H, Hayakawa T. Gastrointestinal endoscopy. 1996; He LJ, Shan HB, Luo GY, Li Y, Zhang R, Gao XY, et al. World journal of gastroenterology. 2014; Heintz A, Hohne U, Schweden F, Junginger T. Surgical endoscopy. 1991; Hunerbein M, Dohmoto M, Rau B, Schlag PM. Surgical endoscopy. 1996; Hunerbein M, Ulmer C, Handke T, Schlag PM. Surgical endoscopy. 2003; 1 Kawano T, Ohshima M, Iwai T. Abdominal imaging.	**Funding Sources:** This work was supported by the Science and Technology Plan Projects of Guangdong Province, P.R. China (No: 2012B061700076 and 2014A020212146); and Sun Yat-Sen University Cancer Center Clinical Research 308 Program and Plan Project of Guangdong Esophageal Cancer Research Institute. **COI:** The authors have declared that no competing interests exist. **Study Quality:** prospective designs (43%)and retrospective designs (57%). The included studies had a median quality score. **Heterogeneity:** I^2 between 22% and 91% **Publication Bias:** -- **Notes:**

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			Adachi Y, Kuwano H, Sugimachi K. Hepato-gastroenterology. 1993 Vazquez-Sequeiros E, Norton ID, Clain JE, Wang KK, Affi A, Allen M, et al. Gastrointestinal endoscopy. 2001; Vickers J. Annals of the Royal College of Surgeons of England. 1998; Vickers J, Alderson D. The British journal of surgery. 1998; Wakelin SJ, Deans C, Crofts TJ, Allan PL, Plevris JN, Paterson-Brown S. European journal of radiology. 2002; Wu LF, Wang BZ, Feng JL, Cheng WR, Liu GR, Xu XH, et al. World journal of gastroenterology.2003; Yanai H. 1996. Yen TJ, Chung CS, Wu YW, Yen RF, Cheng MF, Lee JM, et al. Diseases of the esophagus: official journal of the International Society for Diseases of the Esophagus / ISDE. 2012; Yoshikane H, Tsukamoto Y, Niwa Y, Goto H, Hase S, Shimodaira M, et al. The American journal of gastroenterology. 1994; Ziegler K, Sanft C, Zeitz M, Friedrich M, Stein H, Haring R, et al. Gut. 1991;	

van Rossum, P. S. et al. Endoscopic biopsy and EUS for the detection of pathologic complete response after neoadjuvant chemoradiotherapy in esophageal cancer: a systematic review and meta-analysis. Gastrointest Endosc. 83. 866-79. 2016

Evidence level/Study Types	Population	Outcomes/Results	Literature References	Methodical Notes
Evidence level: 2a- **Study type:** Systematic Review, Meta Analysis, 23 studies, N=1281 patients. **Databases:** PubMed/Medline, Embase, Cochrane library **Search period:** - July 14, 2015 **Inclusion Criteria:** - Diagnostic studies that reported on the accuracy of endoscopic biopsy or EUS after nCRT for esophageal cancer and discriminating between ypTþ and ypT0 or between ypNþ and ypN0 - studies that used histopathologic examination after surgical resection as the reference standard **Exclusion Criteria:** - Reviews, editorials, letters to the editor, studies with less than 10 included patients, case reports, and congress abstracts - languages other than Dutch, English, or German	**Intervention:** Endoscopic biopsy or EUS **Comparison:** Histopathology as the reference standard	**Primary:** Diagnostic accuracy in detecting residual cancer versus complete response after neoadjuvant chemoradiotherapy **Secondary:** --- **Results:** Pooled estimates for sensitivity of endoscopic biopsy after nCRT for predicting ypTþ were 34.5% (95% confidence interval [CI], 26.0%-44.1%) and for specificity 91.0% (95% CI, 85.6%-94.5%). Pooled estimates for sensitivity of EUS after nCRT were 96.4% (95% CI, 91.7%-98.5%) and for specificity were 10.9% (95% CI, 3.5%-29.0%) for detecting ypTþ, and 62.0% (95% CI, 46.0%-75.7%) and 56.7% (95% CI, 41.8%-70.5%) for detecting ypNþ, respectively. Subgroup analysis Sensitivity of endoscopic biopsy after nCRT was significantly higher for studies mainly including patients with squamous cell carcinoma (n Z 5) compared with studies mainly including patients with adenocarcinoma (n Z 5) (49.3% vs 23.6%, respectively; P < .001)with similar specificities (90.6% vs 88.2%, respectively; P = .633). **Author's Conclusion:** Endoscopic biopsy after nCRT is a specific but not sensitive method for detecting residual esophageal cancer. Although EUS after nCRT yields a high sensitivity, only a limited number of patients will have negative findings at EUS with still a substantial false-negative rate. Furthermore, EUS provides only	Ajani JA, Correa AM, Hofstetter WL, et al. Ann Oncol 2012; Yang Q, Cleary KR, Yao JC, et al. Dis Esophagus 2004; Miyata H, Yamasaki M, Takiguchi S, et al. Ann Surg 2011; Molena D, Sun HH, Badr AS, et al. Dis Esophagus 2014; Sarkaria IS, Rizk NP, Bains MS, et al. Ann Surg 2009; Schneider PM, Metzger R, Schaefer H, et al. Ann Surg 2008; Kalha I, Kaw M, Fukami N, et al. Cancer 2004; Griffin JM, Reed CE, Denlinger	**Funding Sources:** --- **COI:** All authors disclosed no financial relationships relevant to this publication. **Study Quality:** Most studies included a consecutive series of patients with appropriate exclusions only. In general, the endoscopic procedures and pathologic assessments were sufficiently described and considered valid. Partial verification bias was of particular concern in most studies because often not all patients who underwent post-nCRT endoscopic examination

		moderate accuracy for detecting residual lymph node involvement. Based on these findings, these endoscopic modalities cannot be used to withhold surgical treatment in test-negative patients after nCRT.	CE. Ann Thorac Surg 2012; Yen TJ, Chung CS, Wu YW, et al. Dis Esophagus 2012; Owaki T, Matsumoto M, Okumura H, et al. Am J Surg 2012; Eloubeidi MA, Cerfolio RJ, Bryant AS, et al. Eur J Cardiothorac Surg 2011; Chao YK, Yeh CJ, Lee MH, et al. Medicine (Baltimore)2015; Bowrey DJ, Clark GW, Roberts SA, et al. J Gastrointest Surg 1999; Agarwal B, Swisher S, Ajani J, et al. EAm J Gastroenterol 2004; Cerfolio RJ, Bryant AS, Ohja B, et al. J Thorac Cardiovasc Surg 2005; Kim JH, Choi EK, Kim SB, et al. Int J Radiat Oncol Biol Phys 2001; Shaukat A, Mortazavi A, Demmy T, et al. Dis Esophagus 2004; Peng HQ, Halsey K, Sun CC, et al. Cancer 2009; Dittler HJ, Fink U, Siewert GR. Endoscopy 1994; Giovannini M, Seitz JF, Thomas P, et al. Endoscopy 1997; Laterza E, de Manzoni G, Guglielmi A, et al. Ann Thorac Surg 1999; Zuccaro G Jr, Rice TW, Goldblum J, et al. Am J Gastroenterol 1999;9 Willis J, Cooper GS, Isenberg G, et al. Gastrointest Endosc 2002;	underwent subsequent surgical resection, which could lead to underestimation of both sensitivity and specificity estimates. **Heterogeneity:** -- **Publication Bias:** -- **Notes:** Clinical trial registration number: CRD42015016527.

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Schlüsselfrage:

***AG 2** Erweiterte Diagnostik: Stellenwert des endoskopischen Ultraschalls EUS*

Bewertungsvorlage:

OXFORD Appraisal Sheet 2: RCT

Russell, I. T. et al. Cancer of Oesophagus or Gastricus - New Assessment of Technology of Endosonography (COGNATE): report of pragmatic randomised trial. Health Technol Assess. 17. 1-170. 2013			
Population	**Intervention**	**Outcomes/Results**	**Methodical Notes**
Evidence level: 1b **Study type:** RCT **Number of Patient:** 223 **Recruitung Phase:** 2005-2009 **Inclusion Criteria:** diagnosis of gastro-oesophageal cancer, had not started treatment, were free of metastatic disease, were fit for surgery (even if not planned) and had American Society of Anesthesiologists and World Health Organization grades of less than 3. **Exclusion Criteria:** evidence of metastases or plans for palliative treatment or known to be medically unfit for surgery	**Intervention:** 1. All patients should receive biochemistry, haematology, pulmonary function tests and cardiac assessment, not least to exclude patients whose World Health Organization (WHO) status is 3 or 4, or who are medically unsuitable for either surgery or chemotherapy. 2. Patients who are medically fit for surgery without evidence of metastases should undergo CT following an agreed protocol using spiral scanner and intravenous contrast. 3. Patients with any suspicion of peritoneal disease should undergo laparoscopy as the best means of detecting peritoneal tumour deposits. 4. Fit patients with localised tumours and no contraindications were eligible for randomisation to EUS In the resulting intervention group (or 'EUS group'), the final choice of treatment followed the EUS scan. **Comparison:** no EUS In the resulting control group (or 'non-EUS group`), the choice of treatment depended on the results of the completed initial staging investigations, revisited if necessary.	**Primary:** quality-adjusted survival **Secondary:** (1) survival censored at between 12 months (for those last recruited) and 54 months (2) participant-reported quality of life using three questionnaires: European Quality of Life – 5 Dimensions (EQ-5D) (generic), Functional Assessment of Cancer Therapy – General (FACT-G) scale (cancer related) and FACT Additional Concerns (FACT-AC) scale (gastro-oesophageal cancer specific) (3) process of care: - changes in management plans agreed by MDTs - complete resection rate, and - adverse events related to EUS (4) use of health-care resources **Results:** 1. Endoscopic ultrasound significantly improved participant survival, with a hazard ratio of 0.706 [95% confidence interval (CI) from 0.501 to 0.996] and an increase of 121 days in estimated median survival – from 1.63 years in the control group to 1.96 years in the intervention group. 2. Participants reported consistent, although non-significant, improvements in mean outcomes at 12 months, notably a difference of 0.061 (95% CI from –0.043 to 0.164) in mean EQ-5D scores between 0.449 in the control group and 0.509 in the intervention group; and a difference of 0.12 (95% CI from –0.27 to 0.51) in mean FACT-G between 2.15 in the control group and 2.27 in the intervention group. Combining survival and quality of life, EUS improved survival adjusted for generic quality of life with a hazard ratio of 0.705 (95% CI from 0.499 to 0.995) and an increase of 66 days in estimated median quality-adjusted survival – from 0.94 QALYs in the control group to 1.12 QALYs in the intervention group. 3-4. Trial sites reported consistent, although non-significant, reductions in total resource use in secondary and pharmaceutical care (including EUS scans when undertaken), generating mean savings of about £2860 (95% 'bootstrapped' CI from –£2200 to £8000) from an average of £32,000 [with a standard deviation (SD) of £22,000] in the control group to £29,200 (SD £14,900) in the intervention group. Combining these estimated benefits and savings yields probability of 96.6% that EUS is cost-effective in the sense of achieving the NICE criterion of costing less than £20,000 to gain a QALY. There were no serious adverse reactions attributable to EUS. Both management plans and final treatment varied between centres. EUS increased the proportion of tumours completely resected from 80% (44 out of 55) to 91% (48 out of 53). **Author's Conclusion:** Endoscopic ultrasound significantly improves (quality-adjusted) survival, has the potential to reduce health-care resource use (not statistically significant) and is probably cost-effective (with 96% probability). We recommend research into the best time to evaluate new technologies.	**Funding Sources:** This project was funded by the NIHR Health Technology Assessment programme and will be published in full in Health Technology Assessment; Vol. 17, No. 39. See the HTA programme website for further project information. **COI:** H Barr received money from pharmaceutical companies for consultancy, travel and accommodation **Randomization:** in equal proportions between EUS and not **Blinding:** those responsible for analysis remained blind until the Trial Steering Committee had reviewed the definitive analysis **Dropout Rate/ITT-Analysis:** --- **Notes:** Trial registration ISRCTN1444215

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Schlüsselfrage:

***AG 2** Erweiterte Diagnostik: Stellenwert des endoskopischen Ultraschalls EUS*

Bewertungsvorlage:

NEWCASTLE - OTTAWA Checklist 4: Cohort

Findlay, J. M. et al. Pragmatic staging of oesophageal cancer using decision theory involving selective endoscopic ultrasonography, PET and laparoscopy. Br J Surg. 102. 1488-99. 2015			
Evidence level	**Methodical Notes**	**Patient characteristics**	**Interventions**
Evidence level: 1b **Study type:** Cohort	**Funding sources:** --- **Conflict of Interests:** The authors declare no conflict of interest. **Randomization:** --- **Blinding:** --- **Dropout rates:** ---	**Total no. patients:** 953 **Patient characteristics:** Data development (n=829)between May 2006 and July 2013 Data validation (n=124)from July 2013 to July 2014 **Inclusion criteria:** Consecutive patients with oesophageal/GOJ cancer staged beyond CT **Exclusion criteria:** ---	**Interventions:** Patients without unequivocal metastases on CT were - routinely staged sequentially using [18F]fluorodeoxyglucose (FDG) PET–CT, EUS and laparoscopy, with oesophagogastroduodenoscopy (OGD) for GOJ tumours and distal oesophageal tumours extending below the diaphragm. - Neoadjuvant chemotherapy was considered for disease beyond T1 N0. - ER was used from 2008 for possible T1a tumours. **Comparison:** Data development vs validation
Notes:	**Author's conclusion:** Although EUS provided additional information on T and N category, its risk outweighed potential benefit in patients with T2–T4a disease on CT. Laparoscopy seemed justified for distal oesophageal tumours of T2 or greater.		
Outcome Measures/results	**Primary** Calculate the net benefits and risks of EUS, PET–CT and laparoscopy, their primary utilities (probability of alteringmanagement) and probability thresholds (Pt; at which test benefit equals risk), using decision theory in a development data set. **Secondary** - Determine whether clinical, radiological and histopathological factors could be identified that were related to these endpoints, in order to generate predictive models to identify patient subgroups for selective staging. - Refine existing staging algorithms on the basis of optimal pragmatism, maximal efficiency and minimal patient risk, evaluated using a validation data set.	**Results:** A total of 953 consecutive patients were staged following CT by [18F]FDGPET–CT (918), EUS (798) and laparoscopy (458). Of these, 829 comprised the development data set (800, 698 and 397 respectively) and 124 the validation set (118, 100 and 61). **PET-CT** [18F]FDGPET–CT altered management in 23·0 per cent: confirming metastases (7·1 per cent), identifying unsuspected metastases (13·0 per cent) and additional pathology (2·1 per cent), and staging synchronous cancers (0·8 per cent). Predicting unsuspected metastases Analysis was restricted to the 700 patients with CT M0 examinations. No factors could be used to identify patients with a probability below the Pt (0·083 per cent), that is patients in whom the risk of demonstrating metastases was sufficiently low not to justify the risk of PET–CT. Although there was zero incidence in EUS T1 disease, the 95 % CI was broad (0–6·12 per cent), suggesting that, contrary to common clinical practice, PET–CT may have utility in tumours staged by EUS as T1. **Endoscopic ultrasonography** In 501 patients (71·8 per cent) without possible T1 or T4b disease on CT, EUS altered management in just two (0·4 per cent). In the 81 patients with impassable tumours, EUS altered management in three (4 per cent), confirming T4b with miniprobe EUS. Excluding the 17 patients who, after EUS, underwent ER without surgical resection (in whom pN status could not be assessed), EUS was 83 per cent sensitive and 84 per cent specific for pT1N0 (PPV 83 per cent; NPV 84 per cent). The Pt for EUS T4b disease was 2·02 per cent (based on T4 disease overall). **Staging laparoscopy** Some 397 patients underwent laparoscopy, and metastases were demonstrated in 28 (7·1 per cent). Metastases were demonstrated in two (4 per cent) of 54 distal oesophageal tumours not involving the GOJ endoscopically. No factor could identify patients below the Pt (0·38 per cent). **Refinement of existing algorithm** As a result of the findings that the incidence of T1N0 disease on EUS among patients staged as T2–T4a by CT was minimal, and insufficient to justify the EUS test risk, it is proposed that EUS should be reserved only for patients with possible T1 or T4b disease on CT.	

		Validation of new endoscopic ultrasonography algorithm Some 91 patients in the validation set underwent PET–CT and EUS. No patient was staged by EUS as having T1N0 disease among the 60 with avid nodes. Twelve had possible T4b disease on CT; seven underwent EUS refuting T4b and EUS was omitted in five. **Modelling** The optimal model for identifying T1N0 disease by EUS before PET–CT was a decision tree; this reserved EUS for those with possible T1 disease on CT, and was identical to the pragmatic CT-guided algorithm. After PET–CT, the optimal model was a modified decision tree; this reserved EUS for patients with possible T1 disease on CT without FDG-avid nodes, or CT T2–T4a disease with SUVmax below 6·38 and length less than 3·4 cm on PET–CT. The optimal model for identifying T4b disease by EUS was a decision tree identical to the proposed algorithm; this reserved EUS for patients with possible T4b disease on CT (100 per cent sensitivity). **Suggested staging algorithm** Based on these findings, the following staging algorithm is proposed when considering patients for resection. Following CT, EUS (with or without FNA or staging ER) should be reserved for patients with either: Tx/possible T1 disease on CT, passable at OGD; or possible T4b disease without metastases on PET–CT. For all other patients EUS can be omitted, thereby reducing risk, delay and expenditure.

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Schlüsselfrage:

AG 2 <u>Erweiterte Diagnostik:</u> Stellenwert der PET-CT

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Schlüsselfrage:

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

Bewertungsvorlage:

OXFORD Appraisal Sheet 1: Systematic Reviews

Goense, L. et al. Diagnostic Performance of (1)(8)F-FDG PET and PET/CT for the Detection of Recurrent Esophageal Cancer After Treatment with Curative Intent: A Systematic Review and Meta-Analysis. J Nucl Med. 56. 995-1002. 2015				
Evidence level/Study Types	**Population**	**Outcomes/Results**	**Literature References**	**Methodical Notes**
Evidence level: 2a **Study type:** Systematic Review, Meta Analysis,8 studies with n=486 patients **Databases:** PubMed, Embase, and Cochrane library **Search period:** - December 16, 2014 **Inclusion Criteria:** Studies that included patients who were previously treated with curative intent for esophageal cancer and that reported on the diagnostic accuracy of 18F-FDG PET or PET/CT for the detection of disease recurrence were included. Treatment with curative intent should have had at least included surgery, either or not combined with neoadjuvant chemoradiotherapy. The reference standard was recurrent esophageal cancer as confirmed by histopathologic biopsy or clinical follow-up. **Exclusion Criteria:** Case reports, studies with fewer than 10 included patients, reviews, poster abstracts, and animal studies Language other than Dutch, English, or German.	**Intervention:** Assess the diagnostic performance of 18F-FDG PET and integrated 18F-FDG PET/CT for diagnosing recurrent esophageal cancer after initial treatment with curative intent. **Comparison:** ---- histopathologic biopsy or clinical follow-up	**Primary:** Presence of recurrent esophageal cancer as determined by histopathologic biopsy or clinical follow-up. **Secondary:** --- **Results:** Pooled estimates of sensitivity and specificity for 18F-FDG PET and PET/CT in diagnosing recurrent esophageal cancer were 96% (95% confidence interval, 93%–97%) and 78% (95% confidence interval, 66%–86%), respectively. Subgroup analysis revealed no statistically significant difference in diagnostic accuracy according to type of PET scanner (standalone PET vs. integrated PET/CT) or indication of scanning (routine follow-up vs. on indication). **Author's Conclusion:** 18F-FDG PET and PET/CT are reliable imaging modalities with a highsensitivity and moderate specificity for detecting recurrent esophageal cancer after treatment with curative intent. The use of 18F-FDG PET or PET/CT particularly allows for a minimal false-negative rate. However, histopathologic confirmation of 18F-FDG PET– or PET/CTsuspected lesions remains required, because a considerable falsepositive rate is noticed.	Sharma P, Jain S, Karunanithi S, et al. Eur J Nucl Med Mol Imaging. 2014; Sun L, Su XH, Guan YS, et al. World J Gastroenterol. 2009; Roedl JB, Harisinghani MG, Colen RR, et al. Ann Thorac Surg. 2008; Guo H, Zhu H, Xi Y, et al. J Nucl Med. 2007; Jadvar H, Henderson RW, Conti PS. Mol Imaging Biol. 2006; Teyton P, Metges JP, Atmani A, et al. J Gastrointest Surg. 2009; Kato H, Miyazaki T, Nakajima M, Fukuchi M, Manda R, Kuwano H. Br J Surg. 2004; Flamen P, Lerut A, Van Cutsem E, et al. J Thorac Cardiovasc Surg. 2000;	**Funding Sources:** The costs of publication of this article were defrayed in part by the payment of page charges. Therefore, and solely to indicate this fact, this article is hereby marked “advertisement” in accordance with 18 USC section 1734. **COI:** No potential conflict of interest relevant to this article was reported. **Study Quality:** The quality of the included studies assessed by the QUADAS-2 tool was considered reasonable; there were few concerns with regard to the risk of bias and applicability. The risk of bias concerning patient selection was low in 7 of the included studies. **Heterogeneity:** --- **Publication Bias:** --- **Notes:**

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Schlüsselfrage:

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

Bewertungsvorlage:

NEWCASTLE - OTTAWA Checklist 4: Cohort

Findlay, J. M. et al. Pragmatic staging of oesophageal cancer using decision theory involving selective endoscopic ultrasonography, PET and laparoscopy. Br J Surg. 102. 1488-99. 2015			
Evidence level	**Methodical Notes**	**Patient characteristics**	**Interventions**
Evidence level: 1b **Study type:** Cohort	**Funding sources:** --- **Conflict of Interests:** The authors declare no conflict of interest. **Randomization:** --- **Blinding:** --- **Dropout rates:** ---	**Total no. patients:** 953 **Patient characteristics:** Data development (n=829)between May 2006 and July 2013 Data validation (n=124)from July 2013 to July 2014 **Inclusion criteria:** Consecutive patients with oesophageal/GOJ cancer staged beyond CT **Exclusion criteria:** ---	**Interventions:** Patients without unequivocal metastases on CT were - routinely staged sequentially using [18F]fluorodeoxyglucose (FDG) PET–CT, EUS and laparoscopy, with oesophagogastroduodenoscopy (OGD) for GOJ tumours and distal oesophageal tumours extending below the diaphragm. - Neoadjuvant chemotherapy was considered for disease beyond T1 N0. - ER was used from 2008 for possible T1a tumours. **Comparison:** Data development vs validation
Notes:	**Author's conclusion:** Although EUS provided additional information on T and N category, its risk outweighed potential benefit in patients with T2–T4a disease on CT. Laparoscopy seemed justified for distal oesophageal tumours of T2 or greater.		
Outcome Measures/results	**Primary** Calculate the net benefits and risks of EUS, PET–CT and laparoscopy, their primary utilities (probability of alteringmanagement) and probability thresholds (Pt; at which test benefit equals risk), using decision theory in a development data set. **Secondary** - Determine whether clinical, radiological and histopathological factors could be identified that were related to these endpoints, in order to generate predictive models to identify patient subgroups for selective staging. - Refine existing staging algorithms on the basis of optimal pragmatism, maximal efficiency and minimal patient risk, evaluated using a validation data set.	**Results:** A total of 953 consecutive patients were staged following CT by [18F]FDGPET–CT (918), EUS (798) and laparoscopy (458). Of these, 829 comprised the development data set (800, 698 and 397 respectively) and 124 the validation set (118, 100 and 61). **PET-CT** [18F]FDGPET–CT altered management in 23·0 per cent: confirming metastases (7·1 per cent), identifying unsuspected metastases (13·0 per cent) and additional pathology (2·1 per cent), and staging synchronous cancers (0·8 per cent). Predicting unsuspected metastases Analysis was restricted to the 700 patients with CT M0 examinations. No factors could be used to identify patients with a probability below the Pt (0·083 per cent), that is patients in whom the risk of demonstrating metastases was sufficiently low not to justify the risk of PET–CT. Although there was zero incidence in EUS T1 disease, the 95 % CI was broad (0–6·12 per cent), suggesting that, contrary to common clinical practice, PET–CT may have utility in tumours staged by EUS as T1. **Endoscopic ultrasonography** In 501 patients (71·8 per cent) without possible T1 or T4b disease on CT, EUS altered management in just two (0·4 per cent). In the 81 patients with impassable tumours, EUS altered management in three (4 per cent), confirming T4b with miniprobe EUS. Excluding the 17 patients who, after EUS, underwent ER without surgical resection (in whom pN status could not be assessed), EUS was 83 per cent sensitive and 84 per cent specific for pT1N0 (PPV 83 per cent; NPV 84 per cent). The Pt for EUS T4b disease was 2·02 per cent (based on T4 disease overall). **Staging laparoscopy** Some 397 patients underwent laparoscopy, and metastases were demonstrated in 28 (7·1 per cent). Metastases were demonstrated in two (4 per cent) of 54 distal oesophageal tumours not involving the GOJ endoscopically. No factor could identify patients below the Pt (0·38 per cent). **Refinement of existing algorithm** As a result of the findings that the incidence of T1N0 disease on EUS among patients staged as T2–T4a by CT was minimal, and insufficient to justify the EUS test risk, it is proposed that EUS should be reserved only for patients with possible T1 or T4b disease on CT.	

		Validation of new endoscopic ultrasonography algorithm Some 91 patients in the validation set underwent PET–CT and EUS. No patient was staged by EUS as having T1N0 disease among the 60 with avid nodes. Twelve had possible T4b disease on CT; seven underwent EUS refuting T4b and EUS was omitted in five. **Modelling** The optimal model for identifying T1N0 disease by EUS before PET–CT was a decision tree; this reserved EUS for those with possible T1 disease on CT, and was identical to the pragmatic CT-guided algorithm. After PET–CT, the optimal model was a modified decision tree; this reserved EUS for patients with possible T1 disease on CT without FDG-avid nodes, or CT T2–T4a disease with SUVmax below 6·38 and length less than 3·4 cm on PET–CT. The optimal model for identifying T4b disease by EUS was a decision tree identical to the proposed algorithm; this reserved EUS for patients with possible T4b disease on CT (100 per cent sensitivity). **Suggested staging algorithm** Based on these findings, the following staging algorithm is proposed when considering patients for resection. Following CT, EUS (with or without FNA or staging ER) should be reserved for patients with either: Tx/possible T1 disease on CT, passable at OGD; or possible T4b disease without metastases on PET–CT. For all other patients EUS can be omitted, thereby reducing risk, delay and expenditure.

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Schlüsselfrage:

AG 2 <u>Pathologie:</u> Korrelation Tumorregressionsgrad (TRG)

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Schlüsselfrage:

AG 2 *Pathologie: Korrelation Tumorregressionsgrad (TRG)*

Bewertungsvorlage:

OXFORD Appraisal Sheet 2: RCT

Robb, Wb et al. Impact of neoadjuvant chemoradiation on lymph node status in esophageal cancer: post hoc analysis of a randomized controlled trial. Annals of surgery. 261. 902-8. 2015

Population	Intervention	Outcomes/Results	Methodical Notes
Evidence level: 1b **Study type:** RCT post hoc analysis **Number of Patient:** 195 **Recruitung Phase:** June 2000 until June 2009 **Inclusion Criteria:** - younger than 75 years, - World Health Organization (WHO) performance status 0 or 1, - suitable for curative surgical resection with clinical stage I and II (cT1-T2 N0 or N+, cT3N0) thoracic epidermoid or glandular EC. **Exclusion Criteria:** ---	**Intervention:** Neoadjuvant Chemoradiation nCRT, 5 weeks. Clinical reevaluation and surgery after 4-6 weeks after completion nCRT. **Comparison:** Surgery alone	**Primary:** Effects of nCRT on the pN status, lymph nodes resected NLNr, and lymph nodes invaded NLNi in the resected specimen **Secondary:** ---- **Results:** RCT: After a median follow-up of 93.6 months, the overall survival was not significantly different between the groups [hazards ratio (HR) group nCRT vs group S, 0.99; 95% confidence interval (CI): 0.69–1.40, P = 0.94]. This result, in conjunction with an in-hospital postoperative mortality that was significantly higher in the nCRT group than surgery alone (11.1% vs 3.4%, P = 0.049), meant that the trial was halted on the basis of futility and led to the conclusion that nCRT does not provide a survival benefit in stage I and II EC. Post hoc analysis: nCRT resulted in tumoral downstaging (pT0, 40.7% vs 1.1%, P < 0.001), LN downstaging (pN0, 69.1% vs 47.2%, P = 0.016), and reduction in the median NLNr [16.0 (range, 0–47.0) vs 22.0 (range, 3.0–58.0), P = 0.001] and NLNi [0 (range, 0–25) vs 1.0 (range, 0–25), P = 0.001]. A good histological response (TRG1/2) in the resected esophageal specimen correlated with reduced median NLNi [0 (range, 0–10) vs 1.0 (range, 0–4), P = 0.007]. After adjustment by treatment, NLNi [hazards ratio (HR) (1–3 vs 0) 3.5, 95% confidence interval (CI): 2.3–5.5, and HR (> 3 vs 0) 3.5, 95% CI: 2.0–6.2, P < 0.001] correlated with prognosis, whereas NLNr [HR (< 15 vs ≥ 15) 0.95, 95% CI: 0.6–1.4, P = 0.807 and HR (< 23 vs ≥ 23) 1.4, 95% CI: 0.9–2.0, P = 0.131] did not. In Poisson regression analysis, nCRT was an independent predictive variable for reduced NLNr [exp(coefficient) 0.80, 95% CI: 0.66–0.96, P = 0.018]. **Author's Conclusion:** nCRT is not only responsible for disease downstaging but also predicts fewer LNs being identified after surgical resection for EC. This has implications for the current quality criteria for surgical resection.	**Funding Sources:** --- **COI:** --- **Randomization:** --- **Blinding:** ---- **Dropout Rate/ITT-Analysis:** --- **Notes:** Registered on the ClinicalTrials.gov Web site under the identifying number NCT00047112. Original RCT: Mariette C, Dahan L,Mornex F, et al. Surgery alone versus chemoradiotherapy followed by surgery for stage I and II esophageal cancer: final analysis of a randomized controlled phase III trial FFCD 9901. J Clin Oncol. 2014;32:2416–2422.

Smyth, E. C. et al. Effect of Pathologic Tumor Response and Nodal Status on Survival in the Medical Research Council Adjuvant Gastric Infusional Chemotherapy Trial. J Clin Oncol. 34. 2721-7. 2016

Population	Intervention	Outcomes/Results	Methodical Notes
Evidence level: 1b **Study type:** RCT, MAGIC-Trial, Sub-Study **Number of Patient:** n= 330 resection specimens± (171 from the surgery-alone arm, 159 from the chemotherapy-plus-surgery arm) **Recruitung Phase:** 1994-2002 **Inclusion Criteria:** --- **Exclusion Criteria:** ---	**Intervention:** RCT: use of perioperative chemotherapy for patients with resectable adenocarcinoma of the stomach, gastroesophageal junction, and lower esophagus. **Comparison:** Surgery alone.	**Primary:** whether pathologic response and lymph node status after neoadjuvant chemotherapy are prognostic in patients treated in the MAGIC trial. **Secondary:** ---- **Results:** In chemotherapy-treated patients with a TRG of 1 or 2,median OSwas not reached, whereas for patientswith a TRG of 3, 4, or 5,median OS was 20.47 months. On univariate analysis, high TRG and lymph node metastases were negatively related to survival (Mandard TRG 3, 4, or 5: hazard ratio [HR], 1.94; 95% CI, 1.11 to 3.39; P = .0209; lymph nodemetastases: HR, 3.63; 95%CI, 1.88 to 7.0; P < .001). On multivariate analysis, only lymph node status was independently predictive of OS (HR, 3.36; 95% CI, 1.70 to 6.63; P < .001). **Author's Conclusion:** Lymph node metastases and not pathologic response to chemotherapy was the only independent predictor of survival after chemotherapy plus resection in the MAGIC trial. Prospective evaluation of whether omitting postoperative chemotherapy and/or switching to a noncross-resistant regimen in patients with lymph node-positive disease whose tumor did not respond to preoperative epirubicin, cisplatin, and fluorouracil may be appropriate.	**Funding Sources:** Supported by Cancer Research UK (CEA A18052), European Union FP7 (CIG 334261), and the National Institute for Health Research (NIHR) Biomedical Research Centre (BRC) at The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research (grants A62, A100, A101) to N.V. E.C.S., D.C., C.P., A.W., and N.V. acknowledge funding from the NIHR ICR/RMH BRC. **COI:** disclosure information provided by authors **Randomization:** -- **Blinding:** Two independent

			pathologists using the Mandard tumor regression grading system (TRG). **Dropout Rate/ITT-Analysis:** --- RCT: ITT **Notes:** the results do not differentiate the individual tumor entities No description of the original RCT. Medical Research Council Oesophageal Cancer Working Group: Surgical resection with or without preoperative chemotherapy in oesophageal cancer: A randomised controlled trial. Lancet 359: 1727-1733, 2002 Cunningham D, Allum WH, Stenning SP, et al: Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 355:11-20, 2006

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Schlüsselfrage:

AG 2 *Pathologie: Korrelation Tumorregressionsgrad (TRG)*

Bewertungsvorlage:

NEWCASTLE - OTTAWA Checklist 4: Cohort

Davies, A. R. et al. Tumor stage after neoadjuvant chemotherapy determines survival after surgery for adenocarcinoma of the esophagus and esophagogastric junction. J Clin Oncol. 32. 2983-90. 2014

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 2b **Study type:** Prospective cohort study	**Funding sources: Research Funding: David Cunningham, Roche, sanofi-aventis, AstraZeneca, Amgen, Merck, Celgene, Novartis** **Conflict of Interests: Employment or Leadership Position: None Consultant or Advisory Role: None Stock Ownership: None Honoraria: William H. Allum, Eli Lilly, Nestle, Astellas Pharma Expert Testimony: None Patents, Royalties, and Licenses: None Other Remuneration: None** **Radnomization: -** **Blinding: -** **Dropout rates: -**	**Total no. patients:** 584 patients with ACC of esophagus or EGJ. **Patient characteristics:** Between 2000 and 2010 in two high volume institutions for esophageal Cancer in London. **Inclusion criteria:** Patients with adenocarcinoma of the esophagus or esophago-gastric junction. Study characteristics:584 patients, the mean age was 63 years (range, 28 to 83 years), 86% male. Overall survival of the cohort was 80% and 45% at 1 and 5 years, respectively. **Exclusion criteria:** -	**Interventions:** Chemotherapy: 400 out of 580 underwent pre-operative chemotherapy. Tumor staging: Each patient was allocated a tumor stage (cTNM) before commencement of neoadjuvant chemotherapy as decided by the multidisciplinary team. After neoadjuvant chemotherapy, patients were restaged using CT (thorax, abdomen, and pelvis), but not routinely using endoscopy, EUS, or fluorode- oxyglucose PET. Resection and staging: All patients underwent definitive resection and, therefore, had final tumor histology available for comparison (ypTNM). This pathologic stage was determined using the seventh edition of the American Joint Committee on Cancer TNM staging system. Downstaging was defined as a reduction in T stage or N stage of pathologic staging (ypTNM) compared with clinical staging (cTNM). Pathologic tumor regression used a categorical scale between 1 and 5 as described by Mandard. **Comparison:** -
Notes:	Criteria for inclusion or exclusion are inadequately described. **Author's conclusion:** "This study indicates that tumor stage after neo-adjuvant chemotherapy determines survival in patients with adenocarcinoma of the esophagus and esophagogastric junction. The importance of of tumor downstaging in terms of survival, complete surgical resection, and recurrence pattern has significant clinical implications."		
Outcome Measures/results	**Primary** Tumor staging: Each patient was allocated a tumor stage (cTNM) before commencement of neoadjuvant chemotherapy as decided by the multidisciplinary team. After neoadjuvant chemotherapy, patients were restaged using CT but not routinely using endoscopy, EUS, or FDG-PET. All patients underwent definitive resection; final tumor histology available for comparison (ypTNM), and analyzed by a member of a team of dedicated upper GI histopathologists. This pathologic stage was determined using the 7th edition of the American Joint Committee on Cancer TNM staging system. Downstaging was defined as a reduction in T stage or N stage of pathologic staging (ypTNM) compared with clinical staging (cTNM). Pathologic tumor regression used a categorical scale between 1 and 5 accordin to Mandard. **Secondary** -	**Results: Downstaging Effect of Chemotherapy** Primary: neoadjuvant chemotherapy group: 175 patients (44%) benefitted from a downstaging effect. This group of responders, compared with nonresponders, had improved rates of clear surgical resection margins (R0: 74% vs 40%, respectively; P < .001) and lower rates of isolated local recurrence (6% v 13%) p = .03). The responders also experienced lower rates of systemic metastatic recurrence compared with non-responders, both alone (19 v 29%, p < .027) and in combination with locoregional recurrence (30% v 48%, p < 0.001). The majority of down-staged patients had evidence of pathologic response to neoadjuvant chemotherapy (Mandard score 1-4 in 144 of 162 patients, 89%). This group of downstaged patients had significantly improved Mandard scores compared with those who were not downstaged (p < .001).	

Shapiro, J. et al. Prognostic Value of Pretreatment Pathological Tumor Extent in Patients Treated With Neoadjuvant Chemoradiotherapy Plus Surgery for Esophageal or Junctional Cancer. Ann Surg. 265. 356-362. 2017

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 1b **Study type:** Post hoc analysis RCT	**Funding sources: ----** **Conflict of Interests: ----** **Radnomization: ----** **Blinding: The interobserver agreement was determined between 3 independently scoring upper-GI pathologists**	**Total no. patients:** 180 **Patient characteristics:** 2003 - 2011 **Inclusion criteria:** Potentially curable esophageal or junctional cancer, who were treated with neoadjuvant chemoradiotherapy (nCRT) plus surgery according to the CROSS regimen.	**Interventions:** from the nCRT plus surgery group: resection specimens (primary tumor and all resected lymph nodes) **Comparison:**

	Dropout rates: ----	Both squamous cell carcinoma and adenocarcinoma tumor types were included. **Exclusion criteria:** Patients who did not receive at least 80% of the planned dose of chemoradiotherapy, who received a different nCRT regimen or in whom surgical resection could not be completed.	
Notes:	Original RCT not described: van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med. 2012;366: 2074–2084. **Author's conclusion:** PrepT-stage and prepN-stage can be estimated reproducibly. Prognostic strength of prepT-stage is comparable with clinical T-stage, whereas prepN-stage is better than cN-stage. PrepNþ patients who become ypN0 after nCRT have a worse survival compared with prepN0 patients. Pretreatment pathological staging should be considered useful as a new staging parameter for esophageal cancer and could also be of interest for other tumor types.		
Outcome Measures/results	**Primary** - determine the interobserver reproducibility of this new pretreatment pathological staging system, - compare this pretreatment pathological staging system with the pretreatment clinical staging system, - determine the value of this new pretreatment pathological staging system for posttreatment prognostication. **Secondary** ----	**Results:** Overall concordance for prepT-stage and prepN-stage was 0.69 and 0.84, respectively. Prognostic strength of prepT-stage was similar to clinical T-stage and worse compared with ypT-stage (DAIC 1.3 versus 2.0 and 8.9, respectively). In contrast, prognostic strength of prepN-stage was better than cN-stage and similar to ypN-stage (DAIC 17.9 versus 6.2 and 17.2, respectively). PrepNþ patients who become ypN0 after nCRT have a worse survival compared with prepN0 patients, with a five year overall survival of 51% versus 68%, P ¼ 0.019, respectively.	

Inhaltsverzeichnis der Evidenztabellen

Schlüsselfrage:

AG 3 Chirurgie: Art des operativen Zugangs

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Schlüsselfrage:

AG 3 *Chirurgie: Art des operativen Zugangs*

Bewertungsvorlage:

OXFORD Appraisal Sheet 2: RCT

Kurokawa, Y. et al. Ten-year follow-up results of a randomized clinical trial comparing left thoracoabdominal and abdominal transhiatal approaches to total gastrectomy for adenocarcinoma of the oesophagogastric junction or gastric cardia. Br J Surg. 102. 341-8. 2015

Population	Intervention	Outcomes/Results	Methodical Notes
Evidence level: 1b **Study type:** Randomized trial **Number of Patient:** 167 (82, 85 per arm) **Recruitung Phase:** Between July 1995 and December 2003, 27 hospitals in Japan. **Inclusion Criteria:** • histologically confirmed ACC of the gastric body or cardia with oesophageal invasion of 3 cm or less, cT2 – 4 category • age 75 years or less • no distant metastasis • no lymph nodes larger than 1cm in the hepatoduodenal ligament or para-aortic field • a forced expiratory volume in 1s of at least 50 per cent • arterial oxygen tension of at least 9·3 kPa while breathing ambient air **Exclusion Criteria:** none described	**Intervention:** Transhiatial surgery (TH):total gastrectomy with D2 lymphadenectomy including splenectomy. Additional dissection of the lymph nodes along the left inferior phrenic vessels and the para-aortic nodes lateral to the aorta and above the left renal vein was performed in patients with curable disease. This included patients with positive findings on peritoneal lavage cytology, but without overt peritoneal metastasis. All procedures were undertaken via laparotomy, and the lower mediastinum was accessed transhiatally. Mediastinal resection included the lower oesophagus and perioesophageal lymph nodes only. **Comparison:** Left thoraco-abdominal surgery (LTA): An oblique incision over the left thorax and abdomen was made for the LTA approach, followed by the same procedure in the abdominal cavity as for the TH operation. In the thoracic cavity, a thorough mediastinal node dissection below the left inferior pulmonary vein was undertaken with appropriate oesophagectomy.	**Primary:** Overall survival (OS): Over 10 year follow up period. **Secondary:** Disease-free survival (DFS), Morbidity and Mortality, Postoperative symptoms and postoperative respiratory function **Results:** Median follow-up for all censored patients was 10.6 (range 5·1 – 17·1) years. There had been 52 and 63 deaths in the TH and LTA group respectively, with 42 and 50 patients respectively dying from cancer. **Primary:**OS:The 5- and 10-year OS rates for all randomized patients were 51% (95 % CI 40, 61) and 37% (26 to 47) for the TH approach, and 37% (26, 47) and 24% (15, 34) per cent for the LTA approach. The log rank test showed marginal differences between the groups (2-sided P=0.060, 1-sided P = 0.970), and the hazard ratio (HR) for the LTA versus the TH approach was 1.42 (95% CI 0·98, 2·05). **Author's Conclusion:** "LTA resections should be avoided in the treatment of adenocarcinoma of the OGJ or gastric cardia."	**Funding Sources:** "The study was funded in part by Grants-in-Aid for Cancer Research and for the Second-Term Comprehensive 10-year Strategy for Cancer Control from the Ministry of Health, Labour and Welfare, Japan, and by the National Cancer Centre Research and Development Fund (26-A-4)." **COI:** The authors declare no conflict of interest. **Randomization:** "Randomly generated assignment (1 : 1) into one of the treatment groups. A minimization method was used to stratify treatment groups according to institution, cT category (cT2 versus cT3/4) and Borrmann type (0 – 2 versus 3 or 5) for random number generation." **Blinding:** No blinding was performed, measures are objective (survival). **Dropout Rate/ITT-Analysis:** All analyses were based on an intention-to-treat basis. **Notes:** "Baseline characteristics of the two groups were similar, except for Siewert classification"

Maas, K. W. et al. Quality of Life and Late Complications After Minimally Invasive Compared to Open Esophagectomy: Results of a Randomized Trial. World J Surg. 39. 1986-93. 2015

Population	Intervention	Outcomes/Results	Methodical Notes
Evidence level: 1b **Study type:** Randomized clinical trial multicentric. **Number of Patient:** 115 (56,59 per arm) **Recruitung Phase:** Between June 1,	**Intervention:** Patients in both groups received identical pre and postoperative treatment. For most patients, neoadjuvant treatment consisted of weekly administrations of 50 mg/m2 paclitaxel plus carboplatin and concurrent radiotherapy (41,4 Gy in 23 fractions for 5 days per week). After 6–8 weeks, neoadjuvant treatment was followed by surgery by open or minimally invasive	**Primary:** Postoperative pulmonary infection:, defined as clinical manifestation of pneumonia or bronchopneumonia confirmed by thoracic radiographs or CT scan and a positive sputum culture, within the first 2 weeks of surgery and during the whole stay in hospital. **Secondary: Short term endpoints:** Postoperative complications: (e.g., anastomotic	**Funding Sources:** Digestive Surgery Foundation of the Unit of Digestive Surgery of the VU University Medical Centre. (original paper)

2009 and March 31, 2011 at five centers: 3 in the Netherlands, 1 in Spain, 1 in Italy. **Inclusion Criteria:** • resectable esophageal cancer (cT1–3,N0–1, M0) • histologically proven AC, SCC, or undifferentiated carcinoma of the intrathoracic esophagus and GEJ • Patients were aged 18–75 years • WHO performance status of two or less. **Exclusion Criteria:** • patients with cervical esophageal cancer or another malignancy	esophagectomy. Both procedures included a two-field esophageal resection with 3–4 cm wide gastric tube formation followed by a cervical or intrathoracic anastomosis. Open esophagectomy (OE): involved a right posterolateral thoracotomy in the lateral decubitus position with double tracheal intubation and lung block, midline laparotomy, and cervical or intrathoracic anastomosis. MIE was performed through a right thoracoscopy in the prone position with single-lumen tracheal intubation, upper abdominal laparoscopy, and cervical incision. **Comparison:** Minimally invasive esophagectomy (MIE): was performed through a right thoracoscopy in the prone position with single-lumen tracheal intubation, upper abdominal laparoscopy, and cervical incision. For patients undergoing MIE with an intrathoracic anastomosis, a bronchus blocker was placed in the right bronchus to help with one-lung ventilation during anastomosis.	leakage, vocal cord paralysis confirmed by laryngoscopy), QoL: quality of life assessed by SF 36 Health Survey (version 2) and EORTC QoL questionnaires C30 and OES18 module. **Mid-term endpoints:** QoL at 1 year:(assessed by SF 36 and EORTC C30 and OES18 module incidence of late complications: (e.g., anastomotic stenosis) overall and disease-free survival **Results: Secondary:** QoI after 1 year: Significantly better scores after 1-year follow-up for the MIE group as compared to the OE group. These differences are present in three domains: physical activity [SF36: 50 (6; 48–53) vs .45 (9; 42–48) p .003]; global health [C30: 79 (10; 76–83) vs. 67 (21; 60–75) p .004]; and pain [OES18: 6 (9; 2–8) versus 16 (16; 10–22) p .001]. Late complications: After 1 year, 26 patients (44 %) in the MIE and 22 patients (39 %) in the OE group were diagnosed and treated for symptomatic stenosis of the anastomosis. Recurrence: 32 patients died during the first year, 18(32%) in the OE group and 14(23%) in the MIE group (p = 0.314). Death was related principally to distant metastases (19 patients), without significant differences between the two groups (p = 0.167). Local recurrence was observed in three patients in the OE group (p = 0.072). overall and disease-free survival:: No significant differences between the two groups. **Author's Conclusion:** "In conclusion, this first randomized trial shows that MIE for esophageal cancer is associated with a better mid-term 1-year quality of life compared to open esophagectomy."	**COI:** No description. **Randomization:** e used a computer-generated randomisation sequence to randomly assign patients, in a 1:1 ratio, to undergo either open or minimally invasive esophagectomy. Randomisation was stratified by study center. **Blinding:** No blinding was performed. **Dropout Rate/ITT-Analysis:** "Data were analysed according to the intention-to-treat principle." Similar distribution of dropouts (less than 20% total). **Notes:** Male surplus in both groups. No description of potential COI or funding sources. Primary outcome not reported, likely due to intial study that was previously published.

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**	**Outcomes/Results**	**Methodical Notes**
Evidence level: 1b **Study type:** Randomized clinical trial. **Number of Patient:** 115 (56, 59 per arm). **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	**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 intrathoracic anastomosis, a bronchus blocker was placed in the right bronchus to help with 1-lung ventilation during anastomosis. Open esophagectomy: Open esophagectomy involved a right posterolateral thoracotomy in the lateral decubitus position with double tracheal intubation and lung block, midline laparotomy, and cervical incision. No cervical incision was used for patients in this treatment group with an intrathoracic anastomosis. **Comparison:** 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.	**Primary:** Respiratory infections were defined as clinical manifestation of pneumonia or bronchopneumonia confirmed by thoracic radiographs or CT scan (assessed by independent radiologists) and a positive sputum culture, within the first 2 weeks of surgery and during the whole stay in hospital. **Secondary:** surgery, 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:** Mean age 62±8,4 years per group. Patients received nCRT according CROSS scheme (92.2%) or chemotherapy alone (7.8%). **Primary:**Respiratory infections:At 2 weeks postoperatively, 5(9%) in the MIS had a pulmonary infection, versus 16(29%) in the open group (P= 0.05). Similar	**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:** Male surplus in both groups. "The principal investigator visited all

status of 0,1 or 2 • Participating surgeons performed, and had experience with, both open and minimally invasive procedures, with a minimum of 10 MIE performed before start of the trial • Only institutions that performed more than 30 esophagectomies per year **Exclusion Criteria:** none described.		results were seen for total in-hospital pulmonary infection rates, being 7 (12%) in the minimally invasive group versus 19 (34%) in the open group (P=0.005). **Secondary:**Complications: No differences were seen in complications due to the operative technique P=0.302.Survival: 3 years follow-up: No differences were observed for overall survival and disease-free survival in patients who underwent MIS compared with open esophagectomy. **Author's Conclusion:** "In conclusion, the TIME trial showed less pulmonary complications and a better QoL in the short-term follow-up for MIE. For the long-term follow up, it showed an equally safe outcome regarding survival and disease-free survival."	participating centers, where he observed at least 2 MIE by thoracoscopy in prone position per surgeon, in order to assure quality and standardized treatment." could potentially have a large impact on the results or introduce selection bias.

Inhaltsverzeichnis der Evidenztabellen

Schlüsselfrage:

AG 3 Chirurgie: Ausmaß der Lymphadenektomie

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Schlüsselfrage:

***AG 3** Chirurgie: Ausmaß der Lymphadenektomie*

Bewertungsvorlage:

OXFORD Appraisal Sheet 2: RCT

Li, B. et al. Comparison of Ivor-Lewis vs Sweet esophagectomy for esophageal squamous cell carcinoma: a randomized clinical trial. JAMA Surg. 150. 292-8. 2015

Population	Intervention	Outcomes/Results	Methodical Notes
Evidence level: 1b **Study type:** Randomized clinical trial **Number of Patient:** 300 **Recruitung Phase:** DESIGN,SETTING,ANDPARTICIPANTS ArandomizedclinicaltrialwasconductedfromMay 2010 to July 2012 at Fudan University Shanghai Cancer Center, Shanghai, China. **Inclusion Criteria:** • Patients with resectable disease (cT1-T3, N0-N1, and M0) • no evidence of distant metastases • histologically confirmed SCC or high-grade dysplasia in the middle and lower thirds of the thoracic esophagus **Exclusion Criteria:** • age older than 75 years • presence of enlarged lymph nodes in the upper mediastinum (>5 mm) • history of other malignant disease • previous gastric or esophageal surgery • neoadjuvant chemotherapy or radiotherapy • severe major organ dysfunction • Karnofsky Index score less than 80	**Intervention:** Sweet procedure: patients were placed in a right lateral decubitus position at an angle of 80°. A thoracic incision was performed through the sixth or seventh intercostal space. The diaphragm was incised to access and expose the abdominal cavity. The esophagus was mobilized and a gastric tube, about 4 cm in width, was placed along the greater curvature. The tumor was then resected with at least 5 cm of proximal clearance, and a frozen-section histological analysis of the proximal margin performed. Finally, an end-to-side esophagogastric anastomosis was fashioned with a circular staple at the sub- or supra-aortic level. Anastomosis with manual suture on the left side of the neck was performed in selected cases. A feeding tube was inserted in the jejunum and nasogastric tube positioned in the gastric tube. **Comparison:** Ivor-Lewis procedure: patients were placed initially supine. Through an upper midline abdominal incision, gastric tubulization was completed and feeding jejunostomy performed. Then, the patient was positioned in the left lateral decubitus, and a right thoracotomy with a muscle- sparing incision was made in the fourth intercostal space. Af- ter ligating and dissecting the azygos vein, the esophagus was resected. Then, the gastric tube was delivered into the thorax and a circular stapled end-to-side esophagogastric anastomosis was fashioned in the upper mediastinum. A nasogastric tube was also positioned in the gastric tube to prevent vomiting and acute gastric tube distension. It should be noted that thoracic duct ligation was routinely conducted in the Ivor-Lewis procedure but not in the Sweet procedure.	**Primary:** Operative morbidity **Secondary:** Oncologic efficacy: number of lymph nodes resected and positive lymph nodes Postoperative mortality:: defined as death from any cause Postoperative complication: anastomotic leak, respiratory complications (pneumonia or bronchopneumonia); cardiovascular complications (persistent arrhythmia); chylothorax; wound infections; other complications (delayed gastric emptying, pleural effusion, recurrent nerve injury) **Results: Primary**: Morbitiy Significantly higher morbidity rate was found in Sweet (62 of 150 [41.3%]) vs Ivor-Lewis esophagectomy (45 of 150 [30%]) (P=0.04). **Secondary:**Postoperative mortality:Did not differ significantly between the 2 cohorts (3 of 150 [2.0%] in the Sweet vs 1 of 150 [0.7%] in the Ivor-Lewis groups; P=0.25). Postoperative complications: The incidences of anastomotic leakage, chylothorax, and pulmonary infections were numerically, but not significantly, higher in the Sweet group. Oncologic efficacy: Resection without macroscopical residual (R0/R1) was achieved in 149 of 150 patients (99.3%). A significantly higher number of lymph nodes was retrieved in the Ivor-Lewis group (median, 22; range, 8-56) compared with the Sweet group (median, 18; range, 3-51; P < .001). Disection area: The Ivor-Lewis procedure showed superiority in the dissection of lymph nodes both in the upper mediastinum and areas around the common hepatic and celiac arteries, whereas the number of lymph nodes retrieved in the middle/lower esophagus and perigastric regions was similar between the 2 groups. Consequently, more patients in the upper mediastinum had positive lymph nodes following the Ivor-Lewis procedure (18 of 150 [12.0%]) than the Sweet procedure (5 of 150 [3.3%]) (P=0.005). **Author's Conclusion:** "Our data provide evidence for the superiority of the Ivor-Lewis esophagectomy over the Sweet procedure with regard to short-term outcomes such as lymph node retrieval and overall morbidity for patients with squamous cell cancer in the middle and lower third of the thoracic esophagus."	**Funding Sources:** "This study was funded by the Key Construction Program of the National 985 Project (grant 985III-YFX0102)." **COI:** None reported. **Randomization:** "Randomization, by the sealed envelope method, took place on the morning of the planned resection. Sealed envelopes were prepared and provided by the Department of Biostatistics, Fudan University." **Blinding:** "Masking was not done. Patients, surgeons, and trial management staff who collected the data were aware of the assigned treatment" **Dropout Rate/ITT-Analysis:** Intent-to-treat analysis was performed. No dropouts occurred. **Notes:** Male surplus in both groups. Randomization sequence not described. Patients could have been blinded.

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Schlüsselfrage:

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

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Schlüsselfrage:

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

Bewertungsvorlage:

OXFORD Appraisal Sheet 2: RCT

Ma, D. Y. et al. Concurrent three-dimensional conformal radiotherapy and chemotherapy for postoperative recurrence of mediastinal lymph node metastases in patients with esophageal squamous cell carcinoma: a phase 2 single-institution study. Radiat Oncol. 9. 28. 2014

Population	Intervention	Outcomes/Results	Methodical Notes
Evidence level: 1b- **Study type:** Randomized controlled trial. **Number of Patient:** 98 (49 per group) **Recruitung Phase:** Between January 2002 and June 2003, from the First Hospital affiliated with North Sichuan Medical College, P.R. China **Inclusion Criteria:** Patients with histopathologically confirmed advanced locoregional ESCC. Post operative normal liver, kidney, and bone marrow functions were demonstrated by blood tests. Good tolerance for radiotherapy or chemotherapy according to the World Health Organization performance status of 0 or 1. **Exclusion Criteria:** "Patients who underwent neoadjuvant or adjuvant radiotherapy and/or chemotherapy were excluded from our study. In addition, those with supraclavicular lymph node involvement, only anastomotic stoma recurrence, or hematogenous metastases."	**Intervention:** -Initial radical esophagectomy and lymph node dissection for ESCC with a R0 margin -Assessment of locoregional mediastinal recurrence (confirmed by the presence of a growing irregular mass by chest CT or MRI.) **Intervention:** group A: three-dimensional conformal radiotherapy: "The prescribed dosage for 95% PTV was calculated using 4–6 fields of the coplanar or noncoplanar 3-DCRT plan, which was determined to be 62–70 Gy/31–35 fractions. for 1 week, divided into two phases" details see paper **Comparison: Comparison:** Group B: Concurrent chemotherapy; intravenously administered cisplatin at a dose of 30 mg per m^2 of body-surface area weekly.	**Primary:** Overall survival [%]: calculated as the time interval from initiation of treatment to death and was analyzed using the Kaplan–Meier method. **Secondary:** Severe morbidity [%]: of grade 2 or higher. **Results: Primary: overall survival** For survivers, the median follow-up was 60 months (range, 8–63). The ITT analyses showed a median overall survival of 19 months in group A versus 35 months in group B (P=0.051 log-rank test; HR, 0.76; 95% CI, 28–34). No difference in the overall survival rate at five years between both groups (P = 0.051), the overall survival rates at 1 year and 3 years in group B were significantly better than those in group A (P = 0.032, P = 0.038). Mortality: 5 (10.2%); vs 13 (26.5%) in group B,A died from distant metastases of ESCC ($\chi 2$ = 4.356, P = 0.036). **Secondary: Morbidities and adverse effects:** No life-threatening toxic effects were observed in either group. The adverse effects in the hematological and gastrointestinal systems in group B were obviously more common than in group A. However, there was no significant difference between the incidence of late adverse effects between both groups. **Author's Conclusion:** "In summary, the combined modality of 3-DCRT and chemotherapy was well tolerated compared to radiation alone and yielded superior overall survival rates in patients with postoperative recurrence of mediastinal lymph node metastases of ESCC."	**Funding Sources:** This work was supported by Medjaden. **COI:** The authors declare that they have no competing interests. **Randomization:** Assignment by using "a random number table", **Blinding:** no blinding is mentioned, but at least partial blinding could have been achieved. **Dropout Rate/ITT-Analysis:** The intention-to-treat analyses, no mentioning of dropouts **Notes:** -No blinding or concealment of allocation was performed. This might not impact the primary endpoint (survival), but it is still a risk of bias and could have partially been achieved -Only 31% female participants -Potentially unequal treatment between groups: "In parallel with concurrent radiochemotherapy, the thymic peptide α1 was injected i.h. at a dose of 1.6 mg per day for 3 weeks in order to retain systematic immune function. "

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Schlüsselfrage:

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

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Schlüsselfrage:

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

Bewertungsvorlage:

OXFORD Appraisal Sheet 2: RCT

Zhao, Y et al. Perioperative versus preoperative chemotherapy with surgery in patients with resectable squamous-cell carcinoma of esophagus: A phase III randomized trial. Journal of clinical oncology. 32. . 2014

Population	Intervention	Outcomes/Results	Methodical Notes
Evidence level: 1b **Study type:** Randomized controlled trial. **Number of Patient:** 346 (175, 171 per arm). **Recruitung Phase:** Between January 2005 and April 2007, in two Chinese hospitals (First Affiliated Hospital and the Second Affiliated Hospital of Xi'an Jiaotong University). **Inclusion Criteria:** -no evidences of previous chemotherapy or radiotherapy, Patients aged 18 years and older; WHO performance status 0 or 1 were eligible if they had histopathologically proven squamous cell carcinoma of esophagus that was considered as suitable for curative resection. The disease had to be confined to primary and regional nodes, although celiac nodal involvement (M1a) was permitted for primary tumor localized in the distal esophagus or gastroesophageal junction. Patients had to be operative candidates without excessive clinical risks and had no evidences of distant disease or involvement of tracheobronchial tree or other structures that would preclude a complete resection. Laboratory parameters included adequate bone marrow reserve consisting of a white blood cell count of more than 3500 cells/ml, platelet count of more than 100,000 cells/ml, normal liver function with total bilirubin of less than 1.5mg/100ml, and creatinine clearance of more than 60ml/min. **Exclusion Criteria:** none described.	**Intervention:** Each arm received two pre-operative cycle of chemotherapy, followed by surgery. The intervention arm (arm A) received two additional cycles of PCF post surgery. Each 3-week cycle consisted of PCF: paclitaxel (100 mg per square meter of body surface area) by a 3-hour intravenous infusion on day 1, cisplatin (60 mg per square meter of body surface area) intravenously with hydration on day 1, and 5- uorouracil (700mg per square meter of body surface area) daily through day 1 to 5 by continuous intravenous infusion with a double-lumen Hickman catheter. **Comparison:** Comparison patients received two pre-operative cycles of PCF before surgery (arm B).	**Primary: Relapse-free survival** was calculated from randomization to the first event (i.e., local recurrence, distant recurrence, or death from any cause), **Secondary: Overall survival:** was calculated from randomization to death from any causes. **Results:** The median follow-up was 60 and 61 months in arm A and arm B. Before deaths, local recurrence was confirmed in 25 patients (14.2%) in arm A and 35 patients (20.5%) in arm B, and distant metastasis was confirmed in 41 patients (23.4%) in arm A and 62 patients (36.3%) in arm B. **The median relapse-free survival and overall survival** were 23 and 29 months in arm A versus 15 and 22 months in arm B. Comparing with arm B, arm A had the significantly higher possibility of relapse-free survival (hazard ratio for relapse, 0.62; 95% confidence interval [CI], 0.49–0.73; p < 0.001, Fig. 2A) and of overall survival (hazard ratio for death, 0.79; 95% CI, 0.59–0.95; p < 0.001, Fig. 2B). Five-year relapse-free survival rate was 35.0% (95% CI, 26.1–47.2) in arm A compared with 19.1% (95% CI, 15.3–28.7) in arm B. Five-year survival rate was 38.0% (95% CI, 29.5–43.0) in arm A compared with 22.0% (95% CI, 16.6–29.4) in arm B. **Author's Conclusion:** "In conclusion, our results showed that perioperative chemotherapy with the regimen of PCF improved 5-year relapse-free and overall survival in patients with resectable squamous cell carcinoma of esophagus compared with preoperative che-motherapy alone. Therefore, this treatment should be considered as an option for patients with resectable squamous cell carcinoma of esophagus."	**Funding Sources:** This work was supported by National Natural Science Foundation of China (No. 81301847) and the Fundamental Research Funds for the Central Universities. **COI:** The authors declare no con ict of interest. **Randomization:** Randomization not specified. **Blinding:** non blinded study. **Dropout Rate/ITT-Analysis:** Itention-to-treat analysis. 3 out of 175 and 2 out of 171 patients were excluded in group A and B. **Notes:** Randomization protocol not described. No blinding was performed. Significant surplus of men in both groups.

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

Bewertungsvorlage:

OXFORD Appraisal Sheet 2: RCT

Klevebro, F. et al. A randomized clinical trial of neoadjuvant chemotherapy versus neoadjuvant chemoradiotherapy for cancer of the oesophagus or gastro-oesophageal junction. Ann Oncol. 27. 660-7. 2016

Population	Intervention	Outcomes/Results	Methodical Notes
Evidence level: 1b **Study type:** Randomized clinical trial **Number of Patient:** 181 (90 and 91 per group). **Recruitung Phase:** The neoadjuvant chemotherapy versus chemoradiotherapy in resectable cancer of the oesophagus and gastric cardia (NeoRes) trial was performed in Norway and Sweden during the period 2006–2013. **Inclusion Criteria:** Patients with histologically confirmed SCC or AC of the oesophagus or GOJ (including Siewert types I and II) who were eligible for curative treatment with surgical resection were enrolled. Clinical tumour stage; T1–3, any N (with the excep- tion of T1N0) were included, cervical cancers were required to be resectable without laryngectomy. **Exclusion Criteria:** none described.	**Intervention: Neoadjuvant chemotherapy (nCT):** Treatment had to be started within 2 weeks of randomization. Three cycles of cisplatin, 100 mg/m2 day 1, and fluorouracil 750 mg/m2/24 h, days 1–5, were given. Each cycle lasted 21 days. The same chemotherapy regimen was administered in each treatment arm. Surgery: in both arms, Patients were scheduled to undergo resection 4–6 weeks after having completed neoadjuvant treatment. The protocol required two-field lymphadenectomy, and the recommended procedure was oesophagectomy with intrathoracic anastomosis through a laparotomy and a right-sided thoracotomy (Ivor Lewis procedure). A three-stage resection, with a right-sided thoracotomy, laparotomy, and cervical incision (McKeown procedure), was recommended for tumours in the middle and upper thirds of the oesopha- gus. Other procedures were accepted in cases where the individual surgeon considered it appropriate. **Comparison:** Neoadjuvant Radiotherapy (nCRT) In patients randomized to receive chemoradiotherapy, 40 Gy was given (2 Gy once daily in 20 fractions, 5 days a week) with a photon beam linear accelerator concomitant with chemotherapy cycles 2 and 3. A 3D dose planning system was used.	**Primary:** Histological complete response **Secondary:** • Overall survival • number of lymph-node metastases • R0-resection rate • progression-free survival • site of recurrence **Results: Primary:** Histological complete response was achieved in 7 (9%) of the patients in the nCT arm versus 22 (28%) in the nCRT arm (P = 0.002). **Secondary:** Three-year overall survival: was 49% in the nCT arm, and 47% in the nCRT arm (P = 0.77). R0 resection was achieved in 58 (74%) patients in the nCT arm versus 68 (87%) in the nCRT arm (P = 0.04). Number of lymph node metastases: Of the patients with histological complete response, 26 (90%) did not have any metastatic lymph nodes, whereas 3 patients (10%), all treated with nCRT, had at least one metastatic lymph node. Of patients resected in the nCT arm, 48 (62%) had lymph-node metastases versus 27 (35%) in the nCRT arm (P = 0.001). Progression-free survival: was 44% in both treatment arms. **Author's Conclusion:** In conclusion, this trial confirms previous findings that the addition of radiotherapy to neoadjuvant chemotherapy increases the complete histological response and R0 resection rates and decreases the proportion of patients with lymph-node metastases, without significantly affecting survival. Moreover, we conclude that this trial does not provide any evidence in support of using complete histological response as a surrogate marker for survival.	**Funding Sources:** This work was financially supported by the Swedish Society of Medicine, the Swedish Cancer Society, the Cancer Research Foundations of Radiumhemmet, and the Stockholm County Council, grant number not applicable. The sponsors had no involvement in the study design, data collection, or interpretation of the results. **COI:** The authors have declared no conflicts of interest. **Randomization:** No description of the randomization sequence or protocol. **Blinding:** The pathologist reviewing the surgical specimen was blinded to the randomization outcome of each individual patient. **Dropout Rate/ITT-Analysis:** "Data were analyzed according to the intention-to-treat principle in all randomized patients." **Notes:** Randomization sequence not described; male surplus in both groups; primary outcome: histological complete response is not described

Klevebro, F. et al. Morbidity and mortality after surgery for cancer of the oesophagus and gastro-oesophageal junction: A randomized clinical trial of neoadjuvant chemotherapy vs. neoadjuvant chemoradiation. Eur J Surg Oncol. 41. 920-6. 2015

Population	Intervention	Outcomes/Results	Methodical Notes
Evidence level: 1b **Study type:** Randomized controlled trial **Number of Patient:** 181 patients (91, 90 per arm) **Recruitung Phase:** "to this end, between 2006 and 2013, we have performed a	**Intervention:** Chemotherapy: The nCT treatment cycle was 21 days (treatment during weeks 1, 4, and 7). Cisplatin in a dose of 100 mg/m2 (day 1) was given intravenously, in combination with 5-fluorouracil in the amount of 750 mg/m2/24 h (days 1e5). In patients with borderline renal function or with severely impaired hearing, cisplatin was replaced by oxaliplatin (130 mg/m2) in adenocarcinoma patients or with carboplatin (AUC 5) in squamous carcinoma patients. Surgery: Patients were scheduled to undergo resection 4e6 weeks	**Primary:** Incidence of perioperative complications: directly caused by surgery or nonsurgical complications. Severity of perioperative complications:	**Funding Sources:** The Swedish Society of Medicine has financially supported the conduct of the study.

randomized controlled trial, the Neoadjuvant Chemotherapy versus Chemoradiotherapy in Resectable Cancer of the Esophagus and Gastric Cardia Trial (NeoRes)." **Inclusion Criteria:** All patients with histologically confirmed, non-distant-metastatic SCC or AC of the oesophagus or GOJ, considered to tolerate oesophagectomy, were eligible for inclusion. Tumours located any-where in the oesophagus or Siewert types I and II junctional tumours, were included, although cervical cancers were required to be resectable without laryngectomy. Study participants were allowed to be no more than 75 years of age, considered fit for oesophagectomy, and have a WHO performance status of 0 or 1. All patients were also required to be suitable for chemotherapy and concomitant radiotherapy in terms of adequate renal and haematological functions. Using TNM-6, patients with T1e3, any N (with the exception of T1N0) without evidence of distant metastatic disease, were eligible for inclusion. **Exclusion Criteria:** Manifestations of major heart disease within the last year or a concurrent malignancy within the last five years constituted grounds for exclusion.	after having completed neoadjuvant treatment. All participating centres performed oesophagectomies regularly, and the protocol required two-field lymphadenectomy. The recommended procedure was transthoracic oesophagectomy with intrathoracic anastomosis through a right-sided thoracotomy (Ivor-Lewis) for distal oesophageal and junctional cancers. Three-stage resection with neck anastomosis (McKeown) was recommended for tumours in the mid oesophagus and the upper third of the oesophagus. **Comparison:** Chemoradiotherapy: In addition to the same chemotherapy as in the nCT group, patients in the nCRT group also received external beam radiation to a total dose of 40 Gy, delivered in 2 Gy fractions five days per week, starting day one (week 4) of the second chemotherapy cycle and ending at the completion of the third chemotherapy cycle (week 7). All dose planning was performed with a CT-based three-dimensional planning system with inhomogeneity correction. Dose level to heart, lung, and spinal cord was minimized using the multiple-field technique. During the radiation therapy, patients were assessed for adverse events at least once every week.	classified according to the Clavien-Dindo scoring system for postoperative complications and comprehensive complication index (CCI) including all postoperative complications (score 0-100). **Secondary:** - **Results:** Surgical complication: 38% (n=29) and 35% (n=27) nCRT vs nCT group. Nonsurgical complications: were 31% (n=24) and 21% (n=16) nCRT vs nCT group. Any type of complication: was 55% (n=42) for nCRT and 45% (n=35) for nCT (P=0.23). Severity of perioperative complications: 30 % (n=23) of nCRT vs 17% (n=13) of nCT petients (P=0.05) experienced a complication that scored IIIb or higher in the Clavien-Dindo system. Mean severity scores: The mean CCI was 41 in the nCRT group and 31 in the nCT group (P=0.03). The median Clavien-Dindo complication severity score among those with any complication was IIIb in the nCRT group (n=42) and IIIa in the nCT group (n=35). This difference was statistically significant (P=0.001). **Author's Conclusion:** "In conclusion, the results from this randomized clinical trial suggest that nCRT is not associated with a higher overall incidence of postoperative complications or of postoperative mortality after oesophagectomy than nCT. However, the complications that occurred in patients who received chemoradiotherapy were more severe."	**COI:** The authors declare no conflict of interest. The Swedish Society of Medicine has financially supported the study but has not influenced the study design or conduct in any way. **Randomization:** Patients were stratified by histological tumour type, and all patients were randomized independently through the use of computerized software at the Regional Oncological Centre in Stockholm. **Blinding:** No blinding was performed. **Dropout Rate/ITT-Analysis:** Data were analysed according to the intention-to-treat principle. 13 (out of 90) and 13 (out of 91) dropped out in each arm. **Notes:** Male surplus in both groups.

Mariette, C. et al. Surgery alone versus chemoradiotherapy followed by surgery for stage I and II esophageal cancer: final analysis of randomized controlled phase III trial FFCD 9901. J Clin Oncol. 32. 2416-22. 2014

Population	Intervention	Outcomes/Results	Methodical Notes
Evidence level: 1b **Study type:** Phase III randomized controlled trial, multicentric study (30 centers in France). **Number of Patient:** 195 patients (98, 97 per arm). **Recruitung Phase:** From June 2000 to June 2009. **Inclusion Criteria:** Patients age < 75 years,	**Intervention:** Radiotherapy. Three-dimensional conformal radiation treatment was administered. Planning was performed using a simulator, esophagogram, and CT scan to define the extent of the tumor and involved lymph nodes. A total dose of 45 Gy was delivered in 25 fractions (five fractions per week) over 5 weeks. The clinical target volume (CTV) extended to 3 cm of mediastinal tissue above and below the gross tumor volume. The planning target volume contained the CTV and additional proximal,	**Primary:** Overall survival (OS) Patients were seen every 4 months during the first 2 years after date of random assignment, every 6 months for the next 2 years, and annually after 5 years. **Secondary:** Disease-free survival (DFS), in-hospital postoperative mortality and morbidity, and identification of prognostic factors for OS. Disease recurrence was defined as locoregional (esophageal bed or anasto- motic or regional lymph nodes) or	**Funding Sources:** None disclosed. **COI:** Employment or Leadership Position: None Consultant or Advisory Role: Franc¸oise Mornex, Roche (C), Merck (C) Stock Ownership: None

judged suitable for curative resection, with untreated stage I or II (T1 or T2, N0 or N1 and T3N0, M0)5 thoracic esophageal adenocarcinoma or squamous cell carcinoma, as assessed by computed tomography (CT) scan and endoscopic ultrasound (EUS), were included. All patients were required to be capable of receiving either treatment, with WHO performance status of 0 or 1. **Exclusion Criteria:** Reasons for patient exclusion included weight loss > 10% at baseline and respiratory, liver, or cardiac insufficiency. Patients with a previously treated malignancy, evidence of supraclavicular or celiac nodes, a multifocal tumor, a tumor with a proximal limit < 19 cm from the incisor teeth, or evidence of invasion of the tracheobronchial tree were excluded.	distal, and lateral margins of 1 cm to account for uncertainties in repositioning and patient movement. Photon beams from a linear accelerator with energy 6 MeV were used throughout this study. Chemotherapy. Chemotherapy was delivered concomitantly; two cycles of fluorouracil (FU) and cisplatin. FU 800 mg/m2 per 24 hours was administered as a continuous infusion from days 1 to 4 and 29 to 32. Cisplatin 75 mg/m2 was delivered by infusion on day 1 or 2 and again on day 29 or 30. Alternatively, it was delivered as an infusion at a dose of 15 mg/m2 from days 1 to 5 and 29 to 33. Administration of the second cycle of chemotherapy as a half dose was permitted in cases of moderate hematologic toxicity (granulocytes between 1,000 and 1,500/mm3 and/or platelets between 75,000 and 100,000/mm3); it could be omitted in cases of severe hematologic toxicity (granulocytes 1,000/mm3 and/or platelets 75,000/mm3) or persistent grade 3 to 4 digestive toxicity. **Comparison:** Surgery: All patients in group CRT underwent clinical re-evaluation 2 to 4 weeks after finishing NCRT, including physical examination, weight evaluation, blood laboratory analysis, and thoracoabdominal CT scan. Surgery was performed 4 to 8 weeks after completion of NCRT in group CRT and within 4 weeks of random assignment in group S. A transthoracic esophagec- tomy was mandatory with an extended two-field lymphadenectomy and high intrathoracic anastomosis for tumors with infracarinal proximal margin; cervical anastomosis was mandatory when the proximal margin was above the carina.	metastatic (supraclavicular lymph nodes or distant organs). **Results: Primary:** OS: Median follow-up was 93.6 months. Total number of deaths was 125 (64.1%; 61 [62.4%] in group CRT v 64 [66.0%] in group S). Median, 3-year, and 5-year OS were 31.8 months (95% CI, 25.2 to 67.8 months), 47.5% (95% CI, 37.1% to 57.2%), and 41.1% (95% CI, 30.8% to 51.0%) in group CRT versus 41.2 months (95% CI, 29.0 to 53.9 months), 53.0% (95% CI, 42.3% to 62.5%), and 33.8% (95% CI, 23.9% to 43.9%) in group S. OS was not significantly different between groups (HR for group CRT versus group S, 0.99; 95% CI, 0.69 to 1.40; P=.94. **Secondary:** DFS In the overall population, recurrent disease was observed in 71 patients (36.4%; 28.6% in group CRT vs 44.3% in group S; P=.02). Locoregional recurrence was diagnosed in 43 patients (22.1%; 15.3% in group CRT v 28.9% in group S; P=.02), whereas distant recurrence was diagnosed in 50 patients (25.6%; 22.5% in group CRT v 28.9% in group S; P=.31). Median DFS was 27.8 (95% CI, 15.0 to 42.9) and 26.7 months (95% CI, 22.9 to 41.1), and 5-year DFS was 35.6% (95% CI, 25.9% to 45.4%) and 27.7% (95% CI, 18.6% to 37.6%) in groups CRT and S. DFS did not differ between groups (HR for group CRT vs group S, 0.92; 95% CI, 0.66 to 1.30; P=.648). Postop Morbidity and Mortality similar between groups (55.6% v 52.8%; P=.720); in-hospital postop mortality was significantly higher in the CRT group (11.1% v 3.4%; P=.049). **Author's Conclusion:** "Compared with surgery alone, NCRT with cisplatin plus fluorouracil does not improve R0 resection rate or survival but enhances postoperative mortality in patients with stage I or II EC."	Honoraria: Franc ,oise Mornex, Roche, Merck Research Funding: None Expert Testimony: None Patents, Royalties, and Licenses: None Other Remuneration: None **Randomization:** "Randomization was performed centrally with a minimization technique that ensured equal distribu- tion of patients regarding stratification factors." **Blinding:** Non blinded trial. **Dropout Rate/ITT-Analysis:** Analyses were performed using an intent-to-treat approach, including all patients as randomly assigned regardless of eligibility or treatment. **Notes:** Male surplus in both groups.

Nederlof, N. et al. Using the Comprehensive Complication Index to Assess the Impact of Neoadjuvant Chemoradiotherapy on Complication Severity After Esophagectomy for Cancer. Ann Surg Oncol. 23. 3964-3971. 2016

Population	Intervention	Outcomes/Results	Methodical Notes
Evidence level: 1b **Study type:** Randomized controlled trial **Number of Patient:** 368 (180, 188 per arm) **Recruitung Phase:** **Inclusion Criteria:** Patients with histologically proven SCC or AC of the esophagus or GEJ; The tumor must not extend more than 2 cm into the gastric cardia. Longitudinal tumor length must not exceed 8 cm, radial size must not exceed 5 cm. cT1N0 tumors are not eligible. Patients must have adequate hematological, renal, hepatic and pulmonary functions defined as: granulocytes ≥ 1.5 × 109/L, platelets ≥ 100 × 109/L, total bilirubin ≤ 1.5 × upper normal limit, creatinine ≤ 120 µmol/L and FEV1 ≥ 1.5 L. In the absence of local irresectability and/or distant dissemination patients with an acceptable general condition (ECOG performance status 0, 1, 2; weight loss < 10%) will be invited to participate in the randomized trial. **Exclusion Criteria:** none described.	**Intervention:** Chemotherapy regimen Paclitaxel 50 mg/m2 and Carboplatin AUC = 2 will be given by intravenous infusion on days 1, 8, 15, 22 and 29. All patients receiving Paclitaxel will receive half an hour before the start of the Paclitaxel infusion premedication: Dexamethason 10 mg i.v., Clemastine 2 mg i.v. and Ranitidine 50 mg i.v.. At hour 0, the total calculated dose of Paclitaxel, diluted in 500 ml of normal saline will be infused over one hour. After the completion of the Paclitaxel infusion, 100 ml NaCl 0.9% will be infused over 0.5 h, followed by an infusion of 8 mg Ondansetron or its equivalent diluted in 100 ml NaCl 0.9% over 0.5 hour. Hereafter the total calculated dose of Carboplatin, diluted in 500 ml glucose 5% will be infused over one hour. Radiotherapy treatment A total dose of 41.4 Gy will be given in 23 fractions of 1.8 Gy, 5 fractions per week, starting the first day of the first cycle of chemotherapy. All patients will be radiated by external beam radiation, using 3-D conformal radiation technique. The patient will be positioned in supine position. **Comparison:** Surgery:Patients randomized for surgery alone will be treated asap after randomization. In the chemoradiation arm, surgery will be performed preferably within 6 weeks after the completion of the chemoradiation. For carcinomas proximal to the tracheal bifurcation a transthoracic esophageal resection with a two field lymph node dissection is preferred. For carcinomas distal of the tracheal bifurcation but proximal to the gastro-	**Primary:** 30 days post operative complications: Definition according to the National Cancer Institute's Common Terminology Criteria for Adverse effects, 4.0. Severity of complications: Grading of complications using CCI index for complication index, based on Clavien-Dindo classification **Secondary:** Subgroup analysis of complications: • Anastomotic leakage • Pulmonary complications • Cardiac complications • Thromboembolic events • Chyle leakage • Wound infections **Results: Primary:** Complications:Grade I complications were seen in 43 % of patients in NCRT versus 49 % of patients after surgery alone (p =	**Funding Sources:** none described. **COI:** The authors declare that they have no competing interests(in the study protocol). **Randomization:** "Block randomization was performed centrally by telephone or at the central trial office, according to computer-generated randomization lists for each stratum, with random block sizes of 4 or 6." **Blinding:** No blinding was performed. **Dropout Rate/ITT-Analysis:** Dropouts: 19(11%) and 27(14%) dropped out of

	esophageal junction, a transthoracic approach with a two field lymph node dissection or a transhiatal approach can be performed, depending on both patient characteristics and local expertise.For distal tumors involving the gastro-esophageal junction a transhiatal esophageal resection is preferred.	0.37). There also was no statistically significant difference for grade II-grade V complications. Severity of complications: There was no statistically significant difference in the CCI between both groups. Median CCI in the combined treatment group was 26.22 (IQR 17.28–42.43) compared with 25.74 (IQR 8.66–43.01) in the surgery alone group (p = 0.58). **Secondary:** Subgroup analysis of complications In subgroup analyses of the specific complications, CCI for patients who developed an anastomotic leak was not statistically different between groups: 8.66 [8.66–33.73] vs. 8.66 [8.66–33.73] (p = 0.78). The same was true for the other subgroups with patients who developed pulmonary or cardiac complications, thromboembolic event, chyle leakage, or wound infection. **Author's Conclusion:** "Neoadjuvant chemoradiotherapy according to CROSS did not have a negative impact on postoperative complication severity expressed by CCI compared with patients who underwent surgery alone for potentially curable esophageal or junctional cancer."	the nCRT and surgery group. "Data will be analyzed according to the 'Intention to treat' principle." **Notes:**

Shapiro, J. et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. Lancet Oncol. 16. 1090-8. 2015

Population	Intervention	Outcomes/Results	Methodical Notes
Evidence level: 1b **Study type:** Randomized controlled trial **Number of Patient:** 368, (178 and 188 per study arm) **Recruitung Phase:** Between March 30, 2004, and Dec 2, 2008, patients from 8centres (five academic centres and three large non-academic teaching hospitals) in the Netherlands were enrolled . **Inclusion Criteria:** Aged 75 years or younger; adequate haematological, renal, hepatic, and pulmonary function; a WHO performance score of 2 or better, without a past or present history of other malignancy. Only patients with locally advanced (clinical stage T1N1M0 or clinical stage T2–3N0–1M0, according to UICC TNM cancer staging, 6th edition10), histologically proven, and potentially curable	**Intervention:** Chemoradiotherapy followed by esophagectomy 4-6 weeks after completion of the regiment. Details: Carboplatin (AUC 2 mg/mL per min) and paclitaxel (50 mg/m2 of body-surface area) intravenously for five cycles, starting on days 1, 8, 15, 22, and 29. A total concurrent radiation dose of 41·4 Gy was given in 23 fractions of 1·8 Gy, on 5 days per week (excluding weekends), starting on the first day of the first chemotherapy cycle. The total duration of neoadjuvant treatment was 23 days (5 days per week in weeks 1, 2, 3, 4, then 3 days in week 5). **Comparison:** Surgery only, as soon as possible Details (for both groups): For carcinomas at or above the level of the carina, a transthoracic oesophageal resection with two-field lymph node dissection was done. For carcinomas located well below the level of the carina, either a transthoracic approach with two-field lymph node dissection or a transhiatal approach was used, depending on both patient characteristics and local preferences. For carcinomas involving the oesophagogastric junction, a transhiatal oesophageal resection was preferred. In both approaches, an upper abdominal lymphadenectomy, including resection of nodes along the hepatic artery, splenic artery, and left gastric artery, was done.	**Primary: Overall survival:** Calculated from the randomization date to date of all-cause death or last day of follow-up. Follow-ups were conducted up to 96 months. **Secondary: progression-free survival:** defined as the interval between randomisation and the earliest occurrence of disease progression resulting in primary (or peroperative) irresectability of disease, loco- regional recurrence (after completion of therapy), distant dissemination (during or after completion of treatment), or death from any cause and disease recurrence patterns. **Results:** Median follow-up for surviving patients of 84,1 months (range 61,1–116,8, IQR 70,7–96,6), **overall survival** Median was 48·6 months (95% CI 32,1–65,1) in the neoadjuvant chemoradiotherapy plus surgery group and 24·0 months (14,2–33,7) in the surgery alone group (HR 0·68 [95% CI 0·53–0·88]; log-rank p=0·003). Subgroup analysis: Median overall survival for patients with SCCs was 81,6 months (95% CI 47·2–116·0) in the neoadjuvant chemoradiotherapy plus surgery group and 21·1 months (15·4–26·7) in the surgery alone	**Funding Sources:** Dutch Cancer Foundation (KWF Kankerbestrijding). **COI:** "JJBvL has received grants from the Dutch Cancer Foundation (KWF Kankerbestrijding) during the conduct of the study, and grants from the Dutch Cancer Foundation (KWF Kankerbestrijding), the Coolsingel Stichting, and the Erasmus MC/MRace fund, outside the submitted work. The other authors declare no competing interests." **Randomization:** Patients were randomly assigned 1:1 to each group, and were stratified according to histological tumour type (AC vs SCC), treatment centre, clinical nodal status (cN0 vs cN1), and WHO performance score (WHO-0 vs WHO-1 vs WHO-2). Randomisation was done centrally.. by computer-generated randomisation lists for each stratum, with random permuted block sizes of four or six.

squamous cell carcinoma or adenocarcinoma of the oesophagus or oesophagogastric junction (ie, tumours involving both the cardia and the oesophagus on endoscopy) were eligible **Exclusion Criteria:** Past or current history of malignancy other than the oesophageal malignancy, previous chemotherapy and/or radiotherapy, and weight loss of more than 10% of the original bodyweight.		group (HR 0·48 [95% CI 0·28–0·83]; log-rank p=0·008); for patients with ACs, it was 43·2 months (24·9–61·4) in the neoadjuvant chemoradiotherapy plus surgery group and 27·1 months (13·0–41·2) in the surgery alone group (HR 0·73 [95% CI 0·55–0·98]; log-rank p=0·038). **Author's Conclusion:** "In conclusion, chemoradiotherapy according to the CROSS regimen improves long-term overall and progression-free survival in patients with oesophageal and junctional cancer. This improvement is statistically significant and clinically relevant for both squamous cell carcinoma and adenocarcinoma subtypes. Neoadjuvant chemoradiotherapy according to CROSS followed by surgical resection should be viewed as a standard of care for patients with resectable locally advanced oesophageal or junctional cancer."	**Blinding:** No blinding was performed. **Dropout Rate/ITT-Analysis:** Data were analysed according to an intention-to-treat principle. Two patients dropped out of the chemoradiotherapy group by withdrawing consent. **Notes:** No blinding was performed; male surplus in both study arms; time between immediate surgery and surgery after chemoradio-therapy (29 days regiment + 4-6 weeks) might influence comparability.

Stahl, M. et al. Preoperative chemotherapy versus chemoradiotherapy in locally advanced adenocarcinomas of the oesophagogastric junction (POET): Long-term results of a controlled randomised trial. Eur J Cancer. 81. 183-190. 2017

Population	Intervention	Outcomes/Results	Methodical Notes
Evidence level: 1b **Study type:** Unblinded, prospective and randomised phase III study. **Number of Patient:** 126, (59, 60 per arm) from 19 German centres. **Recruitung Phase:** Between November 2000 and December 2005. **Inclusion Criteria:** Patients up to 70 years old, histologically proven (type I to III Siewert's classification) untreated locally AC of the oesophagogastric junction; locally advanced diseases(T3-T4 NX mo) according to computed tomography scan, endoscopic ultrasound (EUS), and diagnostic laparoscopy, good general condition (WHO performance status grade 0 to 1) allowing major surgery, normal liver, renal and bone marrow function. **Exclusion Criteria:** None described.	**Intervention:** **Chemotherapy:** Arm A: Patients received 12 applications of peroperative chemotherapy with weekly 5-fluorouracil (2000 mg/m2, 24 h infusion)/folinic acid (500 mg/m2, 2 h infusion) and biweekly cisplatin (50 mg/ m2, 1 h infusion), within 14 weeks, followed by another 3-weekly applications. Both groups were followed by surgery, for details see original article. **Comparison:** Radiochemotherapy: Patients assigned to arm B received the same 14-weeks preoperative chemotherapy for induction, followed by a 3-week course of combined CRT with cisplatin (50 mg/m2, 1 h infusion, days 2 and 8) and etoposide (80 mg/m2, 1 h infusion, days 3e5). A total dose of 30 Gy was applied, using 15 fractions of 2 Gy within 3 weeks.	**Primary:** Overall survival: The primary end-point of the study was overall survival at 3 years which was calculated from the date of randomisation to the date of death or to the last day of follow-up. **Secondary:** Progression-free survival: was defined as the interval from randomisation to disease progression at any site or to death from any cause. Local progression-free survival: was defined as the interval from randomisation to disease progression within the (potential) radiation field or to death. **Results: Primary:** Overall survival: Median overall survival was 21.1 months in arm A and 30.8 months in arm B. Survival at 3 and 5 years reached 26.1% (16.9-40.3%) and 24.4% (15.5-38.4%) in the chemotherapy plus surgery group compared with 46.7% (35.6-61.2%) and 39.5% (28.8-54.2%), respectively, in the CRT plus surgery group (HR 0.65; 0.42e1.01, p value 0.055 in favour of the CRT group). **Secondary** Progression-free survival was increased for patients receiving combined preoperative therapy (HR 0.64, 0.39-1.06, p=0.03). Local progression-free survival after resection was significantly improved by CRT (HR 0.37; 0.16=0.85, p=value 0.01). **Author's Conclusion:** "Although the primary end-point overall survival of the study was not met, our long-term follow-up data suggest a benefit in local progression-free survival when radio- therapy was added to preoperative chemotherapy in patients with locally advanced adenocarcinoma of the oesophagogastric junction."	**Funding Sources:** This research was supported by grants from Ortho Biotech (Janssen) and from Baxter for conducting and monitoring the study. The funding companies had no role in the study design, data analysis, data interpreta- tion or the writing of the report. **COI:** None declared. **Randomization:** "Randomisation was done centrally at the Institute for Medical Informatics, Biometry and Epidemiology, University of Duisburg-Essen, Germany." **Blinding:** No blinding was performed. **Dropout Rate/ITT-Analysis:** Data analysis was done according to the intention-to- treat principle. **Notes:** No tests for differences in group demographics are displayed. The chemoradiotherapy regiment in group B consists of the induction chemotherapy regiment in group A plus additional radio and chemotherapy. The differences in observed effect might not be solely related to the addition of radiotherapy. Male surplus in both arms.

Ajani, J. A. et al. A phase II randomized trial of induction chemotherapy versus no induction chemotherapy followed by preoperative chemoradiation in patients with esophageal cancer. Ann Oncol. 24. 2844-9. 2013

Population	Intervention	Outcomes/Results	Methodical Notes
Evidence level: 1b- **Study type:** Phase II Randomized controlled trial **Number of Patient:** 126 (63 per group)	**Intervention: Arm A:** consisted of preoperative chemoradiation: Patients received 50.4 Gy of proton or photon (intensity modulated) radiation in 28 fractions.	**Primary: Primary:** Pathological complete response rate (pathCR): in three groups: 0% tumor cells (pathCR), 1-50%, 51-100% tumor cells. **Secondary: Secondary:** Disease free survival	**Funding Sources:** The trial was partly supported by Sanofi Oncology, NJ and partly funded by the Sultan,

Recruitung Phase: The study was conducted at the University of Texas M. D. Anderson Cancer Center between 2005 and 2011. **Inclusion Criteria:** Patients with local-regional thoracic esophageal or gastroesophageal junction carcinoma (histologic documentation of AC or SCC) who could physiologically withstand surgery; Patients had to have adequate organ function, performance status of 0–1, chronological age <76 years, eusT1N+ or eusT2–3 with any N baseline clinical stage. **Exclusion Criteria:** Patients with eusT1N0, T4 with any N, and any M1 cancer were not included.	Concurrently, patients received fluorouracil (250 mg/m2/daily as 24-h infusion from Monday to Friday for 5 weeks) and oxaliplatin (40 mg/m2 intravenously once a week for five doses). Esophagectomy: Upon completion the chemoradiation regiment (minimally invasive esophagectomy, three-field approach, transhiatal, or transthoracic), as chosen by the operating team. Follow-up: Upon completion of all protocol treatment, patients were followed every 3 months for 1 year, then every 6 months for two additional years, and finally once a year for up to 5 years. **Comparison: Arm B** induction chemotherapy followed by full protocol of Arm A Induction chemotherapy: up to 8 weeks, with each 4-week cycle consisting of oxaliplatin 100 mg/m2 on days 1 and 15 and fluorouracil 2200 mg/m2 over 48 h as infusion starting on days 1 and 15. This particular regimen was a modification of a colon regimen and agreed upon by the Sponsor. A maximum of two cycles (four doses) were administered.	(DFS), overall survival (OS). **Results: Primary:** PathCR: 7 (11% of 63 randomized) in Arm A achieved a pathCR, compared with 14 (22% of 63 randomized) in Arm B (P = 0.094, Fisher's exact test). Secondary: Overall survival: The median actuarial OS for all patients (54 deaths) was 45.62 months [95% CI, 27.63–NA], with median OS 45.62 months (95% CI 25.56–NA) in Arm A and 43.68 months (95% CI 27.63–NA) in Arm B (P = 0.69). **Author's Conclusion:** In conclusion, our data demonstrate that the use of induction chemotherapy before chemoradiation may not meaningfully increase the rate of pathCR, almost certainly does not increase 30-day surgical mortality, does not prolong OS, does not increase the rate of surgical complications, and is associated with no significant increase in grade 3 or 4 toxic effects. Based on the results of this first randomized study addressing this strategy, we cannot recommend the use of induction chemotherapy in trimodality-eligible patients undergoing therapy.	Cantu, Dallas, Park, Oaks, Fairman, Caporella, Vanstekelenberg, Dio, Milrod, and Frazier families and Schecter Foundation, the Kevin Fund, as well as the Rivercreek Foundation. **COI:** The authors have declared no conflict of interest. **Randomization:** The randomization was conducted using an in-house web-based software program that dynamically balanced the two groups for histology, baseline stage, gender, race, and age. **Blinding:** No blinding was performed **Dropout Rate/ITT-Analysis:** Total dropouts were 8(13%) and 9(14%) per group. ITT analysis was performed, which consideres all patients that were initially randomized. **Notes:** Male surplus in both groups (94% male participants). Incomplete reporting of initially mentioned outcomes (DFS not available). Lacking outcome definition. Lack of blinding of the pathologists could have influenced the results.

Rajabi Mashhadi, M. et al. The Effect of Neoadjuvant Therapy on Early Complications of Esophageal Cancer Surgery. Iran J Otorhinolaryngol. 27. 279-84. 2015

Population	Intervention	Outcomes/Results	Methodical Notes
Evidence level: 1b- **Study type:** Randomized controlled trial. **Number of Patient:** 100 (50 per arm). **Recruitung Phase:** Between 2009 and 2011. **Inclusion Criteria:** Inclusion criteria were (1) lower esophageal cancer; (2) general condition suitable for surgery, as well as lack of previous cardiac, pulmonary, or renal problems; (3) no contraindication to neoadjuvant treatment; and (4) lack of distant macroscopic metastases. **Exclusion Criteria:** Exclusion criteria included (1) cervical, upper, and middle-part esophageal cancer; (2) no desire for surgery following NACR; (3) intolerance to surgery after receiving NACR; (4) acute malnutrition (albumin< 2.5g/dl); (5) macrometastases (Stage 4); and (6) serious complication during surgery such as airway damage or intense bleeding.	**Intervention:** Chemoradiotherapy: Group A patients received chemoradiotherapy and cisplatin, followed by 50 Gy radiation and then undergoing surgery 3–4 weeks later (see comparison). The proximal field of radiation therapy was 5–7 cm to the tumor and the distal field was adjacent to L1. **Comparison:** Surgery: Group B included 50 patients undergoing surgery only. Patients underwent undertranshiatal esophagectomy, and the stomach was used as a conduit.	**Primary:** Post-operative complications: Anastomotic site leakeage; Pulmonary complications (atelectasia, pneumonia, empyema, and pulmonary insufficiency); chylotharx; cardiovascular; **Secondary:** 30 day-Mortality; perio-perativeblood loss, time of surgery number of lymph nodes resected **Results: Primary:** Complications: • Anastomosis site leakage was detected in none of the patients in the group receiving NACR plus surgery and one patient in the surgery-only group, although the difference was not statistically significant (P>0.05) • Pulmonary complications were observed in four patients in each of the groups, with no significant difference between the two groups (P>0.99). • Chylothorax was observed in two cases in Group A and one case in Group B (P>0.99). • Cardiovascular: In Group A, five patients developed post-operative accidents (myocardial infarction [MI] in three patients and arrhythmia requiring	**Funding Sources:** not disclosed. **COI:** not disclosed. **Randomization:** "Patients were randomly assigned to one of two groups using computer-generated random numbers." **Blinding:** Non blinded study. **Dropout Rate/ITT-Analysis:** ITT analysis was performed. **Notes:** No disclosure of potential conflicts of interest or funding. Outcomes not explicitly stated or described, which gives way to data dredging and risk of bias.

		treatment in two patients). In Group B, six patients showed complications (three cases of MI and three cases of arrhythmia). Two patients from Group A and three patients from Group B developed deep vein thrombosis (DVT) and underwent appropriate treatment. **Secondary:** Mortality In the first 30 days after surgery, mortalities occurred in 4 patients in the nCRT group (two MI complications and 2 pulmonary embolism) and in 3 patients in the surgery group (2 MI and 1 pulmonary embolism). Significant differences ($p<0.05$) between the two groups were identified in terms of time of surgery (185±20 and 175±25 in group A and B(, perioperative blood loss(405cc±25 and 390cc±15 in group A and B) , and number of lymph nodes resected (5±2 and 7±2 in group A and B). **Author's Conclusion:** "There was no significant difference between the groups receiving or not receiving NACR in terms of early side effects of transhiatal esophagectomy for esophageal SCC. Only the emergence of chylothorax in the group receiving NACR was higher. Therefore, the use of NACR does not cause an increase in early post-operative complications."	

Inhaltsverzeichnis der Evidenztabellen

Schlüsselfrage:

AG 3 Multimodale Therapie: Stellenwert und Indikation der definitiven Radiochemotherapie

Citation	Evidence Level	Study Type
Teoh, A. Y. 2013	1b-	prospective multicentered randomized controlled study

Evidenztabellen

zurück

Schlüsselfrage:

AG 3 *Multimodale Therapie: Stellenwert und Indikation der definitiven Radiochemotherapie*

Bewertungsvorlage:

OXFORD Appraisal Sheet 2: RCT

Teoh, A. Y. et al. Long-term survival outcomes after definitive chemoradiation versus surgery in patients with resectable squamous carcinoma of the esophagus: results from a randomized controlled trial. Ann Oncol. 24. 165-71. 2013

Population	Intervention	Outcomes/Results	Methodical Notes
Evidence level: 1b- **Study type:** prospective multicentered randomized controlled study **Number of Patient:** 80 (44, 36 per arm) **Recruitung Phase:** Between July 2000 and December 2004 in five regional hospitals in Hong Kong. **Inclusion Criteria:** patients <75 years with resectable mid-or lower thoracic esophageal SCC. Staging workup included esophagoscopy, bronchoscopy for midthoracic tumor, EUS, CT of thorax and abdomen with contrast and ultrasonography of the cervical region with fine-needle aspiration cytology for any suspicious nodes. Positive emission tomography was not routinely performed. **Exclusion Criteria:** Patients were excluded if there was evidence of distant metastasis or adjacent organ invasion. They were also excluded if the premorbid condition precluded a thoracotomy or if the creatinine clearance was less than 50 ml/min.	**Intervention: Standard esophagectomy with two-field lymphadenectomy** Surgery was performed by the respective upper gastrointestinal specialists in each hospital. A two or three-stage esophagectomy was performed to achieve a 5-cm proximal margin clearance. An en bloc two-field lymphadenectomy was performed through an open approach that included removal of mediastinal and abdominal lymph nodes. The continuity of the gastrointestinal tract was restored using a transposed stomach or the colon when the patient had previous history of gastrectomy. A curative surgical resection was defined as macroscopic clearance of the esophageal tumor. **Comparison: Chemoradiotherapy** Patients received two 3-weekly cycles of cisplatin and 5-FU chemotherapy. Cisplatin 60 mg/m2 with hydration therapy was given on days 1 and 22, whereas 5-FU was administrated as a continuous infusion at 200 mg/m2/day from day 1 to 42. Radiotherapy was delivered in a three- dimensional conformal mode with a total of 50–60 Gy given in 25–30 fractions over 5–6 weeks. Phase I started with anterior– posterior-opposing portals to 30 Gy, while phase II was given with three fields to another 20 Gy. Phase III used reduced portal length to give up to 10 Gy, subject to limiting radiation dose to the heart, lung and spinal cord. The dosage for individual patients was governed by the dose constraints of normal organs. Target volume length included 5 cm on each side of image visible tumor and malignant nodes.	**Primary:** 2-year overall survival **Secondary:** 5-year overall survival, disease-free survival, patterns of recurrence **Results:** The median follow-up time was 93 months (95% CI 83.65–102.36). **Primary:** 2-year overall survival: No significant differences in the 2-year cumulative survival and disease-free survival were detected in our previous report. **Secondary:** overall 5-year survival: favors CRT and was 29.4% (95% CI 15.9–42.9) in the surgery group and 50% (95% CI 32.5–64.7) in the CRT group. The difference was, however, insignificant (P = 0.147). 5-year disease-free survival showed a trend to significance favoring CRT, with surgery being 25% (95% CI 12.06–37.54) and CRT being 47.2% (95% CI 32.5–64.7, P = 0.068). Recurrence: The mean (SD) time to recurrence was 481.88 (424.39) days in the surgery group and 525.74 (790.83) days in the CRT group (P = 0.219). The patterns of recurrences in both groups were similar. About 31.8% of the patients in the surgery group and 25% of the patients in the CRT group suffered from mediastinal recurrences (P = 0.385). While 29.5% of the patients in the surgery group and 36.1% of the patients in the CRT group suffered from recurrences in other sites (P = 0.209). **Author's Conclusion:** "In conclusion, definitive CRT for squamous esophageal carcinoma resulted in comparable long-term survival to surgery. Further large-scale studies would be required to confirm the results of the current study and to further investigate the role of CRT in node-positive patients."	**Funding Sources:** This work was supported by the Research Grant Council of Hong Kong Special Administrative Region, China. **COI:** The authors have declared no conflicts of interest. **Randomization:** Sequence bot described, no centralized randomization. **Blinding:** Non blinded study. **Dropout Rate/ITT-Analysis:** "Statistical analyses were carried out according to the intention-to-treat principle." **Notes:** • No description of randomization sequence • randomization was not centralized • No information on age or gender in the characteristics • Tests for group differences are not mentioned.

Inhaltsverzeichnis der Evidenztabellen

Schlüsselfrage:

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

Citation	Evidence Level	Study Type
Hall, P. S. 2017	1b-	Randomised phase II trial

Evidenztabellen

zurück

Schlüsselfrage:

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

Bewertungsvorlage:

OXFORD Appraisal Sheet 2: RCT

Hall, P. S. et al. A randomised phase II trial and feasibility study of palliative chemotherapy in frail or elderly patients with advanced gastroesophageal cancer (321GO). Br J Cancer. 116. 472-478. 2017

Population	Intervention	Outcomes/Results	Methodical Notes
Evidence level: 1b- **Study type:** Randomised phase II trial **Number of Patient:** 55 (17,19,19 per group) **Recruitung Phase:** The 321GO trial took place in six UK centres across two Cancer Research Networks, between June 2009 and January 2011. **Inclusion Criteria:** "The patient should not be considered a candidate for standard full-dose three-drug chemotherapy regimens." "judged as fit and suitable for reduced-dose chemotherapy by the clinician". Histologically confirmed carcinoma of the oesophagus, GEJ or stomach of either squamous, adenocarcinoma or undifferentiated type and planned for treatment with palliative intent. Patients were required to be over the age of 18 years but there was no upper age limit. **Exclusion Criteria:** Patients were excluded if they had previously received chemotherapy for gastric or oesophageal cancer; had another malignancy that in the opinion of the treating consultant would potentially impede interpretation of the outcome of 321GO therapy; had treatment with another investigational agent within 30 days of commencing treatment; and had previously been treated with anthracyclines to a total cumulative dose of epirubicin of 900 mg m^{-2} (or equivalent) including the treatment to be administered within this trial. Patients were not excluded for a medical condition unless this impaired their ability to consent or was so severe as to preclude protocol treatment.	**Intervention:** Trial regimens (at 80% of full dose) were EOX: epirubicin 40 mg m 2 i.v. bolus and oxaliplatin 104 mg m 2 i.v. infusion over 2 h and capecitabine 500 mg m 2 b.d. on days 1–21, repeated every 21 days. OX was identical to EOX other than the omission of epirubicin. Before each cycle, toxicity was scored with Common Terminology Criteria for Adverse Events version 3.0 (CTCAEv3). At 6 weeks, doses could be escalated to 100% of standard doses provided that no grade two or worse non-haematological toxic effects had occurred and that the patient consented. After week 12, radiological response was assessed with RECIST v1.1 criteria; the clinician assessed whether there had been clinical deterioration in the patient and the CHA was repeated. Thereafter, patients without radiological or clinical evidence of deterioration could continue the same regimen for up to 12 further weeks. **Comparison:** X was capecitabine 1000 mg m 2 b.d. on days 1–14 only of a cycle repeated every 21 days.	**Primary:** Rate of recruitment achieveable: The primary outcome measure to determine feasibility was the rate of recruitment achievable over 18 months in two UK cancer networks. For a national phase three trial planned as a non-inferiority trial, using a non-inferiority margin of a 1-month reduction in median PFS between any two of the three regimens, with 80% power at the one-sided 5% significance level, 720 patients would be needed. **Secondary:** • Incidence of CTCAEv3 grade &ge • non-haematological toxicities at 6 weeks • incidence of SAEs and dose delays/reductions • the ability/willingness to dose escalate to 100% at week 6 • patient acceptability scores • quality of life and nutritional and symptom changes • Progression-free survival (PFS) • overall survival (OS) **Results:** Median age was 75 years (range 50–87). **Secondary:** PFS: Overall, median PFS was 4.4 months. Median PFS was 5.4, 5.6 and 3.0 months for patients receiving EOX, OX and X, respectively. OS: Median overall survival was 7.1 months. Median OS was 8.1, 9.5 and 3.6 months for patients receiving EOX, OX and X. QoL: At 12 weeks, the mean global QoL score, adjusted for baseline values, was 67.8, 70.3 and 64.8 for patients receiving EOX, OX and X. **Author's Conclusion:** It is feasible to recruit elderly and/or frail patients with advanced GO cancer to a randomised clinical trial. The OX is the preferred regimen	**Funding Sources:** This trial was run within the National Health Service and supported by the National Institute of Health Research (NIHR) National Cancer Research Network. We thank the 55 participating patients, clinicians, research nurses and other support staff in the participating centres. This work was supported by a Feasibility Study Project Grant from Cancer Research UK (CRUK/08/033) and an unconditional grant from Roche. **COI:** Roche provided an unconditional grant but had no influence over the design or publication of this study. MTS has received travel, accommodation and departmental research funding rom Roche. PSH was formerly employed by the University of Leeds on a research grant from Roche as a trial administrator for an unconnected project. SRL has received travel and accommodation funding from Roche. MTS, HM, MJ, and HH are employed by the University of Leeds, the study sponsor. **Randomization:** Patients were randomly assigned in a 1:1:1 ratio using a central telephone randomisation service. Stratified permuted block randomisation was used with the stratification factors age (p75 vs 475 years) and the presence of distant metastases (yes vs no). Treatment allocation was not masked. **Blinding:** No blinding was performed. **Dropout Rate/ITT-Analysis:** No description of dropouts, no mention of analysis principle or ITT. **Notes:** With similar treatment regiments at least partial blinding could have been performed; allocation is also not concealed. No tests for group differences are described. No mention of dropouts, analysis priniciple or ITT. Lack of description and reporting reduce the confidence in the primary outcome (recruitment rate achievable)

		for further study. Overall treatment utility shows promise as a comparator between treatment regimens for feasibility and randomised trials in the elderly and/or frail GO cancer population.	