User Group Clinical Guideline Services

Leitlinienprogramm Onkologie

1913 DGVS Deutsche Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten

# Literaturrecherchen und Evidenztabellen für die Version 4 der S3-Leitlinie Diagnostik und Therapie der Plattenepithelkarzinome und Adenokarzinome des Ösophagus

# Inhaltsverzeichnis

# 1 Methodisches Vorgehen

## 1.1 Systematische Literaturrecherche

### 1.1.1 Formulierung von Schlüsselfragen

Es handelt sich um eine Aktualisierung der S3-Leitlinie „Diagnostik und Therapie der Plattenepithelkarzinome und Adenokarzinome des Ösophagus“ von 2021 (AWMF Registernummer 021 - 023OL).
Die formulierten Schlüsselfragen basieren auf den Schlüsselfragen der vorhergehenden Version, wurden aber angepasst. Es wurden insgesamt 12 Recherchen zu den Teilbereichen Chirurgie, multimodale Therapie und palliative Therapie durchgeführt.
Die einzelnen Recherchen sind so konstruiert, dass Sie zum Teil mehrere Schlüsselfragen beantworten können.
Die Auflistung der Schlüsselfragen mit genauer Beschreibung des PICO-Schemas für die de-novo Fragestellungen finden sich im Anhang A_Literaturrecherche.

### 1.1.2 Durchführung der Recherche

Die systematische Literaturrecherche wurde in der Medline Datenbank über die PubMed Suchoberfläche https://pubmed.ncbi.nlm.nih.gov/ , sowie in der Cochrane Library https://www.cochranelibrary.com/ durchgeführt. Der Recherchezeitraum schließt an den der vorhergehenden Leitlinienversion an (Publikationen ab 09.2019). Die Suchen wurden zwischen dem 02.03.2022 und 04.03.2022 durchgeführt.
Es wurden 4118 Suchtreffer in Medline und 3564 Suchtreffer in der Cochrane-Library erzielt. Die Suchtreffer wurden kombiniert und nach Abzug der Duplikate verblieben in Summe 6751 Literaturstellen, die über die Recherche identifiziert wurden. Die Ergebnisse der Suchen zu den einzelnen Datenbanken sind in Tabelle 1 aufgelistet.
Die Suchstrings sowie detaillierte Darstellungen der Recherchen sind im Anhang A zur jeweiligen Schlüsselfrage dargestellt.

Tabelle 1 Ergebnisse der Literaturrecherche nach Kapitel und Datenbank

| Nr. | Pubmed | Cochrane | Summe | Summe ohne Duplikate |
|---|---|---|---|---|
| 1 | 153 | 178 | 331 | 298 |
| 2 | 192 | 122 | 314 | 282 |
| 3 | 1184 | 821 | 2005 | 1819 |
| 4 | 631 | 821 | 1452 | 1347 |
| 5 | 300 | 232 | 532 | 490 |
| 6 | 242 | 248 | 490 | 437 |
| 7 | 179 | 110 | 289 | 261 |
| 8 | 318 | 111 | 429 | 393 |
| 9 | 359 | 278 | 637 | 574 |
| 10 | 508 | 377 | 885 | 793 |
| 11 | 31 | 172 | 191 | 32 |
| 12 | 21 | 94 | 117 | 25 |
| Ergebnis | 4118 | 3564 | 7672 | 6751 |

## 1.2 Auswahl der Evidenz

Die Literaturarbeit wurde über das Leitlinienportal der CGS Clinical Guideline Services GmbH (https://www.guideline-service.de) durchgeführt. Die in den Suchen identifizierten Literaturstellen wurden nach dem Deduplizieren als Literatursammlungen für jede PICO-Frage im Leitlinienportal hinterlegt. Diese Literatursammlungen waren der Leitliniengruppe zu jedem Zeitpunkt zur Einsicht verfügbar.
Die Auswahl der Literatur erfolgte durch Mitarbeiter*innen der CGS sowie durch Mitglieder der AG Leitung und Koordination in mehreren Schritten.

### 1.2.1 Ein- und Ausschlussgründe

Folgende Ein- und Ausschlussgründe wurden für die Recherche und Auswahl der Evidenz festgelegt:

- Deutsche und englische Veröffentlichungen
- Probandenstudien (keine Tierversuche)
- Publikation ist im Volltext verfügbar
- Veröffentlichung ab 01.09.2019 bis zum letzten Zeitpunkt der Recherchen (spätestens 04.03.2022).
- Randomisierte kontrollierte Studien und Kohortenstudien
- Studiengröße
- Kohortenstudien mindestens n ≥ 50 für die Operation und Strahlentherapie (auch bei Kombination wie z.B palliative Radiotherapie)
  Kohortenstudien mindestens n ≥ 250 für alle anderen Bereiche z.B Palliation,

Chemotherapie etc.
n ≥ 50 für randomisierte kontrollierte Studien

Generelle Ausschlussgründe wurden ebenfalls zur Auswahl herangezogen:

- Falsche Population
- Falsche Intervention (bzw. Comparison)
- Arbeit nur Abstract bzw. Protokoll
- Nicht die gesuchte Fragestellung

Im Gegensatz zur vorhergehenden Version wurden keine Übersichtsarbeiten, im Gegenzug aber Kohortenstudien berücksichtigt.

### 1.2.2 Screening

Die Auswahl der Evidenz erfolgte durch ein mehrstufiges Screening. Im Titel-Abstract Screening wurden die Suchtreffer durch Methodiker*innen der CGS anhand der Ein- und Ausschlussgründe auf potentielle Relevanz gescreent. Von den 6751 Suchtreffern wurden 783 als potentiell relevant eingeordnet.
Diese wurden in einem zweiten Titel-Abstract Screening von den Mitgliedern der AG-Leitung zusätzlich auf methodische Revelvanz geprüft, wodurch sich die Zahl auf 285 Titel reduzierte.
Die akquirierten Volltexte der ausgewählten Artikel wurden im nächsten Schritt durch die Methodiker*innen der CGS auf die Erfüllung der o.g. Ausschlüssgründe überprüft.
Es wurden 73 relevante Literaturstellen identifiziert, die schlussendlich bewertet wurden.
Die Teilschritte des Screenings sind im Anhang A zur jeweiligen Recherche grafisch als PRISMA Flussdiagram dargestellt.
Das Ergebnis des Screenings wurde nach Abschluss des Volltextscreenings durch die Koordinatoren auf die Notwendigkeit weiterer Ausschlüsse überprüft.

### 1.2.3 Bewertung der Evidenz

Die Literaturbewertung wurde bei diesem Update nach der Evidenzklassifizierung des Oxford Centre for Evidence-based Medicine 2011 [1, 2] (siehe Tabelle 2) für Interventions-und prognostische Studien durchgeführt. Alle eingeschlossenen Studien wurden darüber hinaus in Evidenztabellen extrahiert. Die methodische Qualität der Literaturstelle wurde mit Hilfe von Checklisten überprüft und die gefundenen Mängel im „Notes“ Bereich der Evidenztabellen festgehalten. Als Checklisten wurden das Cochrane risk of bias tool für randomisierte kontrollierte Studien [3] bzw. die Newcastle-Ottawa Scale für nicht-randomisierte Studien (Kohorten und Fallkontrollstudien) [4] und die Centre for Evidence-Based Medicine) Critical Appraisal tools (2017) für prognostische Fragestellungen herangezogen [5].

Studien mit bedeutenden methodischen Schwächen wurden um eine Note abgewertet. Eine entsprechende detaillierte Begründung findet sich in der Evidenztabelle im Feld „Notes“.
Nach der Bewertung der Literaturstellen wurden diese der jeweils passenden Schlüsselfrage zugeordnet.

Insgesamt wurden 73 Literaturstellen im Volltext-Screening ausgewählt und entsprechende der oben beschriebenen Methodik bewertet. Aus allen eingeschlossenen Literaturstellen wurden im nächsten Schritt Daten extrahiert und in Form von Evidenztabellen zusammengefasst.

*Tabelle 2: Evidenzklassifizierung nach Oxford 2011*

| **Fragestellung** | **Schritt 1** (Level 1*) | **Schritt 2** (Level 2*) | **Schritt 3** (Level 3*) | **Schritt 4** (Level 4*) | **Schritt 5** (Level 5*) |
|---|---|---|---|---|---|
| **Wie häufig ist das Problem?** | Lokale und aktuelle zufällige Stichprobenerhebungen (oder Volkszählungen) | Systematische Reviews von Erhebungen, die eine Anpassung an die örtlichen Gegebenheiten ermöglichen** | Lokale nicht-zufällige Erhebungen | Fall-Serie** | Nicht verfügbar |
| **Ist der diagnostische oder Monitoring Test akkurat?** (Diagnose) | Systematische Reviews von Querschnittsstudien mit konsistent applizierten Referenzstandard und Verblindung | Einzelne Querschnitts-Studien mit konsistent applizierten Referenzstandard und Verblindung | Nicht-konsekutive Studien oder Studien ohne konsistent applizierten Referenzstandard** | Fall-Kontroll Studien, oder minderwertiger, nicht unabhängiger Referenz Standard** | Mechanismus-basierte Argumentation |
| **Was wird ohne Therapie passieren?** (Prognose) | Systematische Reviews von Anfangs-Kohortenstudien | Anfangs-Kohortenstudien | Kohortenstudien oder Kontrollarme von randomisierten Studien* | Fall Serien oder Fall-Kontroll Studien, oder minderwertige prognostische Kohortenstudien | Nicht verfügbar |
| **Hilft die Intervention?** Behandlungsvorteil | Systematische Reviews von randomisierten Studien oder n=1 Studien (Einzelfallstudien) | Randomisierte Studien oder Observationsstudien mit dramatischem Effekt | Nicht-randomisierte kontrollierte Kohorten/Follow-up Studien** | Fall Serien oder Fall-Kontroll Studien, oder historische kontrollierte Studien | Mechanismus-basierte Argumentation |
| **Was sind die häufigen Nachteile/ Schäden durch die Intervention?** Behandlungsnachteil | Systematische Reviews von randomisierten Studien oder Nested Fall-Kontroll Studien, n=1 Studien | Individuell-randomisierte Studien oder (herausragende) Observationsstudien mit dramatischem Effekt | Nicht-randomisierte kontrollierte Kohorten / Follow-up Studien (Beobachtung nach Marktzulassung), ausreichende Fallzahl | Fall Serien oder Fall-Kontroll Studien, oder historische kontrollierte Studien | Mechanismus-basierte Argumentation |

| **Fragestellung** | **Schritt 1** (Level 1*) | **Schritt 2** (Level 2*) | **Schritt 3** (Level 3*) | **Schritt 4** (Level 4*) | **Schritt 5** (Level 5*) |
|---|---|---|---|---|---|
| | (Einzelfallstudien), oder Observationsstudien mit dramatischem Effekt | | vorausgesetzt, um häufige Schäden auszuschließen. (Für Langzeitschäden muss die Follow-Up Dauer ausreichend sein) | | |
| **Was sind die seltenen Nachteile/ Schäden durch die Intervention?** Behandlungsnachteil | Systematische Reviews von randomisierten Studien oder n=1 Studien (Einzelfallstudien) | Randomisierte Studien oder herausragende Observationsstudien mit dramatischem Effekt | | Fall Serien oder Fall-Kontroll Studien, oder historische kontrollierte Studien | Mechanismus-basierte Argumentation |
| **Ist der (frühe Detektion) Test lohnenswert?** (Screening) | Systematische Reviews von randomisierten Studien | Randomisierte Studien | Nicht-randomisierte kontrollierte Kohorten / Follow-up Studien** | Fall Serien oder Fall-Kontroll Studien, oder historische kontrollierte Studien | Mechanismus-basierte Argumentation |

* Das Evidenzlevel kann aufgrund der Studienqualität, Ungenauigkeit, Indirektheit (PICO der Studien passt nicht genau zur PICO der Schlüsselfragen), Inkonsistenz zwischen Studien, oder aufgrund einer kleinen absoluten Effektgröße herabgestuft werden. Das Evidenzlevel kann hochgestuft werden, wenn der beobachtete Effekt groß oder sehr groß ist.

** Wie immer ist ein Systematisches Review generell besser als eine einzelne Studie

[1] Entwickelt von OCEBM Table of Evidence Working Group = Jeremy Howick, Iain Chalmers (James Lind Library), Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, Hazel Thornton, Olive Goddard and Mary Hodgkinson
*2011. Übersetzt und angepasst von CGS Usergroup 2020.*

## 1.3 Erstellung von Evidenztabellen

Aus allen eingeschlossenen Literaturstellen wurden nach der positiven Bewertung die wichtigsten Daten extrahiert. Diese sind je nach Studientyp unterschiedlich, beinhalten aber in jedem Fall eine Beschreibung der Population, Intervention/ Exposure, Endpunkte, Resultate inklusive Zahlenwerte, Konklusion der Autor*innen und eine Auflistung der bei der Durchsicht offenkundigen methodischen Mängel. Diese Daten sind in Form von Evidenztabellen geordnet nach Studientyp im Leitlinienportal zusammengefasst.
Die Evidenztabellen sind im Anhang B zu den jeweiligen PICO-Schlüsselfragen dargestellt. Ebenfalls wurden Inhaltsverzeichnisse zu den Evidenztabellen erstellt. Diese beinhalten eine Auflistung der Literaturstellen der zugeordneten Literatur, das Evidenzlevel und die Angabe des Studientypes.

# 2 Ergebnisse der Recherchen

## 2.1 Recherche 01

| **Schlüsselfrage 01 Indikationen für EMR / ESD / RFA Ablation** |
|---|
| P: Pat mit Dysplasie, ESCC, AEG 1-3 (jeweils Mukosa und Submukosa)<br>I: EMR (endoskopischen Mukosaresektion)/ ESD (endoskopische Submukosadissektion) RFA (radio frequenzablation<br>C: konventionelle operative Verfahren<br>O: Patientenrelevante Endpunkte: Gesamtüberlebensrate, Überlebensrate nach 5 Jahren und 3 Jahren (ggfls. „Ableitung“ aus Überlebenskurven, wenn nicht im Text berichtet), medianes Überleben, Letalität, Rate an Lokalrezidiven im Beobachtungszeitraum, Fernmetastasen, Häufigkeit von Eingriffskomplikationen, (Perforation, Blutung, Striktur) Morbidität, LQ, QoL |

Recherche in PubMed (02.02.2022)

| Nr. | Suchbegriff | Treffer |
|---|---|---|
| #1 | **Neoplasms[MeSH]** OR neoplasm*[tiab] OR carcinom*[tiab] OR adenocarcinom*[tiab] OR adeno-carcinom*[tiab] OR adenom*[tiab] OR malignan*[tiab] OR cancer[tiab] OR tumor[tiab] OR tumour[tiab] | 4.646.434 |
| #2 | **Esophagus[MeSH]** OR esophag*[tiab] OR oesophag*[tiab] OR gastro-esophag*[tiab] OR gastroesophag*[tiab] OR gastro-oesophag*[tiab] OR gastrooesophag*[tiab] OR **Cardia[MeSH]** OR cardia[tiab] | 211.966 |
| #3 | #1 AND #2 | 92.545 |
| #4 | **Esophageal Neoplasms[Mesh]** OR Esophageal Neoplasm[tiab] OR Neoplasm, Esophageal[tiab] OR Esophagus Neoplasm[tiab] OR Esophagus Neoplasms[tiab] OR Neoplasm, Esophagus[tiab] OR Neoplasms, Esophagus[tiab] OR Neoplasms, Esophageal[tiab] OR Cancer of Esophagus[tiab] OR Cancer of the Esophagus[tiab] OR Esophagus Cancer[tiab] OR Cancer, Esophagus[tiab] OR Cancers, Esophagus[tiab] OR Esophagus Cancers[tiab] OR Esophageal Cancer[tiab] OR Cancer, Esophageal[tiab] OR Cancers, Esophageal[tiab] OR Esophageal Cancers[tiab] | 61.764 |
| #5 | #3 OR #4 | 96.869 |

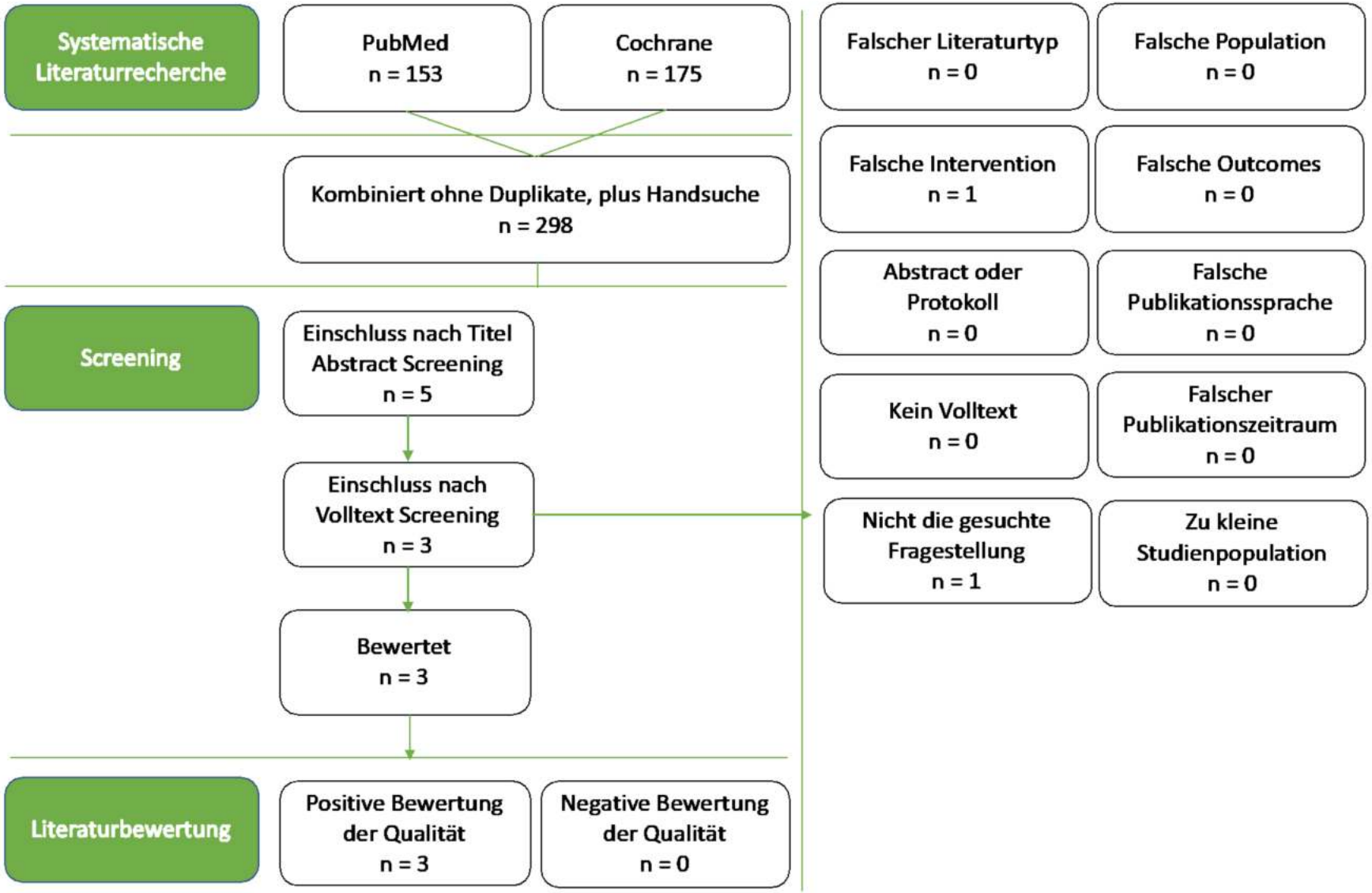
| | | |
|---|---|---|
| #6 | endoscopic mucosal resection[tiab] OR endoscopic submucosal dissection[tiab] OR EMR[tiab] OR ESD[tiab] OR endoscopic treatment[tiab] OR radio frequency ablation[tiab] OR RFA[tiab] OR radiofrequency ablation[tiab] OR **Radiofrequency Ablation[Mesh]** OR ablative therapy[tiab] OR endoscopic ablation[tiab] OR "**Endoscopic Mucosal Resection"[Mesh]** OR **"Ablation Techniques"[Mesh]** OR ablation[tiab] OR Endoscopic Mucosal Resections[tiab] OR Mucosal Resection, Endoscopic[tiab] OR Resection, Endoscopic Mucosal[tiab] OR Strip Biopsy[tiab] OR Biopsy, Strip[tiab] OR Strip Biopsies[tiab] OR Endoscopic Mucous Membrane Resection[tiab] OR Endoscopic Submucosal Dissection[tiab] OR Dissection, Endoscopic Submucosal[tiab] OR Endoscopic Submucosal Dissections[tiab] OR Submucosal Dissection, Endoscopic[tiab] OR Endoscopic Full Thickness Resection[tiab] OR Submucosal Tunneling Endoscopic Resection[tiab] | 212.495 |
| #7 | #5 AND #6 | 4.559 |
| #8 | cohort studies[mesh:noexp] OR longitudinal studies[mesh:noexp] OR follow-up studies[mesh:noexp] OR prospective studies[mesh:noexp] OR cohort[tiab] OR longitudinal[tiab] OR prospective[tiab] | 2.240.015 |
| #9 | "Clinical Trial" [PT:NoExp] OR "clinical trial, phase i"[pt] OR "clinical trial, phase ii"[pt] OR "clinical trial, phase iii"[pt] OR "clinical trial, phase iv"[pt] OR "controlled clinical trial"[pt] OR "multicenter study"[pt] OR "randomized controlled trial"[pt] OR "Clinical Trials as Topic"[mesh:noexp] OR "clinical trials, phase i as topic"[MeSH Terms:noexp] OR "clinical trials, phase ii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iv as topic"[MeSH Terms:noexp] OR "controlled clinical trials as topic"[MeSH Terms:noexp] OR "randomized controlled trials as topic"[MeSH Terms:noexp] OR "early termination of clinical trials"[MeSH Terms:noexp] OR "multicenter studies as topic"[MeSH Terms:noexp] OR “Double-Blind Method”[Mesh] OR ((randomised[tiab] OR randomized[tiab]) AND (trial[tiab] OR trials[tiab])) OR ((single[tiab] OR double[tiab] OR doubled[tiab] OR triple[tiab] OR tripled[tiab] OR treble[tiab] OR treble[tiab]) AND (blind*[tiab] OR mask*[tiab])) OR ("4 arm"[tiab] OR "four arm"[tiab]) | 1.608.903 |
| #10 | #8 OR #9 | 3.425.041 |
| #11 | animals[mh] NOT humans[mh] | 4.952.458 |
| #12 | #10 NOT #11 | 3.348.767 |
| #13 | #7 AND #12 | 1.207 |
| #14 | **#13 Publication date from 09/2019 until date of search, English, German** | 153 |

Recherche in Cochrane Library (04.02.2022)

| ID | Search | Treffer |
|---|---|---|
| #1 | MeSH descriptor: [Neoplasms] explode all trees | 86153 |
| #2 | (neoplasm* OR carcinom* OR adenocarcinom* OR adeno-carcinom* OR adenom* OR malignan* OR cancer OR tumor OR tumour):ti,ab,kw | 236065 |
| #3 | #1 OR #2 | 245738 |
| #4 | MeSH descriptor: [Esophagus] explode all trees | 1368 |
| #5 | MeSH descriptor: [Cardia] explode all trees | 53 |
| #6 | (esophag* OR oesophag* OR gastro-esophag* OR gastroesophag* OR gastro-oesophag* OR gastrooesophag* OR cardia):ti,ab,kw | 21273 |
| #7 | #4 OR #5 OR #6 | 21273 |
| #8 | #3 AND #7 | 8477 |
| #9 | MeSH descriptor: [Esophageal Neoplasms] explode all trees | 1740 |
| #10 | (Esophageal Neoplasm OR Neoplasm, Esophageal OR Esophagus Neoplasm OR Esophagus Neoplasms OR Neoplasm, Esophagus OR Neoplasms, Esophagus OR Neoplasms, Esophageal OR Cancer of Esophagus OR Cancer of the Esophagus OR Esophagus Cancer OR Cancer, Esophagus OR Cancers, Esophagus OR Esophagus Cancers OR Esophageal Cancer OR Cancer, Esophageal OR Cancers, Esophageal OR Esophageal Cancers):ti,ab,kw | 5589 |
| #11 | #9 OR #10 | 5615 |
| #12 | #8 OR #11 | 8484 |
| #13 | MeSH descriptor: [Endoscopic Mucosal Resection] explode all trees | 109 |
| #14 | MeSH descriptor: [Radiofrequency Ablation] explode all trees | 1651 |
| #15 | MeSH descriptor: [Ablation Techniques] explode all trees | 6126 |
| #16 | (endoscopic mucosal resection OR endoscopic submucosal dissection OR EMR OR ESD OR endoscopic treatment OR radio frequency ablation OR RFA OR radiofrequency ablation OR ablative therapy OR endoscopic ablation OR ablation OR Endoscopic Mucosal Resections OR Mucosal Resection, Endoscopic OR Resection, Endoscopic Mucosal OR Strip Biopsy OR Biopsy, Strip OR Strip Biopsies OR Endoscopic Mucous Membrane Resection OR Endoscopic Submucosal Dissection OR Dissection, Endoscopic Submucosal OR Endoscopic Submucosal Dissections OR Submucosal Dissection, Endoscopic OR Endoscopic Full Thickness Resection OR Submucosal Tunneling Endoscopic Resection):ti,ab,kw | 21984 |
| #17 | #13 OR #14 OR #15 OR #16 | 25567 |
| #18 | #12 AND #17 | 926 |
| #19 | #18 with Cochrane Library publication date Between Sep 2019 and Feb 2022, in Cochrane Reviews | 3 |

| | | |
|---|---|---|
| #20 | #18 with Publication Year from 2019 to 2022, in Trials | 175 |

## Recherche 01



## 2.2 Recherche 02

| **Schlüsselfrage 02 Vorgehen bei Lokalrezidiven nach endosk. Resektion, RFA Ablation nach endosk. Resektion, RFA Ablation** |
|---|
| P: Pat mit Dysplasie, ESCC, AEG 1-3<br>I: Endoskopische Nachresektion/-dissektion, RFA , Ablation<br>C: Konservativ / konventionell operativ<br>O: Endpunkte: Gesamtüberlebensrate, Überlebensrate nach 5 Jahren und 3 Jahren, med. ÜL, Morbidität, LQ, Rezidivrate, Komplikationshäufigkeit |

Recherche in PubMed (02.09.2021)

| Nr. | Suchbegriff | Treffer |
|---|---|---|
| #1 | **Neoplasms[MeSH]** OR neoplasm*[tiab] OR carcinom*[tiab] OR adenocarcinom*[tiab] OR adeno-carcinom*[tiab] OR adenom*[tiab] OR malignan*[tiab] OR cancer[tiab] OR tumor[tiab] OR tumour[tiab] | 4.646.434 |
| #2 | **Esophagus[MeSH]** OR esophag*[tiab] OR oesophag*[tiab] OR gastro-esophag*[tiab] OR gastroesophag*[tiab] OR gastro-oesophag*[tiab] OR gastrooesophag*[tiab] OR **Cardia[MeSH]** OR cardia[tiab] | 211.966 |
| #3 | #1 AND #2 | 92.545 |
| #4 | **Esophageal Neoplasms[Mesh]** OR Esophageal Neoplasm[tiab] OR Neoplasm, Esophageal[tiab] OR Esophagus Neoplasm[tiab] OR Esophagus Neoplasms[tiab] OR Neoplasm, Esophagus[tiab] OR Neoplasms, Esophagus[tiab] OR Neoplasms, Esophageal[tiab] OR Cancer of Esophagus[tiab] OR Cancer of the Esophagus[tiab] OR Esophagus Cancer[tiab] OR Cancer, Esophagus[tiab] OR Cancers, Esophagus[tiab] OR Esophagus Cancers[tiab] OR Esophageal Cancer[tiab] OR Cancer, Esophageal[tiab] OR Cancers, Esophageal[tiab] OR Esophageal Cancers[tiab] | 61.764 |
| #5 | #3 OR #4 | 96.869 |

| | | |
|---|---|---|
| #6 | **Endoscopy[Mesh]** OR endoscop*[tiab] OR Surgical Procedures, Endoscopic[tiab] OR Procedure, Endoscopic Surgical[tiab] OR Procedures, Endoscopic Surgical[tiab] OR Surgical Procedure, Endoscopic[tiab] OR Endoscopy, Surgical[tiab] OR Surgical Endoscopy[tiab] OR Endoscopic Surgical Procedure[tiab] OR Endoscopic Surgical Procedures[tiab] OR resection[tiab] OR endoscopic mucosal resection[tiab] OR endoscopic submucosal dissection[tiab] OR EMR[tiab] OR ESD[tiab] OR endoscopic treatment[tiab] OR radio frequency ablation[tiab] OR RFA[tiab] OR radiofrequency ablation[tiab] OR **Radiofrequency Ablation[Mesh]** OR ablative therapy[tiab] OR endoscopic ablation[tiab] OR **"Endoscopic Mucosal Resection"[Mesh]** OR **"Ablation Techniques"[Mesh]** OR ablation[tiab] OR Endoscopic Mucosal Resections[tiab] OR Mucosal Resection, Endoscopic[tiab] OR Resection, Endoscopic Mucosal[tiab] OR Strip Biopsy[tiab] OR Biopsy, Strip[tiab] OR Strip Biopsies[tiab] OR Endoscopic Mucous Membrane Resection[tiab] OR Endoscopic Submucosal Dissection[tiab] OR Dissection, Endoscopic Submucosal[tiab] OR Endoscopic Submucosal Dissections[tiab] OR Submucosal Dissection, Endoscopic[tiab] OR Endoscopic Full Thickness Resection[tiab] OR Submucosal Tunneling Endoscopic Resection[tiab] | 930.773 |
| #7 | **"Recurrence"[Mesh] OR** Recurr*[tiab] OR Recrudescen*[tiab] OR Relaps*[tiab] OR **"Neoplasm Recurrence, Local"[Mesh]** | 909.434 |
| #8 | #5 AND #6 AND #7 | 5.185 |
| #9 | cohort studies[mesh:noexp] OR longitudinal studies[mesh:noexp] OR follow-up studies[mesh:noexp] OR prospective studies[mesh:noexp] OR cohort[tiab] OR longitudinal[tiab] OR prospective[tiab] | 2.240.015 |
| #10 | "Clinical Trial" [PT:NoExp] OR "clinical trial, phase i"[pt] OR "clinical trial, phase ii"[pt] OR "clinical trial, phase iii"[pt] OR "clinical trial, phase iv"[pt] OR "controlled clinical trial"[pt] OR "multicenter study"[pt] OR "randomized controlled trial"[pt] OR "Clinical Trials as Topic"[mesh:noexp] OR "clinical trials, phase i as topic"[MeSH Terms:noexp] OR "clinical trials, phase ii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iv as topic"[MeSH Terms:noexp] OR "controlled clinical trials as topic"[MeSH Terms:noexp] OR "randomized controlled trials as topic"[MeSH Terms:noexp] OR "early termination of clinical trials"[MeSH Terms:noexp] OR "multicenter studies as topic"[MeSH Terms:noexp] OR “Double-Blind Method”[Mesh] OR ((randomised[tiab] OR randomized[tiab]) AND (trial[tiab] OR trials[tiab])) OR ((single[tiab] OR double[tiab] OR doubled[tiab] OR triple[tiab] OR tripled[tiab] OR treble[tiab] OR treble[tiab]) | 1.608.903 |

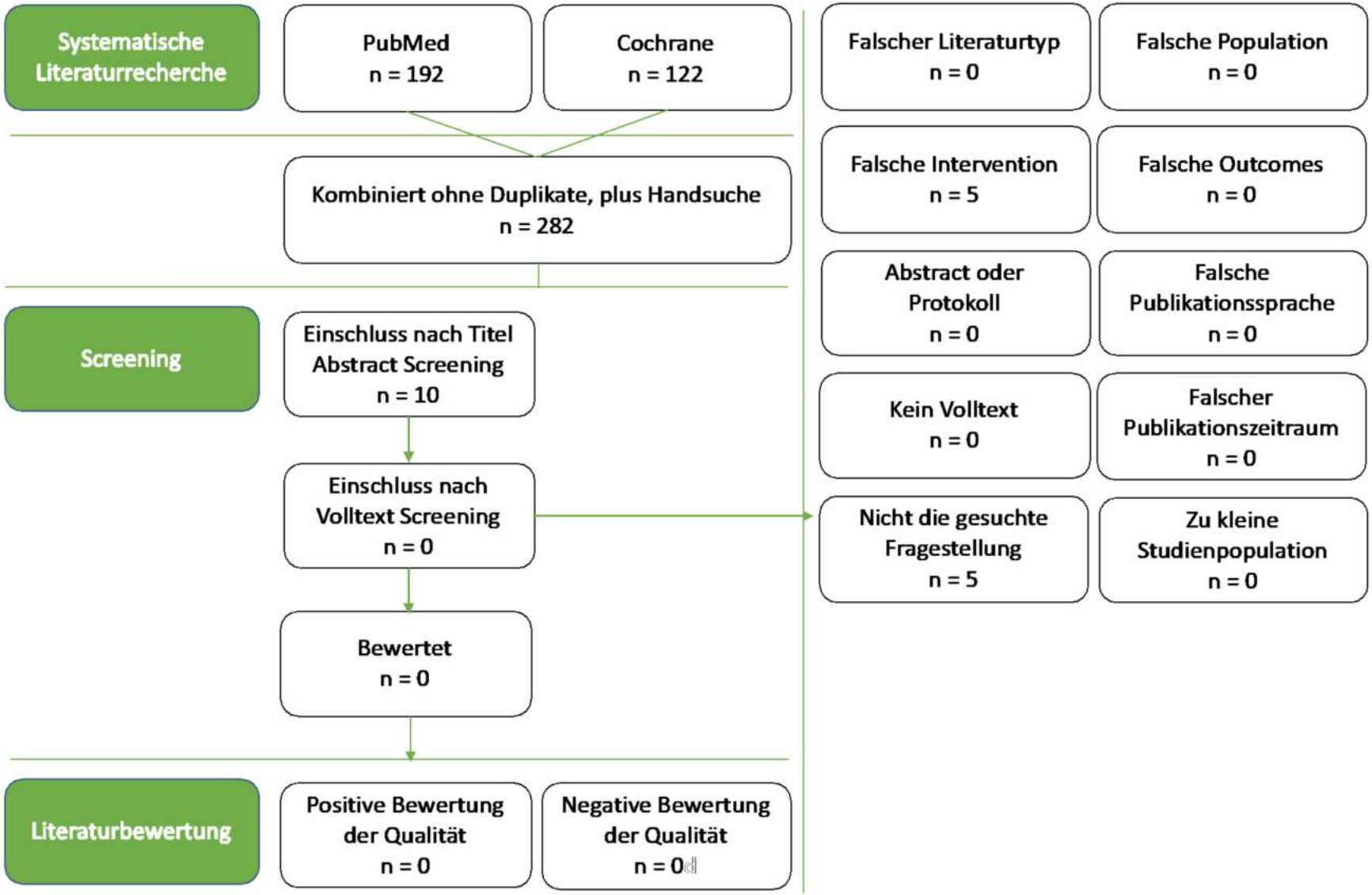
| | | |
|---|---|---|
| | AND (blind*[tiab] OR mask*[tiab])) OR ("4 arm"[tiab] OR "four arm"[tiab]) | |
| #11 | #8 OR #9 | 3.425.041 |
| #12 | animals[mh] NOT humans[mh] | 4.952.458 |
| #13 | #10 NOT #11 | 3.348.767 |
| #14 | #7 AND #12 | 1.774 |
| #15 | **#13 Publication date from 09/2019 until date of search, English, German** | 192 |

Recherche in der Cochrane Library (04.02.2022)

| ID | Search | Treffer |
|---|---|---|
| #1 | MeSH descriptor: [Neoplasms] explode all trees | 86153 |
| #2 | (neoplasm* OR carcinom* OR adenocarcinom* OR adeno-carcinom* OR adenom* OR malignan* OR cancer OR tumor OR tumour):ti,ab,kw | 236065 |
| #3 | #1 OR #2 | 245738 |
| #4 | MeSH descriptor: [Esophagus] explode all trees | 1368 |
| #5 | MeSH descriptor: [Cardia] explode all trees | 53 |
| #6 | (esophag* OR oesophag* OR gastro-esophag* OR gastroesophag* OR gastro-oesophag* OR gastrooesophag* OR cardia):ti,ab,kw | 21273 |
| #7 | #4 OR #5 OR #6 | 21273 |
| #8 | #3 AND #7 | 8477 |
| #9 | MeSH descriptor: [Esophageal Neoplasms] explode all trees | 1740 |
| #10 | (Esophageal Neoplasm OR Neoplasm, Esophageal OR Esophagus Neoplasm OR Esophagus Neoplasms OR Neoplasm, Esophagus OR Neoplasms, Esophagus OR Neoplasms, Esophageal OR Cancer of Esophagus OR Cancer of the Esophagus OR Esophagus Cancer OR Cancer, Esophagus OR Cancers, Esophagus OR Esophagus Cancers OR Esophageal Cancer OR Cancer, Esophageal OR Cancers, Esophageal OR Esophageal Cancers):ti,ab,kw | 5589 |
| #11 | #9 OR #10 | 5615 |
| #12 | #8 OR #11 | 8484 |
| #13 | MeSH descriptor: [Endoscopy] explode all trees | 18825 |
| #14 | MeSH descriptor: [Radiofrequency Ablation] explode all trees | 1651 |
| #15 | MeSH descriptor: [Endoscopic Mucosal Resection] explode all trees | 109 |
| #16 | MeSH descriptor: [Ablation Techniques] explode all trees | 6126 |

| | | |
|---|---|---|
| #17 | (endoscop* OR Surgical Procedures, Endoscopic OR Procedure, Endoscopic Surgical OR Procedures, Endoscopic Surgical OR Surgical Procedure, Endoscopic OR Endoscopy, Surgical OR Surgical Endoscopy OR Endoscopic Surgical Procedure OR Endoscopic Surgical Procedures OR resection OR endoscopic mucosal resection OR endoscopic submucosal dissection OR EMR OR ESD OR endoscopic treatment OR radio frequency ablation OR RFA OR radiofrequency ablation OR ablative therapy OR endoscopic ablation ablation OR Endoscopic Mucosal Resections OR Mucosal Resection, Endoscopic OR Resection, Endoscopic Mucosal OR Strip Biopsy OR Biopsy, Strip OR Strip Biopsies OR Endoscopic Mucous Membrane Resection OR Endoscopic Submucosal Dissection OR Dissection, Endoscopic Submucosal OR Endoscopic Submucosal Dissections OR Submucosal Dissection, Endoscopic OR Endoscopic Full Thickness Resection OR Submucosal Tunneling Endoscopic Resection):ti,ab,kw | 56305 |
| #18 | #13 OR #14 OR #15 OR #16 OR #17 | 71944 |
| #19 | MeSH descriptor: [Recurrence] explode all trees | 12664 |
| #20 | MeSH descriptor: [Neoplasm Recurrence, Local] explode all trees | 4597 |
| #21 | (Recurr* OR Recrudescen* OR Relaps*):ti,ab,kw | 107015 |
| #22 | #19 OR #20 OR #21 | 107096 |
| #23 | #12 AND #18 AND #22 | 580 |
| #24 | #23 with Cochrane Library publication date Between Sep 2019 and Feb 2022, in Cochrane Reviews | 1 |
| #25 | #23 with Publication Year from 2019 to 2022, in Trials | 122 |

## Recherche 02



## 2.3 Recherche 03

| **Schlüsselfrage 03.1 Art des operativen Zugangs** |
|---|
| P: 1) Pat. mit gesichertem Plattenepithel- oder Adenokarzinom des Ösophagus in Abhängigkeit von der Tumorhöhe (zervikal, thorakal suprabifurkal, thorakalinfrabifurkal, abdominell bzw. nur supra-/infrabifurkal) 2)bzw. Pat. mit gesichertem AEG 1-3<br>I: offen-thorakal / offen-abdominalzervikal / offen-abdominaltranshiatal<br>C: Standard: offenabdominothora rakal/thorakoabdominal<br>O: Patientenrelevante Endpunkte: Gesamtüberlebensrate, Überlebensrate nach 5 Jahren und 3 Jahren (ggfls. „Ableitung“ aus Überlebenskurven, wenn nicht im Text berichtet), medianes ÜL, Morbidität, LQ, 30 Tage Hospitalletalität, Rate an Lokalrezidiven im Beobachtungszeitraum, Fernmetastasierung, Häufigkeit der Komplikationen (v.a. pulmonal) |

| **Schlüsselfrage 03.2 Wertung thorakoskopischer/ laparoskopischer Techniken / Robotertechnik** |
|---|
| P: 1)Pat. mit gesichertem Plattenepithel- oder Adenokarzinom des Ösophagus in Abhängigkeit von der Tumorhöhe (zervikal, thorakal suprabifurkal, thorakalinfrabifurkal, abdominell bzw. nur supra-/infrabifurkal) 2)bzw. Pat. mit gesichertem AEG 1-3<br>I: OP-Zugang / Technik: a)thorakoskopisch, b)laparoskopisch, c)thorakoskopisch und laparoskopisch d)Hybridverfahren, (laparoskopisch/offen chir)<br>C: OP-Zugang / Technik offenthorakoabdominal<br>O: Patientenrelevante Endpunkte: Gesamtüberlebensrate, Überlebensrate nach 5 Jahren und 3 Jahren (ggfls. „Ableitung“ aus Überlebenskurven, wenn nicht im Text berichtet), medianes ÜL, Morbidität, LQ, 30 Tage Hospitalletalität, Rate an Lokalrezidiven im Beobachtungszeitraum, Fernmetastasierung, Häufigkeit der Komplikationen (v.a. pulmonal) |

| **Schlüsselfrage 03.3 Stellenwert der limitierten Resektion proximaler Tumore** |
|---|
| P: 1)Pat. mit AEG (Stadium Talle Nalle M0)<br>I: limitierte Resektion<br>C: a) offene Resektion<br>O: Patientenrelevante Endpunkte: Gesamtüberlebensrate, Überlebensrate nach 5 Jahren und 3 Jahren (ggfls. „Ableitung“ aus Überlebenskurven, wenn nicht im Text berichtet), medianes ÜL, Morbidität, LQ, 30 Tage Hospitalletalität, Rate an Lokalrezidiven im Beobachtungszeitraum, Fernmetastasierung, Häufigkeit der Komplikationen (v.a. pulmonal) |

Recherche in PubMed (02.02.2022)

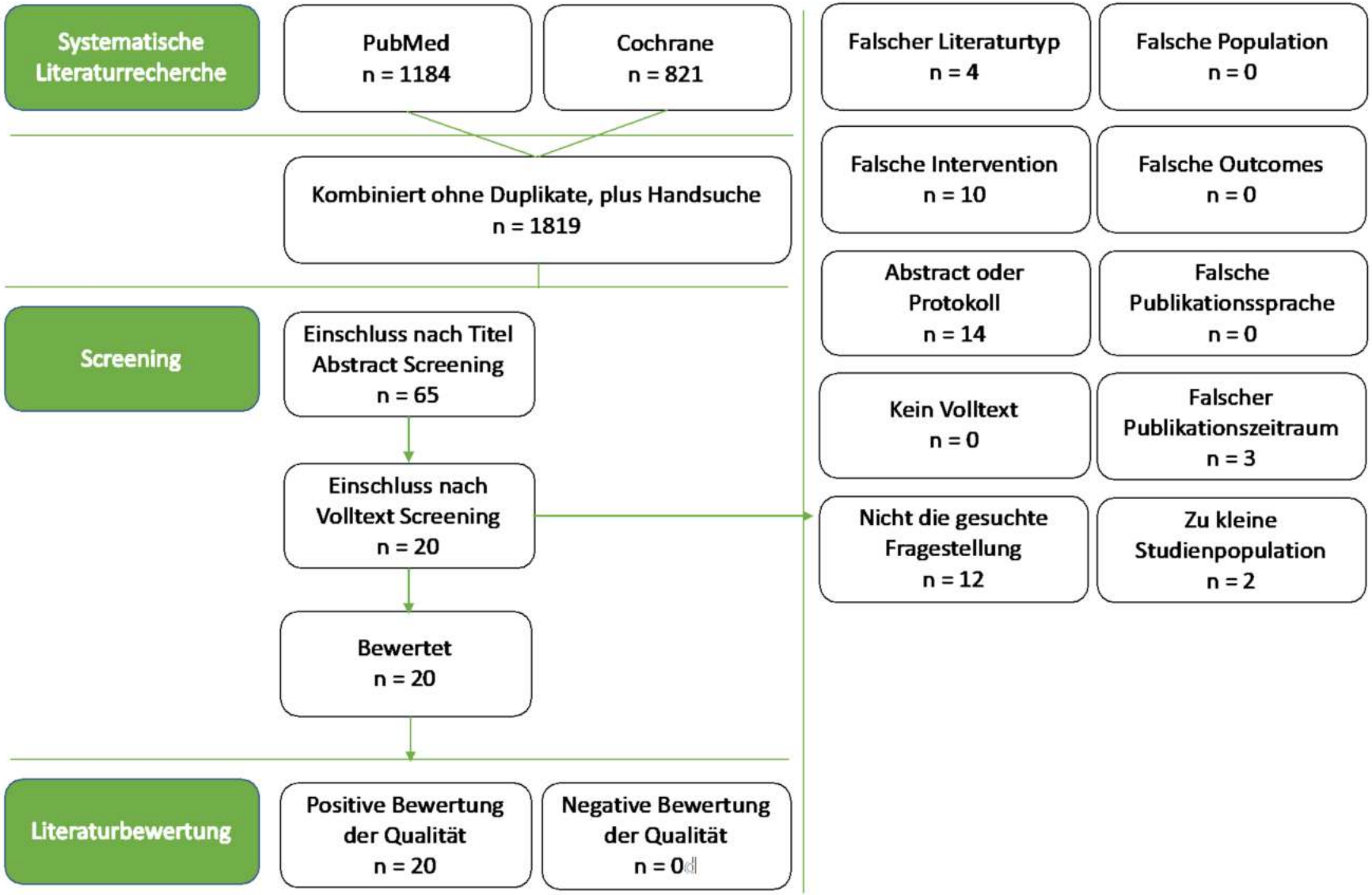
| Nr. | Suchbegriffe | Treffer |
|---|---|---|
| #1 | **Neoplasms[MeSH]** OR neoplasm*[tiab] OR carcinom*[tiab] OR adenocarcinom*[tiab] OR adeno-carcinom*[tiab] OR adenom*[tiab] OR malignan*[tiab] OR cancer[tiab] OR tumor[tiab] OR tumour[tiab] | 4.646.434 |
| #2 | **Esophagus[MeSH]** OR esophag*[tiab] OR oesophag*[tiab] OR gastro-esophag*[tiab] OR gastroesophag*[tiab] OR gastro-oesophag*[tiab] OR gastrooesophag*[tiab] OR **Cardia[MeSH]** OR cardia[tiab] | 211.966 |
| #3 | #1 AND #2 | 92.545 |
| #4 | **Esophageal Neoplasms[Mesh]** OR Esophageal Neoplasm[tiab] OR Neoplasm, Esophageal[tiab] OR Esophagus Neoplasm[tiab] OR Esophagus Neoplasms[tiab] OR Neoplasm, Esophagus[tiab] OR Neoplasms, Esophagus[tiab] OR Neoplasms, Esophageal[tiab] OR Cancer of Esophagus[tiab] OR Cancer of the Esophagus[tiab] OR Esophagus Cancer[tiab] OR Cancer, Esophagus[tiab] OR Cancers, Esophagus[tiab] OR Esophagus Cancers[tiab] OR Esophageal Cancer[tiab] OR Cancer, Esophageal[tiab] OR Cancers, Esophageal[tiab] OR Esophageal Cancers[tiab] | 61.764 |
| #5 | #3 OR #4 | 96.869 |
| #6 | operation[tiab] OR operat*[tiab] OR surgical[tiab] OR surgery[tiab] OR resection[tiab] OR resect*[tiab] | 1.704.317 |
| #7 | #5 AND #6 | 27.485 |
| #8 | cohort studies[mesh:noexp] OR longitudinal studies[mesh:noexp] OR follow-up studies[mesh:noexp] OR prospective studies[mesh:noexp] OR cohort[tiab] OR longitudinal[tiab] OR prospective[tiab] | 2.240.015 |
| #9 | "Clinical Trial" [PT:NoExp] OR "clinical trial, phase i"[pt] OR "clinical trial, phase ii"[pt] OR "clinical trial, phase iii"[pt] OR "clinical trial, phase iv"[pt] OR "controlled clinical trial"[pt] OR "multicenter study"[pt] OR "randomized controlled trial"[pt] OR "Clinical Trials as Topic"[mesh:noexp] OR "clinical trials, phase i as topic"[MeSH Terms:noexp] OR "clinical trials, phase ii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iv as topic"[MeSH Terms:noexp] OR "controlled clinical trials as topic"[MeSH Terms:noexp] OR "randomized controlled trials as topic"[MeSH Terms:noexp] OR "early termination of clinical trials"[MeSH Terms:noexp] OR "multicenter studies as topic"[MeSH Terms:noexp] OR “Double-Blind Method”[Mesh] OR ((randomised[tiab] OR randomized[tiab]) AND (trial[tiab] OR trials[tiab])) OR ((single[tiab] OR double[tiab] OR doubled[tiab] OR triple[tiab] OR tripled[tiab] OR treble[tiab] OR treble[tiab]) AND (blind*[tiab] OR mask*[tiab])) OR ("4 arm"[tiab] OR "four arm"[tiab]) | 1.608.903 |

| | | |
|---|---|---|
| #10 | #8 OR #9 | 3.425.041 |
| #11 | animals[mh] NOT humans[mh] | 4.952.458 |
| #12 | #10 NOT #11 | 3.348.767 |
| #13 | #7 AND #12 | 7.910 |
| #14 | **#13 Publication date from 09/2019 until date of search, English, German** | 1.184 |

Recherche in der Cochrane Library (04.02.2022)

| ID | Search | Treffer |
|---|---|---|
| #1 | MeSH descriptor: [Neoplasms] explode all trees | 86153 |
| #2 | (neoplasm* OR carcinom* OR adenocarcinom* OR adeno-carcinom* OR adenom* OR malignan* OR cancer OR tumor OR tumour):ti,ab,kw | 236065 |
| #3 | #1 OR #2 | 245738 |
| #4 | MeSH descriptor: [Esophagus] explode all trees | 1368 |
| #5 | MeSH descriptor: [Cardia] explode all trees | 53 |
| #6 | (esophag* OR oesophag* OR gastro-esophag* OR gastroesophag* OR gastro-oesophag* OR gastrooesophag* OR cardia):ti,ab,kw | 21273 |
| #7 | #4 OR #5 OR #6 | 21273 |
| #8 | #3 AND #7 | 8477 |
| #9 | MeSH descriptor: [Esophageal Neoplasms] explode all trees | 1740 |
| #10 | (Esophageal Neoplasm OR Neoplasm, Esophageal OR Esophagus Neoplasm OR Esophagus Neoplasms OR Neoplasm, Esophagus OR Neoplasms, Esophagus OR Neoplasms, Esophageal OR Cancer of Esophagus OR Cancer of the Esophagus OR Esophagus Cancer OR Cancer, Esophagus OR Cancers, Esophagus OR Esophagus Cancers OR Esophageal Cancer OR Cancer, Esophageal OR Cancers, Esophageal OR Esophageal Cancers):ti,ab,kw | 5589 |
| #11 | #9 OR #10 | 5615 |
| #12 | #8 OR #11 | 8484 |
| #13 | (operation OR operat* OR surgical OR surgery OR resection OR resect*):ti,ab,kw | 306380 |
| #14 | #12 AND #13 | 3941 |
| #15 | #14 with Publication Year from 2019 to 2022, in Trials | 821 |

## Recherche 03



## 2.4 Recherche 04

| **Schlüsselfrage 04 Stellenwert der standardisierten Nachsorge nach kurativer Ösophagus-Karzinom Therapie** |
|---|
| P: 1)Pat. mit gesichertem Plattenepithel- oder Adenokarzinom des Ösophagus, 2) Pat mit AEG 1-3, 1) und 2) nach kuativer Resektion, oder definitiver Radiochemotherapie, oder watch and wait nach kompletter Remission<br>I: strukturierte Nachsorge<br>C: a) keine Nachsorge, b) symptomorientierte Nachsorge<br>O: Patientenrelevante Endpunkte: Gesamtüberlebensrate, Überlebensrate nach 5 Jahren und 3 Jahren (ggfls. „Ableitung“ aus Überlebenskurven, wenn nicht im Text berichtet), medianes ÜL, Morbidität, LQ, Rate an Lokal- und Fernrezidiven im Beobachtungszeitraum, Fernmetastasierung |

Recherche in PubMed (02.02.2022)

| Nr. | Suchbegriff | Treffer |
|---|---|---|
| #1 | **Neoplasms[MeSH]** OR neoplasm*[tiab] OR carcinom*[tiab] OR adenocarcinom*[tiab] OR adeno-carcinom*[tiab] OR adenom*[tiab] OR malignan*[tiab] OR cancer[tiab] OR tumor[tiab] OR tumour[tiab] | 4.646.434 |
| #2 | **Esophagus[MeSH]** OR esophag*[tiab] OR oesophag*[tiab] OR gastro-esophag*[tiab] OR gastroesophag*[tiab] OR gastro-oesophag*[tiab] OR gastrooesophag*[tiab] OR **Cardia[MeSH]** OR cardia[tiab] | 211.966 |
| #3 | #1 AND #2 | 92.545 |
| #4 | **Esophageal Neoplasms[Mesh]** OR Esophageal Neoplasm[tiab] OR Neoplasm, Esophageal[tiab] OR Esophagus Neoplasm[tiab] OR Esophagus Neoplasms[tiab] OR Neoplasm, Esophagus[tiab] OR Neoplasms, Esophagus[tiab] OR Neoplasms, Esophageal[tiab] OR Cancer of Esophagus[tiab] OR Cancer of the Esophagus[tiab] OR Esophagus Cancer[tiab] OR Cancer, Esophagus[tiab] OR Cancers, Esophagus[tiab] OR Esophagus Cancers[tiab] OR Esophageal Cancer[tiab] OR Cancer, Esophageal[tiab] OR Cancers, Esophageal[tiab] OR Esophageal Cancers[tiab] | 61.764 |
| #5 | #3 OR #4 | 96.869 |
| #6 | **Aftercare[Mesh]** OR After Care[tiab] OR After-Treatment[tiab] OR After Treatment[tiab] OR After-Treatments[tiab] OR Follow-Up Care[tiab] OR Care, Follow-Up[tiab] OR Cares, Follow-Up[tiab] OR Follow Up Care[tiab] OR Follow-Up Cares[tiab] OR Programs, Postabortal[tiab] OR follow-up[tiab] OR follow up[tiab] | 1.440.230 |
| #7 | #5 AND #6 | 9.385 |

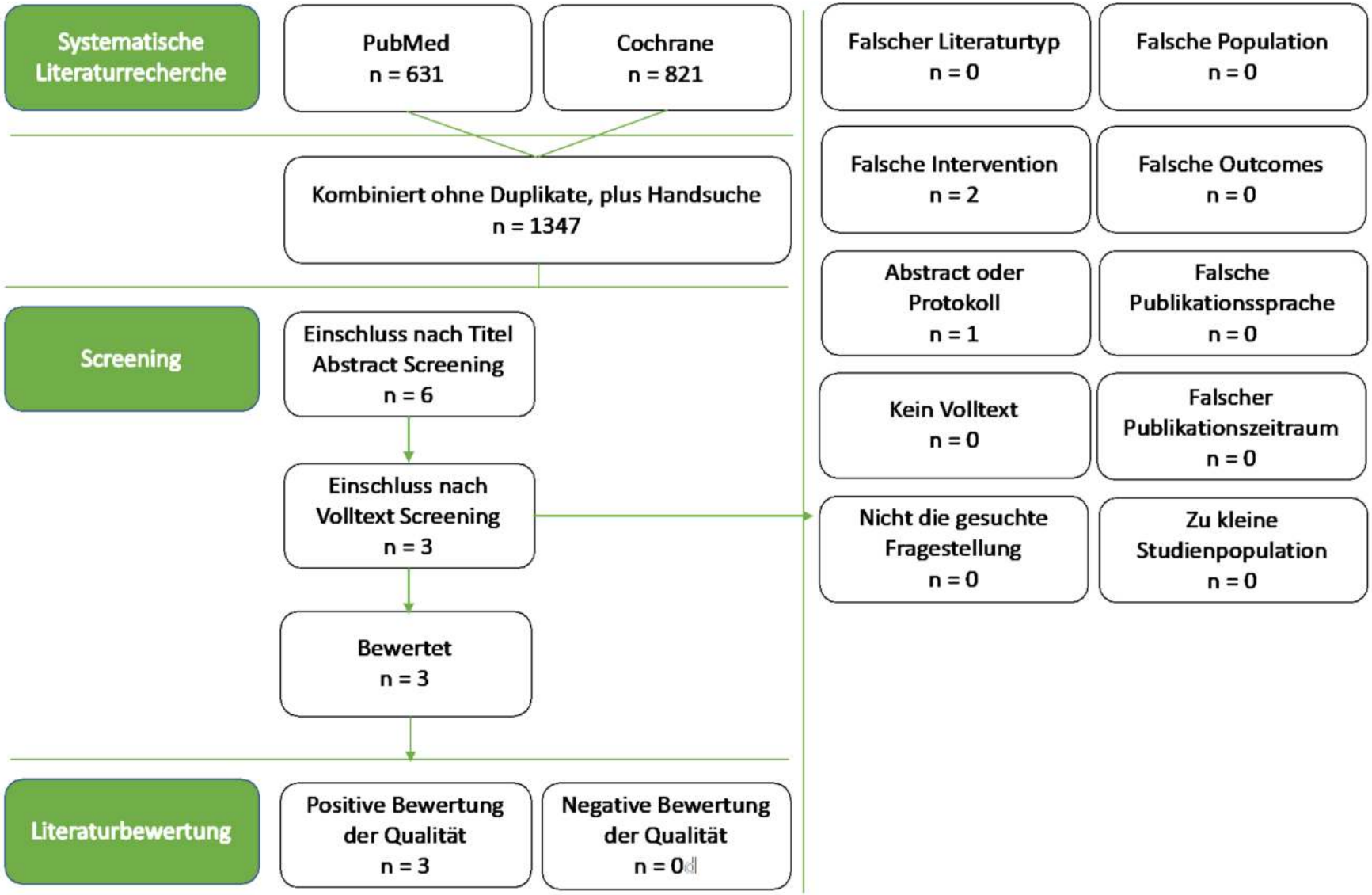
| | | |
|---|---|---|
| #8 | cohort studies[mesh:noexp] OR longitudinal studies[mesh:noexp] OR follow-up studies[mesh:noexp] OR prospective studies[mesh:noexp] OR cohort[tiab] OR longitudinal[tiab] OR prospective[tiab] | 2.240.015 |
| #9 | "Clinical Trial" [PT:NoExp] OR "clinical trial, phase i"[pt] OR "clinical trial, phase ii"[pt] OR "clinical trial, phase iii"[pt] OR "clinical trial, phase iv"[pt] OR "controlled clinical trial"[pt] OR "multicenter study"[pt] OR "randomized controlled trial"[pt] OR "Clinical Trials as Topic"[mesh:noexp] OR "clinical trials, phase i as topic"[MeSH Terms:noexp] OR "clinical trials, phase ii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iv as topic"[MeSH Terms:noexp] OR "controlled clinical trials as topic"[MeSH Terms:noexp] OR "randomized controlled trials as topic"[MeSH Terms:noexp] OR "early termination of clinical trials"[MeSH Terms:noexp] OR "multicenter studies as topic"[MeSH Terms:noexp] OR “Double-Blind Method”[Mesh] OR ((randomised[tiab] OR randomized[tiab]) AND (trial[tiab] OR trials[tiab])) OR ((single[tiab] OR double[tiab] OR doubled[tiab] OR triple[tiab] OR tripled[tiab] OR treble[tiab] OR treble[tiab]) AND (blind*[tiab] OR mask*[tiab])) OR ("4 arm"[tiab] OR "four arm"[tiab]) | 1.608.903 |
| #10 | #8 OR #9 | 3.425.041 |
| #11 | animals[mh] NOT humans[mh] | 4.952.458 |
| #12 | #10 NOT #11 | 3.348.767 |
| #13 | #7 AND #12 | 4.636 |
| #14 | **#13 Publication date from 09/2019 until date of search, English, German** | 631 |

Recherche in der Cochrane Library (04.02.2022)

| ID | Search | Treffer |
|---|---|---|
| #1 | MeSH descriptor: [Neoplasms] explode all trees | 86153 |
| #2 | (neoplasm* OR carcinom* OR adenocarcinom* OR adeno-carcinom* OR adenom* OR malignan* OR cancer OR tumor OR tumour):ti,ab,kw | 236065 |
| #3 | #1 OR #2 | 245738 |
| #4 | MeSH descriptor: [Esophagus] explode all trees | 1368 |
| #5 | MeSH descriptor: [Cardia] explode all trees | 53 |
| #6 | (esophag* OR oesophag* OR gastro-esophag* OR gastroesophag* OR gastro-oesophag* OR gastrooesophag* OR cardia):ti,ab,kw | 21273 |
| #7 | #4 OR #5 OR #6 | 21273 |
| #8 | #3 AND #7 | 8477 |
| #9 | MeSH descriptor: [Esophageal Neoplasms] explode all trees | 1740 |

| | | |
|---|---|---|
| #10 | (Esophageal Neoplasm OR Neoplasm, Esophageal OR Esophagus Neoplasm OR Esophagus Neoplasms OR Neoplasm, Esophagus OR Neoplasms, Esophagus OR Neoplasms, Esophageal OR Cancer of Esophagus OR Cancer of the Esophagus OR Esophagus Cancer OR Cancer, Esophagus OR Cancers, Esophagus OR Esophagus Cancers OR Esophageal Cancer OR Cancer, Esophageal OR Cancers, Esophageal OR Esophageal Cancers):ti,ab,kw | 5589 |
| #11 | #9 OR #10 | 5615 |
| #12 | #8 OR #11 | 8484 |
| #13 | MeSH descriptor: [Aftercare] explode all trees | 25979 |
| #14 | (After Care OR Aftercare OR After-Treatment OR After Treatment OR After-Treatments OR Follow-Up Care OR Care, Follow-Up OR Cares, Follow-Up OR Follow Up Care OR Follow-Up Cares OR Programs, Postabortal OR follow-up OR follow up):ti,ab,kw | 592966 |
| #15 | #13 OR #14 | 605394 |
| #16 | #12 AND #15 | 3617 |
| #17 | #16 with Publication Year from 2019 to 2022, in Trials | 821 |

## Recherche 04



## 2.5 Recherche 05

| **Schlüsselfrage 05 Stellenwert multimodaler incl. chirurgischer Therapiestrategien bei oligometastasierten Tumoren** |
|---|
| P: 1)Pat. mit gesichertem Plattenepithel- oder Adenokarzinom des Ösophagus in Abhängigkeit von der Tumorhöhe (zervikal, thorakal suprabifurkal, thorakalinfrabifurkal, abdominell bzw. nur supra-/infrabifurkal) 2)bzw. Pat. mit gesichertem AEG 1-3, 1) und 2) mit Lungen und/oder Lebermetastasen<br>I: a) Metastasenresektion, b) Radiotherapie (stereotaktische Bestrahlung)<br>C: a) keine Metastasenresektion, b) palliative Chemotherapie, c) Immuntherapie, d) Radio(chemo)therapie<br>O: Patientenrelevante Endpunkte: Gesamtüberlebensrate, Überlebensrate nach 5 Jahren und 3 Jahren (ggfls. „Ableitung“ aus Überlebenskurven, wenn nicht im Text berichtet), medianes ÜL, Rate an Lokal- und Fernrezidiven im Beobachtungszeitraum, Häufigkeit schwerer und lebensbedrohlicher NW bzw. Letalität durch die OP/ Radio/ Chemotherapie im Vergleich zu anderen Therapieverfahren |

Recherche in PubMed (04.02.2022)

| Nr. | Suchbegriff | Treffer |
|---|---|---|
| #1 | **Neoplasms[MeSH]** OR neoplasm*[tiab] OR carcinom*[tiab] OR adenocarcinom*[tiab] OR adeno-carcinom*[tiab] OR adenom*[tiab] OR malignan*[tiab] OR cancer[tiab] OR tumor[tiab] OR tumour[tiab] | 4.646.434 |
| #2 | **Esophagus[MeSH]** OR esophag*[tiab] OR oesophag*[tiab] OR gastro-esophag*[tiab] OR gastroesophag*[tiab] OR gastro-oesophag*[tiab] OR gastrooesophag*[tiab] OR **Cardia[MeSH]** OR cardia[tiab] | 211.966 |
| #3 | #1 AND #2 | 92.545 |
| #4 | **Esophageal Neoplasms[Mesh]** OR Esophageal Neoplasm[tiab] OR Neoplasm, Esophageal[tiab] OR Esophagus Neoplasm[tiab] OR Esophagus Neoplasms[tiab] OR Neoplasm, Esophagus[tiab] OR Neoplasms, Esophagus[tiab] OR Neoplasms, Esophageal[tiab] OR Cancer of Esophagus[tiab] OR Cancer of the Esophagus[tiab] OR Esophagus Cancer[tiab] OR Cancer, Esophagus[tiab] OR Cancers, Esophagus[tiab] OR Esophagus Cancers[tiab] OR Esophageal Cancer[tiab] OR Cancer, Esophageal[tiab] OR Cancers, Esophageal[tiab] OR Esophageal Cancers[tiab] | 61.764 |
| #5 | #3 OR #4 | 96.904 |
| #6 | oligometasta*[tiab] OR oligo metasta*[tiab] OR **"Neoplasm Metastasis"[Mesh]** OR metasta*[tiab] | 646.680 |

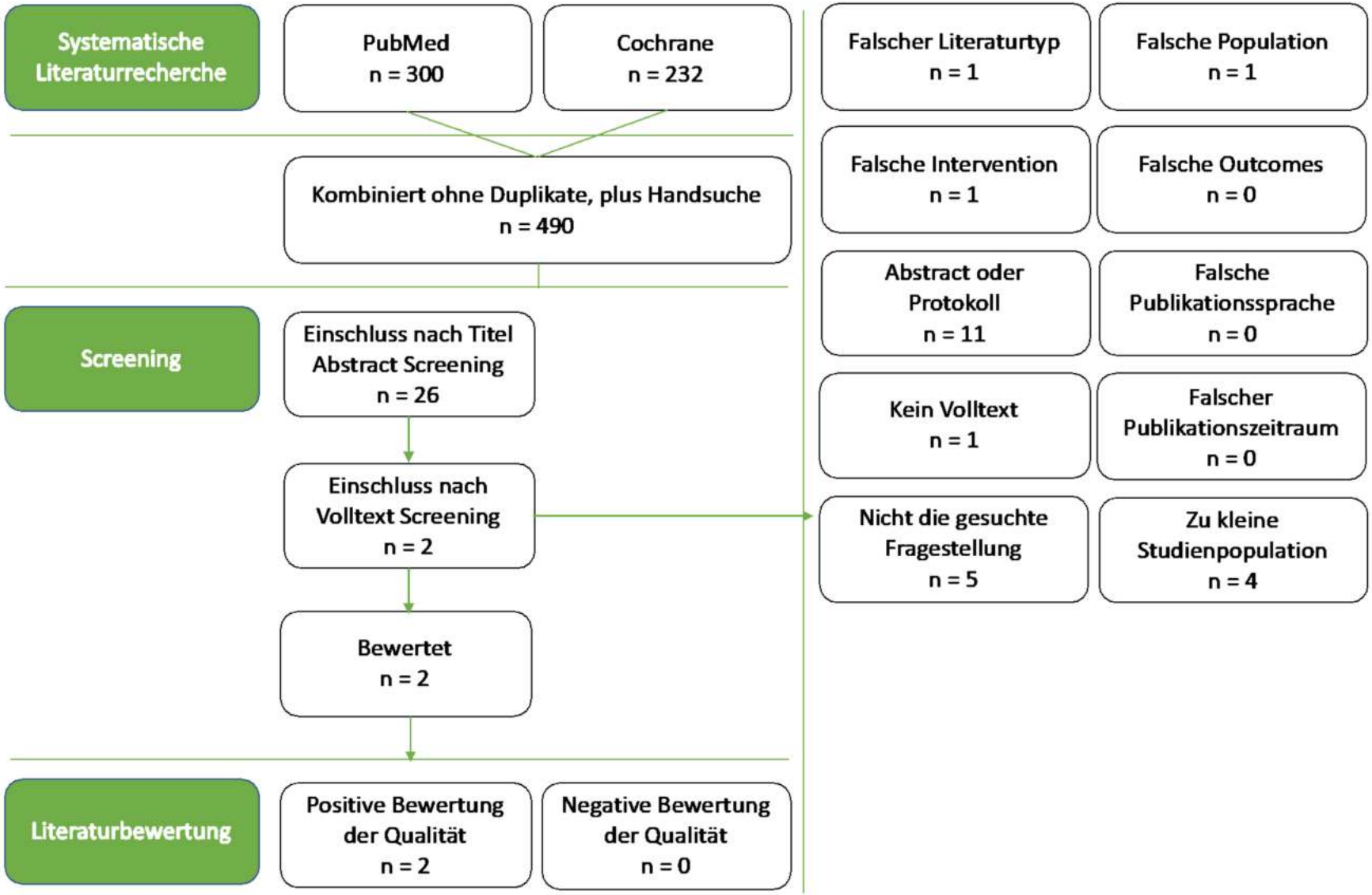
| | | |
|---|---|---|
| #7 | resect*[tiab] OR operation[tiab] OR operat*[tiab] OR surgical[tiab] OR surgery[tiab] OR **"Radiotherapy"[Mesh]** OR radiotherap*[tiab] OR radiation therapy[tiab] OR radiochemotherap*[tiab] OR chemoradiotherapy[tiab] OR **"Chemoradiotherapy"[Mesh]** OR chemoradiation[tiab] | 32.182.370 |
| #8 | #5 AND #6 AND #7 | 9.164 |
| #9 | cohort studies[mesh:noexp] OR longitudinal studies[mesh:noexp] OR follow-up studies[mesh:noexp] OR prospective studies[mesh:noexp] OR cohort[tiab] OR longitudinal[tiab] OR prospective[tiab] | 2.240.015 |
| #10 | "Clinical Trial" [PT:NoExp] OR "clinical trial, phase i"[pt] OR "clinical trial, phase ii"[pt] OR "clinical trial, phase iii"[pt] OR "clinical trial, phase iv"[pt] OR "controlled clinical trial"[pt] OR "multicenter study"[pt] OR "randomized controlled trial"[pt] OR "Clinical Trials as Topic"[mesh:noexp] OR "clinical trials, phase i as topic"[MeSH Terms:noexp] OR "clinical trials, phase ii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iv as topic"[MeSH Terms:noexp] OR "controlled clinical trials as topic"[MeSH Terms:noexp] OR "randomized controlled trials as topic"[MeSH Terms:noexp] OR "early termination of clinical trials"[MeSH Terms:noexp] OR "multicenter studies as topic"[MeSH Terms:noexp] OR “Double-Blind Method”[Mesh] OR ((randomised[tiab] OR randomized[tiab]) AND (trial[tiab] OR trials[tiab])) OR ((single[tiab] OR double[tiab] OR doubled[tiab] OR triple[tiab] OR tripled[tiab] OR treble[tiab] OR treble[tiab]) AND (blind*[tiab] OR mask*[tiab])) OR ("4 arm"[tiab] OR "four arm"[tiab]) | 1.608.903 |
| #11 | #9 OR #10 | 3.426.414 |
| #12 | animals[mh] NOT humans[mh] | 4.953.882 |
| #13 | #11 NOT #12 | 3.350.120 |
| #14 | #8 AND #13 | 2.741 |
| #15 | **#14 Publication date from 09/2019 until date of search, English, German** | 300 |

Recherche in der Cochrane Library (04.02.2022)

| ID | Search | Treffer |
|---|---|---|
| #1 | MeSH descriptor: [Neoplasms] explode all trees | 86153 |
| #2 | (neoplasm* OR carcinom* OR adenocarcinom* OR adeno-carcinom* OR adenom* OR malignan* OR cancer OR tumor OR tumour):ti,ab,kw | 236065 |
| #3 | #1 OR #2 | 245738 |
| #4 | MeSH descriptor: [Esophagus] explode all trees | 1368 |
| #5 | MeSH descriptor: [Cardia] explode all trees | 53 |

| | | |
|---|---|---|
| #6 | (esophag* OR oesophag* OR gastro-esophag* OR gastroesophag* OR gastro-oesophag* OR gastrooesophag* OR cardia):ti,ab,kw | 21273 |
| #7 | #4 OR #5 OR #6 | 21273 |
| #8 | #3 AND #7 | 8477 |
| #9 | MeSH descriptor: [Esophageal Neoplasms] explode all trees | 1740 |
| #10 | (Esophageal Neoplasm OR Neoplasm, Esophageal OR Esophagus Neoplasm OR Esophagus Neoplasms OR Neoplasm, Esophagus OR Neoplasms, Esophagus OR Neoplasms, Esophageal OR Cancer of Esophagus OR Cancer of the Esophagus OR Esophagus Cancer OR Cancer, Esophagus OR Cancers, Esophagus OR Esophagus Cancers OR Esophageal Cancer OR Cancer, Esophageal OR Cancers, Esophageal OR Esophageal Cancers):ti,ab,kw | 5589 |
| #11 | #9 OR #10 | 5615 |
| #12 | #8 OR #11 | 8484 |
| #13 | MeSH descriptor: [Neoplasm Metastasis] explode all trees | 5413 |
| #14 | (oligometasta* OR oligo metasta* OR metasta*):ti,ab,kw | 46368 |
| #15 | #13 OR #14 | 46507 |
| #16 | MeSH descriptor: [Radiotherapy] explode all trees | 6504 |
| #17 | MeSH descriptor: [Chemoradiotherapy] explode all trees | 1098 |
| #18 | (resect* OR operation OR operat* OR surgical OR surgery OR radiotherap* OR radiation therapy OR radiochemotherap* OR chemoradiotherapy OR chemoradiation):ti,ab,kw | 334190 |
| #19 | #16 OR #17 OR #18 | 334338 |
| #20 | #12 AND #15 AND #19 | 1025 |
| #21 | #20 with Publication Year from 2019 to 2022, in Trials | 232 |

## Recherche 05



## 2.6 Recherche 06

| **Schlüsselfrage 06.1 Verbessert eine adjuvante Radio- oder Radio chemotherapie das Überleben?** |
|---|
| P: 1)Pat. mit Plattenepithelkarzinom des Ösophagus (pN0 separat von pN1 (UICC 6th) bzw. pN1-3 (7th Edition) 2)Pat mit Adenokarzinom des Ösophagus oder des ösophago-gastralen Übergangs pN0 separat von pN1 (UICC 6th) bzw. pN1-3 (7th Edition)<br>I: Postoperative adjuvante Radio- oder Radiochemotherapie (für RCT simultan; unabhängig von der Dosierung der Radiotherapie und der gewählten Chemotherapie<br>C: a)keine postoperative adjuvante Radio- oder Radiochemotherapie<br>O: Patientenrelevante Endpunkte: Gesamtüberlebensrate, Überlebensrate nach 5 Jahren und 3 Jahren (ggfls. „Ableitung“ aus Überlebenskurven, wenn nicht im Text berichtet), medianes ÜL, Rate an Lokalrezidiven und Rezidiven im Beobachtungszeitraum, Häufigkeit schwerer und lebensbedrohlicher NW durch adjuvante Therapie |

| **Schlüsselfrage 06.2 Verbessert eine adjuvante Chemotherapie das Überleben?** |
|---|
| P: 1)Pat. mit Plattenepithelkarzinom des Ösophagus (pN0 separat von pN1 (UICC 6th) bzw. pN1-3 (7th Edition) 2)Pat mit Adenokarzinom des Ösophagus oder des ösophago-gastralen Übergangs pN0 separat von pN1 (UICC 6th) bzw. pN1-3 (7th Edition) nach R0 Resektion<br>I: Postoperative Chemotherapie<br>C: keine postoperative Chemotherapie<br>O: Patientenrelevante Endpunkte: Gesamtüberlebensrate, Überlebensrate nach 5 Jahren und 3 Jahren (ggfls. „Ableitung“ aus Überlebenskurven, wenn nicht im Text berichtet), medianes ÜL, Rate an Lokalrezidiven und Rezidiven im Beobachtungszeitraum, Häufigkeit schwerer und lebensbedrohlicher NW durch adjuvante Therapie |

| **Schlüsselfrage 06.3 Verbessert eine adjuvante Immuntherapie das Überleben?** |
|---|
| P: 1)Pat. mit Plattenepithelkarzinom des Ösophagus (pN0 separat von pN1 (UICC 6th) bzw. pN1-3 (7th Edition) 2)Pat mit Adenokarzinom des Ösophagus oder des ösophago-gastralen Übergangs pN0 separat von pN1 (UICC 6th) bzw. pN1-3 (7th Edition) nach R0 Resektion<br>I: Immuntherapie<br>C: keine Immuntherapie, versus adj Chemotherapie<br>O: Patientenrelevante Endpunkte: Gesamtüberlebensrate, Überlebensrate nach 5 Jahren und 3 Jahren (ggfls. „Ableitung“ aus Überlebenskurven, wenn nicht im Text berichtet), medianes ÜL, Rate an Lokalrezidiven und Rezidiven im |

| |
|---|
| Beobachtungszeitraum, Häufigkeit schwerer und lebensbedrohlicher NW durch adjuvante Therapie |

| **Schlüsselfrage 06.4 Verbessert eine präoperative bzw. prä- und) postoperative (fortgesetzte Chemotherapie das Überleben? (Fragestellung 1 für Evidenzbericht: "Indikation, Nutzen und Schaden neoadjuvanter Therapieverfahren")** |
|---|
| P: 1)Pat. mit Plattenepithelkarzinom des Ösophagus (Stadium bis T2N1M0 (UICC6th) bzw. bis T2N1-3M0 (UICC7th) separat von Stadium T3-4NalleM0 2)Pat mit Adenokarzinom des Ösophagus oder des ösophago-gastralen Übergangs (Stadium bis T2N1M0 (UICC6th) bzw. bis T2N1-3M0 (UICC7th) separat von Stadium T3-4NalleM0<br>I: neoadjuvante Chemotherapie unabhängig von Art und Dauer<br>C: keine neoadjuvante Therapie=chirurgische Therapie<br>O: Patientenrelevante Endpunkte: Gesamtüberlebensrate, Überlebensrate nach 5 Jahren und 3 Jahren (ggfls. „Ableitung" aus Überlebenskurven, wenn nicht im Text berichtet), medianes ÜL, Rate an R0 Resektionen, Rate an Fernrezidiven im Beobachtungszeitraum, Häufigkeit schwerer und lebensbedrohlicher NW durch die Chemotherapie in der präoperativen und postoperativen Phase |

| **Schlüsselfrage 06.5 Verbessert eine präoperative Radiochemotherapie das Überleben? Zu betrachtende Parameter: Tumorhöhenlokalisation, lokales Tumorstadium, AC versus SCC (Fragestellung 1 für Evidenzbericht: "Indikation, Nutzen und Schaden neoadjuvanter Therapieverfahren")** |
|---|
| P: 1)Pat. mit Plattenepithelkarzinom des Ösophagus (Stadium bis T2N1M0 (UICC6th) bzw. bis T2N1-3M0 (UICC7th) separat von Stadium T3-4NalleM0 2)Pat mit Adenokarzinom des Ösophagus oder des ösophago-gastralen Übergangs (Stadium bis T2N1M0 (UICC6th) bzw. bis T2N1-3M0 (UICC7th) separat von Stadium T3-4NalleM0<br>I: Neoadjuvante Radiochemotherapie (simultane RCT unabhängig von der Dosierung der Radiotherapie und der gewählten Chemotherapie)<br>C: a)keine neoadjuvante Therapie=chirurgische Therapie oder neoadjuvante Chemotherapie ohne Radiotherapie<br>O: Patientenrelevante Endpunkte: Gesamtüberlebensrate, Überlebensrate nach 5 Jahren und 3 Jahren (ggfls. „Ableitung" aus Überlebenskurven, wenn nicht im Text berichtet), medianes ÜL, Rate an R0 Resektionen, Rate an Lokal- und Fernrezidiven im Beobachtungszeitraum, Häufigkeit schwerer und lebensbedrohlicher NW durch die Radio/ Chemotherapie in der präoperativen Phase |

| **Schlüsselfrage 06.6 Stellenwert der postoperativen (adjuvanten) Therapie nach präoperativer Therapie und Operation beim Ösophaguskarzinom** |
|---|

| |
|---|
| P: 1)Pat. mit Plattenepithelkarzinom des Ösophagus (pN0 separat von pN1 (UICC 6th) bzw. pN1-3 (7th Edition) 2)Pat mit Adenokarzinom des Ösophagus oder des ösophago-gastralen Übergangs pN0 separat von pN1 (UICC 6th) bzw. pN1-3 (7th Edition) nach präoperativer Therapie und R0 Resektion<br>I: Postoperative adjuvante Chemo, Radio- oder Radiochemotherapie (für RCT simultan; unabhängig von der Dosierung der Radiotherapie und der gewählten Chemotherapie<br>C: a)keine postoperative adjuvante Therapie<br>O: Patientenrelevante Endpunkte: Gesamtüberlebensrate, Überlebensrate nach 5 Jahren und 3 Jahren (ggfls. „Ableitung“ aus Überlebenskurven, wenn nicht im Text berichtet), medianes ÜL, Rate an Lokalrezidiven und Rezidiven im Beobachtungszeitraum, Häufigkeit schwerer und lebensbedrohlicher NW durch adjuvante Therapie |

| **Schlüsselfrage 06.7 Stellenwert der präoperativen Radiotherapie im multimodalen Konzept bei AC des Ösophagus und des ösophago-gastralen Übergangs** |
|---|
| P: Pat mit Adenokarzinom des Ösophagus oder des ösophago-gastralen Übergangs (Stadium bis T2N1M0 (UICC6th) bzw. bis T2N1-3M0 (UICC7th) separat von Stadium T3-4NalleM0<br>I: Neoadjuvante Radiotherapie<br>C: a)keine neoadjuvante Therapie=chirurgische Therapie b) neoadjuvante Chemotherapie ohne Radiotherapie c) Radiochemotherapie<br>O: Patientenrelevante Endpunkte: Gesamtüberlebensrate, Überlebensrate nach 5 Jahren und 3 Jahren (ggfls. „Ableitung“ aus Überlebenskurven, wenn nicht im Text berichtet), medianes ÜL, Rate an R0 Resektionen, Rate an Lokal- und Fernrezidiven im Beobachtungszeitraum, Häufigkeit schwerer und lebensbedrohlicher NW durch die Radiotherapie in der präoperativen Phase |

Recherche in PubMed (02.02.2022)

| Nr. | Suchbegriff | Treffer |
|---|---|---|
| #1 | **Neoplasms[MeSH]** OR neoplasm*[tiab] OR carcinom*[tiab] OR adenocarcinom*[tiab] OR adeno-carcinom*[tiab] OR adenom*[tiab] OR malignan*[tiab] OR cancer[tiab] OR tumor[tiab] OR tumour[tiab] | 4.646.434 |
| #2 | **Esophagus[MeSH]** OR esophag*[tiab] OR oesophag*[tiab] OR gastro-esophag*[tiab] OR gastroesophag*[tiab] OR gastro-oesophag*[tiab] OR gastrooesophag*[tiab] OR **Cardia[MeSH]** OR cardia[tiab] | 211.966 |
| #3 | #1 AND #2 | 92.545 |

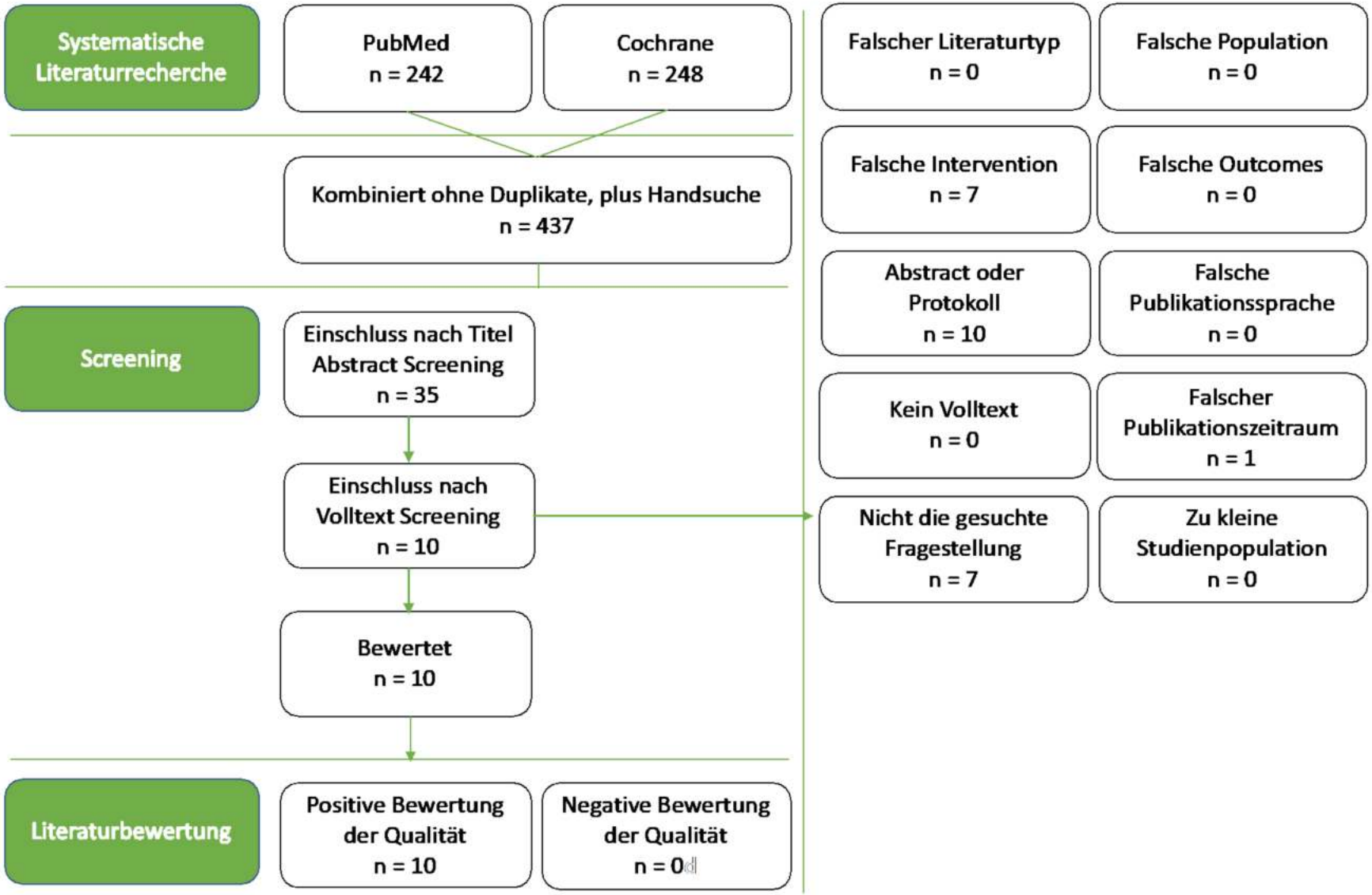
| | | |
|---|---|---|
| #4 | **Esophageal Neoplasms[Mesh]** OR Esophageal Neoplasm[tiab] OR Neoplasm, Esophageal[tiab] OR Esophagus Neoplasm[tiab] OR Esophagus Neoplasms[tiab] OR Neoplasm, Esophagus[tiab] OR Neoplasms, Esophagus[tiab] OR Neoplasms, Esophageal[tiab] OR Cancer of Esophagus[tiab] OR Cancer of the Esophagus[tiab] OR Esophagus Cancer[tiab] OR Cancer, Esophagus[tiab] OR Cancers, Esophagus[tiab] OR Esophagus Cancers[tiab] OR Esophageal Cancer[tiab] OR Cancer, Esophageal[tiab] OR Cancers, Esophageal[tiab] OR Esophageal Cancers[tiab] | 61.764 |
| #5 | #3 OR #4 | 96.869 |
| #6 | preoperative[tiab] OR pre-operative[tiab] OR perioperative[tiab] OR peri-operative[tiab] OR adjuvant[tiab] | 542.556 |
| #7 | chemotherap*[tiab] OR chemo therap*[tiab] OR **"Radiotherapy"[Mesh]** OR radiotherap*[tiab] OR radiation therapy[tiab] OR radiochemotherap*[tiab] OR chemoradiotherapy[tiab] OR **"Chemoradiotherapy"[Mesh]** OR chemoradiation[tiab] OR **"Immunotherapy"[Mesh]** OR Immunotherap*[tiab] OR immune therapy[tiab] OR checkpoint[tiab] OR check point[tiab] OR **"Radiation"[Mesh]** OR radiation[tiab] | 1.681.582 |
| #8 | #5 AND #6 AND #7 | 4.330 |
| #9 | cohort studies[mesh:noexp] OR longitudinal studies[mesh:noexp] OR follow-up studies[mesh:noexp] OR prospective studies[mesh:noexp] OR cohort[tiab] OR longitudinal[tiab] OR prospective[tiab] | 2.240.015 |
| #10 | "Clinical Trial" [PT:NoExp] OR "clinical trial, phase i"[pt] OR "clinical trial, phase ii"[pt] OR "clinical trial, phase iii"[pt] OR "clinical trial, phase iv"[pt] OR "controlled clinical trial"[pt] OR "multicenter study"[pt] OR "randomized controlled trial"[pt] OR "Clinical Trials as Topic"[mesh:noexp] OR "clinical trials, phase i as topic"[MeSH Terms:noexp] OR "clinical trials, phase ii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iv as topic"[MeSH Terms:noexp] OR "controlled clinical trials as topic"[MeSH Terms:noexp] OR "randomized controlled trials as topic"[MeSH Terms:noexp] OR "early termination of clinical trials"[MeSH Terms:noexp] OR "multicenter studies as topic"[MeSH Terms:noexp] OR “Double-Blind Method”[Mesh] OR ((randomised[tiab] OR randomized[tiab]) AND (trial[tiab] OR trials[tiab])) OR ((single[tiab] OR double[tiab] OR doubled[tiab] OR triple[tiab] OR tripled[tiab] OR treble[tiab] OR treble[tiab]) AND (blind*[tiab] OR mask*[tiab])) OR ("4 arm"[tiab] OR "four arm"[tiab]) | 1.608.903 |
| #11 | #9 OR #10 | 3.425.041 |
| #12 | animals[mh] NOT humans[mh] | 4.952.458 |
| #13 | #11 NOT #12 | 3.348.767 |

| | | |
|---|---|---|
| #14 | #8 AND #13 | 1.727 |
| #15 | **#14 Publication date from 09/2019 until date of search, English, German** | 242 |

Recherche in der Cochrane Library (04.02.2022)

| ID | Search | Treffer |
|---|---|---|
| #1 | MeSH descriptor: [Neoplasms] explode all trees | 86153 |
| #2 | (neoplasm* OR carcinom* OR adenocarcinom* OR adeno-carcinom* OR adenom* OR malignan* OR cancer OR tumor OR tumour):ti,ab,kw | 236065 |
| #3 | #1 OR #2 | 245738 |
| #4 | MeSH descriptor: [Esophagus] explode all trees | 1368 |
| #5 | MeSH descriptor: [Cardia] explode all trees | 53 |
| #6 | (esophag* OR oesophag* OR gastro-esophag* OR gastroesophag* OR gastro-oesophag* OR gastrooesophag* OR cardia):ti,ab,kw | 21273 |
| #7 | #4 OR #5 OR #6 | 21273 |
| #8 | #3 AND #7 | 8477 |
| #9 | MeSH descriptor: [Esophageal Neoplasms] explode all trees | 1740 |
| #10 | (Esophageal Neoplasm OR Neoplasm, Esophageal OR Esophagus Neoplasm OR Esophagus Neoplasms OR Neoplasm, Esophagus OR Neoplasms, Esophagus OR Neoplasms, Esophageal OR Cancer of Esophagus OR Cancer of the Esophagus OR Esophagus Cancer OR Cancer, Esophagus OR Cancers, Esophagus OR Esophagus Cancers OR Esophageal Cancer OR Cancer, Esophageal OR Cancers, Esophageal OR Esophageal Cancers):ti,ab,kw | 5589 |
| #11 | #9 OR #10 | 5615 |
| #12 | #8 OR #11 | 8484 |
| #13 | (preoperative OR pre-operative OR perioperative OR peri-operative OR adjuvant):ti,ab,kw | 86753 |
| #14 | MeSH descriptor: [Radiotherapy] explode all trees | 6504 |
| #15 | MeSH descriptor: [Chemoradiotherapy] explode all trees | 1098 |
| #16 | MeSH descriptor: [Immunotherapy] explode all trees | 8506 |
| #17 | MeSH descriptor: [Radiation] explode all trees | 5895 |
| #18 | (chemotherap* OR chemo therap* OR Radiotherapy OR radiotherap* OR radiation therapy OR radiochemotherap* OR chemoradiotherapy OR Chemoradiotherapy OR chemoradiation OR Immunotherapy OR Immunotherap* OR immune therapy OR checkpoint OR check point OR Radiation OR radiation):ti,ab,kw | 140055 |
| #19 | #14 OR #15 OR #16 OR #17 OR #18 | 147565 |
| #20 | #12 AND #13 AND #19 | 1208 |
| #21 | #20 with Publication Year from 2019 to 2022, in Trials | 248 |

## Recherche 06



## 2.7 Recherche 07

| **Schlüsselfrage 07 Stellenwert und Indikation der definitiven Radio(chemo)therapie Zu betrachtende Parameter: Tumorhöhenlokalisation, lokales Tumorstadium, AC versus SCC (Fragestellung 1 für Evidenzbericht: "Indikation, Nutzen und Schaden neoadjuvanter Therapieverfahren")** |
|---|
| P: 1)Pat. mit nicht fernmetastasiertem Plattenepithelkarzinom Ösophagus (Stadium Talle Nalle M0), 2) AEG (Stadium Talle Nalle M0)<br>I: definitive simultane Radiochemotherapie (mindestens 30 Gy (unabhängig von der Fraktionierung und der gewählten Chemotherapie)<br>C: OP alleine oder multimodale Verfahren unter Einschluss der OP<br>O: Patientenrelevante Endpunkte: Gesamtüberlebensrate, Überlebensrate nach 5 Jahren und 3 Jahren (ggfls. „Ableitung" aus Überlebenskurven, wenn nicht im Text berichtet), medianes ÜL, Rate an Lokal- und Fernrezidiven im Beobachtungszeitraum, Häufigkeit schwerer und lebensbedrohlicher NW bzw. Letalität durch die Radio/ Chemotherapie im Vergleich zu anderen Therapieverfahren |

Recherche in PubMed (04.02.2022)

| Nr. | Suchbegriff | Treffer |
|---|---|---|
| #1 | **Neoplasms[MeSH]** OR neoplasm*[tiab] OR carcinom*[tiab] OR adenocarcinom*[tiab] OR adeno-carcinom*[tiab] OR adenom*[tiab] OR malignan*[tiab] OR cancer[tiab] OR tumor[tiab] OR tumour[tiab] | 4.646.434 |
| #2 | **Esophagus[MeSH]** OR esophag*[tiab] OR oesophag*[tiab] OR gastro-esophag*[tiab] OR gastroesophag*[tiab] OR gastro-oesophag*[tiab] OR gastrooesophag*[tiab] OR **Cardia[MeSH]** OR cardia[tiab] | 211.966 |
| #3 | #1 AND #2 | 92.545 |
| #4 | **Esophageal Neoplasms[Mesh]** OR Esophageal Neoplasm[tiab] OR Neoplasm, Esophageal[tiab] OR Esophagus Neoplasm[tiab] OR Esophagus Neoplasms[tiab] OR Neoplasm, Esophagus[tiab] OR Neoplasms, Esophagus[tiab] OR Neoplasms, Esophageal[tiab] OR Cancer of Esophagus[tiab] OR Cancer of the Esophagus[tiab] OR Esophagus Cancer[tiab] OR Cancer, Esophagus[tiab] OR Cancers, Esophagus[tiab] OR Esophagus Cancers[tiab] OR Esophageal Cancer[tiab] OR Cancer, Esophageal[tiab] OR Cancers, Esophageal[tiab] OR Esophageal Cancers[tiab] | 61.764 |
| #5 | #3 OR #4 | 96.904 |
| #6 | definitive[tiab] OR curative[tiab] | 180.524 |

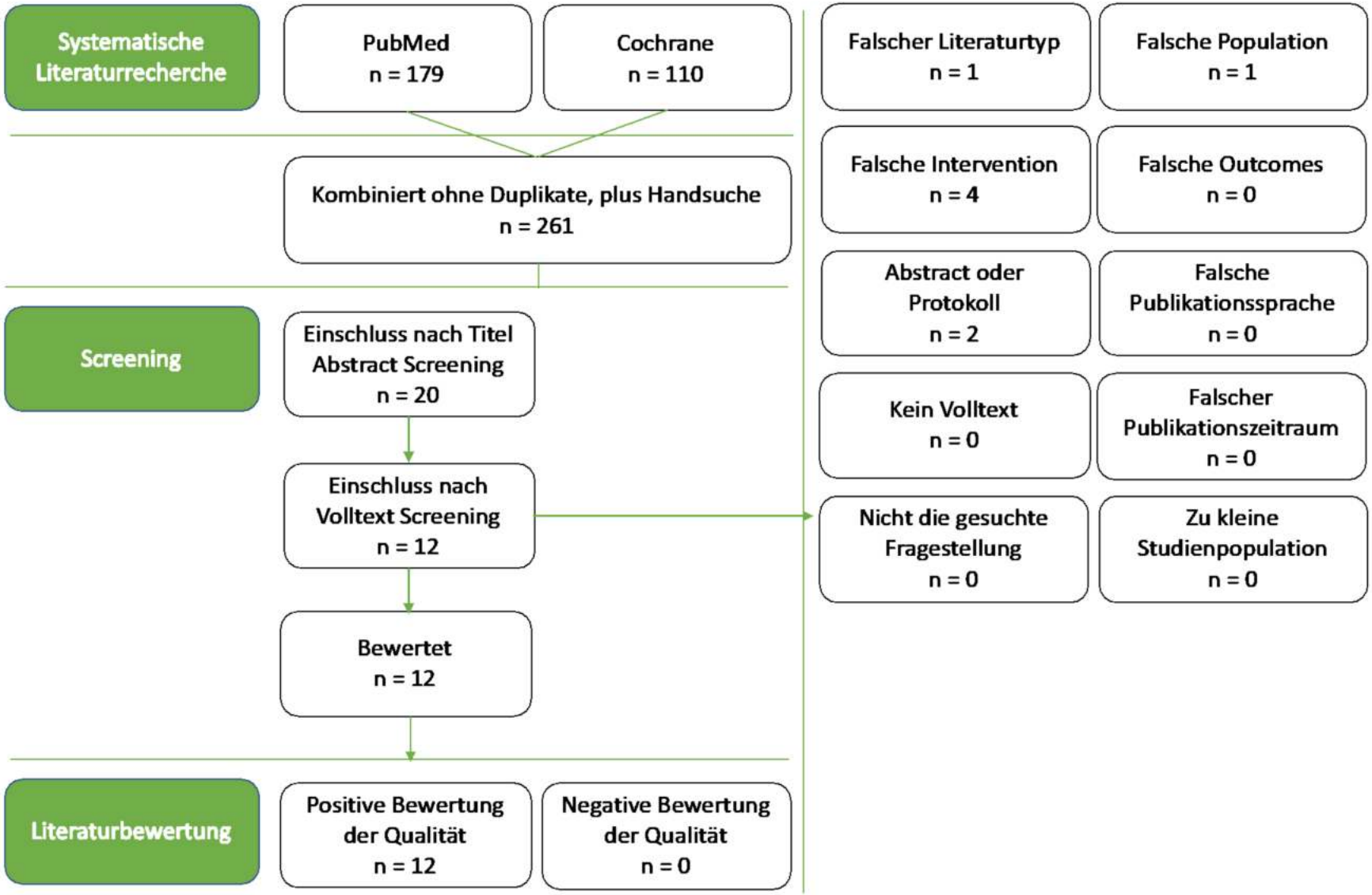
| | | |
|---|---|---|
| #7 | **"Radiotherapy"[Mesh]** OR radiotherap*[tiab] OR radiation therapy[tiab] OR radiochemotherap*[tiab] OR chemoradiotherap*[tiab] OR **"Chemoradiotherapy"[Mesh]** OR chemoradiation[tiab] OR **"Radiation"[Mesh]** OR radiation[tiab] | 972.037 |
| #8 | #5 AND #6 AND #7 | 2.513 |
| #9 | cohort studies[mesh:noexp] OR longitudinal studies[mesh:noexp] OR follow-up studies[mesh:noexp] OR prospective studies[mesh:noexp] OR cohort[tiab] OR longitudinal[tiab] OR prospective[tiab] | 2.240.015 |
| #10 | "Clinical Trial" [PT:NoExp] OR "clinical trial, phase i"[pt] OR "clinical trial, phase ii"[pt] OR "clinical trial, phase iii"[pt] OR "clinical trial, phase iv"[pt] OR "controlled clinical trial"[pt] OR "multicenter study"[pt] OR "randomized controlled trial"[pt] OR "Clinical Trials as Topic"[mesh:noexp] OR "clinical trials, phase i as topic"[MeSH Terms:noexp] OR "clinical trials, phase ii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iv as topic"[MeSH Terms:noexp] OR "controlled clinical trials as topic"[MeSH Terms:noexp] OR "randomized controlled trials as topic"[MeSH Terms:noexp] OR "early termination of clinical trials"[MeSH Terms:noexp] OR "multicenter studies as topic"[MeSH Terms:noexp] OR “Double-Blind Method”[Mesh] OR ((randomised[tiab] OR randomized[tiab]) AND (trial[tiab] OR trials[tiab])) OR ((single[tiab] OR double[tiab] OR doubled[tiab] OR triple[tiab] OR tripled[tiab] OR treble[tiab] OR treble[tiab]) AND (blind*[tiab] OR mask*[tiab])) OR ("4 arm"[tiab] OR "four arm"[tiab]) | 1.608.903 |
| #11 | #9 OR #10 | 3.426.414 |
| #12 | animals[mh] NOT humans[mh] | 4.953.882 |
| #13 | #11 NOT #12 | 3.350.120 |
| #14 | #8 AND #13 | 627 |
| #15 | **#14 Publication date from 09/2019 until date of search, English, German** | 179 |

Recherche in der Cochrane Library (04.02.2022)

| ID | Search | Treffer |
|---|---|---|
| #1 | MeSH descriptor: [Neoplasms] explode all trees | 86153 |
| #2 | (neoplasm* OR carcinom* OR adenocarcinom* OR adeno-carcinom* OR adenom* OR malignan* OR cancer OR tumor OR tumour):ti,ab,kw | 236065 |
| #3 | #1 OR #2 | 245738 |
| #4 | MeSH descriptor: [Esophagus] explode all trees | 1368 |
| #5 | MeSH descriptor: [Cardia] explode all trees | 53 |
| #6 | (esophag* OR oesophag* OR gastro-esophag* OR gastroesophag* OR gastro-oesophag* OR gastrooesophag* OR cardia):ti,ab,kw | 21273 |

| | | |
|---|---|---|
| #7 | #4 OR #5 OR #6 | 21273 |
| #8 | #3 AND #7 | 8477 |
| #9 | MeSH descriptor: [Esophageal Neoplasms] explode all trees | 1740 |
| #10 | (Esophageal Neoplasm OR Neoplasm, Esophageal OR Esophagus Neoplasm OR Esophagus Neoplasms OR Neoplasm, Esophagus OR Neoplasms, Esophagus OR Neoplasms, Esophageal OR Cancer of Esophagus OR Cancer of the Esophagus OR Esophagus Cancer OR Cancer, Esophagus OR Cancers, Esophagus OR Esophagus Cancers OR Esophageal Cancer OR Cancer, Esophageal OR Cancers, Esophageal OR Esophageal Cancers):ti,ab,kw | 5589 |
| #11 | #9 OR #10 | 5615 |
| #12 | #8 OR #11 | 8484 |
| #13 | (definitive OR curative):ti,ab,kw | 22580 |
| #14 | MeSH descriptor: [Radiotherapy] explode all trees | 6504 |
| #15 | MeSH descriptor: [Chemoradiotherapy] explode all trees | 1098 |
| #16 | MeSH descriptor: [Radiation] explode all trees | 5895 |
| #17 | (Radiotherapy OR radiotherap* OR radiation therapy OR radiochemotherap* OR chemoradiotherap* OR Chemoradiotherapy OR chemoradiation OR Radiation OR radiation):ti,ab,kw | 52503 |
| #18 | #14 OR #15 OR #16 OR #17 | 54810 |
| #19 | #12 AND #13 AND #18 | 435 |
| #20 | #19 with Publication Year from 2019 to 2022, in Trials | 110 |

## Recherche 07



## 2.8 Recherche 08

| **Schlüsselfrage 08.1 Rolle des PET-CTs, endoskopischen Ultraschalls bzw. Kontrastmittel-Spiral-CT und Endoskopie zur Therapieprädiktion/Remissionsvorhersage** |
|---|
| P: 1)Pat. (die Therapie bekommen) mit gesichertem PlattenepithelKarzinom o. mit Adenokarzinom des Ösophagus oder AEG 1-3 unter präoperativer Chemotherapie separat von präoperativer Radiochemotherapie<br>I: a)frühe Verlaufskontrolle (innerhalb von 2 Wochen nach Therapiebeginn) b)späte Verlaufskontrolle (zum Abschluss der Therapie bzw. vor der geplanten Operation)<br>C: 1)Kein PETCT 2)bzw. kein endoskopischer Ultraschall 3)bzw. kein KontrastmittelSpiral-CT 4) bzw. keine Endoskopie<br>O: Endpunkte: Vorhersagewahrscheinlichkeit für klinisch komplette Remission, histologisches Ansprechen nach Therapie, progressionsfreies Überleben und Gesamtüberleben durch die frühe bzw. späte Untersuchung (PET-CT bzw. EUS bzw. CT bzw. Endoskopie |

| **Schlüsselfrage 08.2 Stellenwert des PET-CT zur Bestrahlungsplanung** |
|---|
| P: 1)Pat. zur geplanten Radio(chemo)therapie mit gesichertem PlattenepithelKarzinom o. mit Adenokarzinom des Ösophagus oder AEG 1-3, alle Stadien aber M0<br>I: PET-CT<br>C: kein PET-CT, b) CT, c) MRT<br>O: Patientenrelevante Endpunkte: Gesamtüberlebensrate, Überlebensrate nach 5 Jahren und 3 Jahren (ggfls. „Ableitung“ aus Überlebenskurven, wenn nicht im Text berichtet), medianes ÜL, Rate an R0 Resektionen, Rate an Lokal- und Fernrezidiven im Beobachtungszeitraum, Häufigkeit schwerer und lebensbedrohlicher NW durch die Radio(chemo)therapie |

Recherche in PubMed (02.02.2022)

| Nr. | Suchbegriff | Treffer |
|---|---|---|
| #1 | **Neoplasms[MeSH]** OR neoplasm*[tiab] OR carcinom*[tiab] OR adenocarcinom*[tiab] OR adeno-carcinom*[tiab] OR adenom*[tiab] OR malignan*[tiab] OR cancer[tiab] OR tumor[tiab] OR tumour[tiab] | 4.646.434 |
| #2 | **Esophagus[MeSH]** OR esophag*[tiab] OR oesophag*[tiab] OR gastro-esophag*[tiab] OR gastroesophag*[tiab] OR gastro-oesophag*[tiab] OR gastrooesophag*[tiab] OR **Cardia[MeSH]** OR cardia[tiab] | 211.966 |
| #3 | #1 AND #2 | 92.545 |

| | | |
|---|---|---|
| #4 | **Esophageal Neoplasms[Mesh]** OR Esophageal Neoplasm[tiab] OR Neoplasm, Esophageal[tiab] OR Esophagus Neoplasm[tiab] OR Esophagus Neoplasms[tiab] OR Neoplasm, Esophagus[tiab] OR Neoplasms, Esophagus[tiab] OR Neoplasms, Esophageal[tiab] OR Cancer of Esophagus[tiab] OR Cancer of the Esophagus[tiab] OR Esophagus Cancer[tiab] OR Cancer, Esophagus[tiab] OR Cancers, Esophagus[tiab] OR Esophagus Cancers[tiab] OR Esophageal Cancer[tiab] OR Cancer, Esophageal[tiab] OR Cancers, Esophageal[tiab] OR Esophageal Cancers[tiab] | 61.764 |
| #5 | #3 OR #4 | 96.883 |
| #6 | prognostic significance[tiab] OR (predict*[tiab] AND (respon*[tiab] OR prognos*[tiab] OR utility[tiab] OR outcome[tiab])) OR "Prognosis"[Mesh] OR remission[tiab] OR treatment prediction[tiab] OR therapy prediction[tiab] OR therapy, radiation[tiab] OR "Radiation"[Mesh] OR radiation[tiab] | 3.027.981 |
| #7 | (((endoscopic*[tiab] AND (US[tiab] OR ultrasonography[tiab] OR ultrasound[tiab] OR "tri-modal imaging"[tiab])) OR EUS[tiab] OR endosonography[tiab] OR endosonograph*[tiab] OR (("curved array"[tiab] OR radial[tiab]) AND echoendoscop*[tiab])) OR (((contrast-enhanced[tiab] OR spiral[tiab] OR helical[tiab] OR multidetector[tiab] OR multisection[tiab] OR multislice[tiab]) AND ("computerised tomography"[tiab] OR CT[tiab] OR "computed tomography"[tiab])) OR 3D-CT[tiab]) OR (pet[tiab] OR petscan[tiab] OR PET-CT[tiab] OR "PET scan"[tiab] OR FDG-PET[tiab] OR PET-CT[tiab] OR **(**("Positron Emission Tomography"[tiab] OR PET[tiab]) AND (Computed[tiab] OR Computerized[tiab]) AND Tomography[tiab])) OR (endoscopy[tiab] OR endoscopic procedure[tiab])**)** OR **"Endosonography"[Mesh]** OR Endosonograph*[tiab] OR **"Endoscopy"[Mesh]** OR endoscop*[tiab] OR **"Positron-Emission Tomography"[Mesh]** OR PET[tiab] OR **"Positron Emission Tomography Computed Tomography"[Mesh]** | 675.133 |
| #8 | #5 AND #6 AND #7 | 7.834 |
| #9 | cohort studies[mesh:noexp] OR longitudinal studies[mesh:noexp] OR follow-up studies[mesh:noexp] OR prospective studies[mesh:noexp] OR cohort[tiab] OR longitudinal[tiab] OR prospective[tiab] | 2.240.015 |

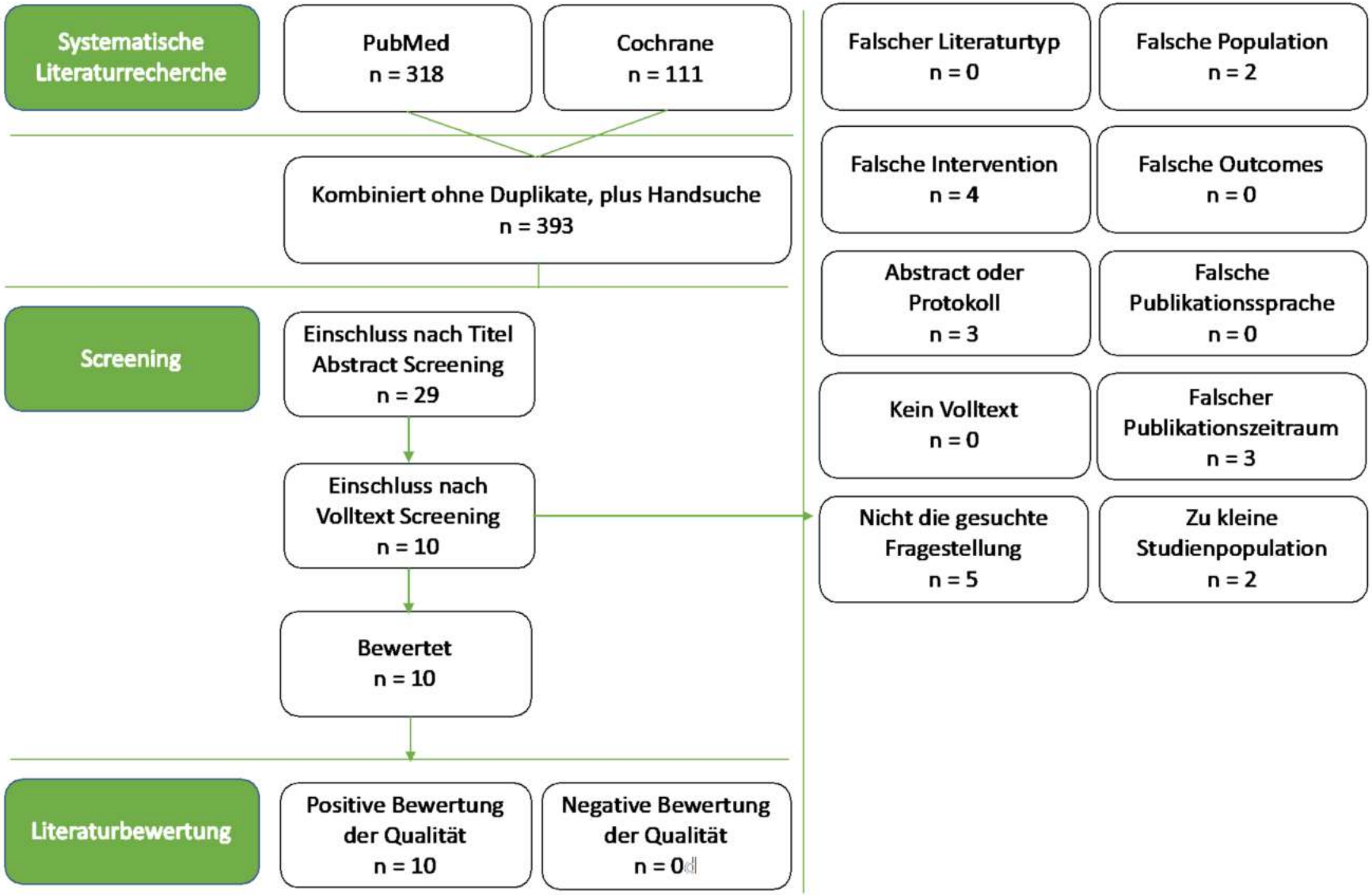
| | | |
|---|---|---|
| #10 | "Clinical Trial" [PT:NoExp] OR "clinical trial, phase i"[pt] OR "clinical trial, phase ii"[pt] OR "clinical trial, phase iii"[pt] OR "clinical trial, phase iv"[pt] OR "controlled clinical trial"[pt] OR "multicenter study"[pt] OR "randomized controlled trial"[pt] OR "Clinical Trials as Topic"[mesh:noexp] OR "clinical trials, phase i as topic"[MeSH Terms:noexp] OR "clinical trials, phase ii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iv as topic"[MeSH Terms:noexp] OR "controlled clinical trials as topic"[MeSH Terms:noexp] OR "randomized controlled trials as topic"[MeSH Terms:noexp] OR "early termination of clinical trials"[MeSH Terms:noexp] OR "multicenter studies as topic"[MeSH Terms:noexp] OR "Double-Blind Method"[Mesh] OR ((randomised[tiab] OR randomized[tiab]) AND (trial[tiab] OR trials[tiab])) OR ((single[tiab] OR double[tiab] OR doubled[tiab] OR triple[tiab] OR tripled[tiab] OR treble[tiab] OR treble[tiab]) AND (blind*[tiab] OR mask*[tiab])) OR ("4 arm"[tiab] OR "four arm"[tiab]) | 1.608.903 |
| #11 | #9 OR #10 | 3.425.041 |
| #12 | animals[mh] NOT humans[mh] | 4.952.458 |
| #13 | #11 NOT #12 | 3.348.767 |
| #14 | #8 AND #13 | 2.924 |
| #15 | **#14 Publication date from 09/2019 until date of search, English, German** | 318 |

Recherche in der Cochrane Library (03.09.2021)

| ID | Search | Treffer |
|---|---|---|
| #1 | MeSH descriptor: [Neoplasms] explode all trees | 86153 |
| #2 | (neoplasm* OR carcinom* OR adenocarcinom* OR adeno-carcinom* OR adenom* OR malignan* OR cancer OR tumor OR tumour):ti,ab,kw | 236065 |
| #3 | #1 OR #2 | 245738 |
| #4 | MeSH descriptor: [Esophagus] explode all trees | 1368 |
| #5 | MeSH descriptor: [Cardia] explode all trees | 53 |
| #6 | (esophag* OR oesophag* OR gastro-esophag* OR gastroesophag* OR gastro-oesophag* OR gastrooesophag* OR cardia):ti,ab,kw | 21273 |
| #7 | #4 OR #5 OR #6 | 21273 |
| #8 | #3 AND #7 | 8477 |
| #9 | MeSH descriptor: [Esophageal Neoplasms] explode all trees | 1740 |

| | | |
|---|---|---|
| #10 | (Esophageal Neoplasm OR Neoplasm, Esophageal OR Esophagus Neoplasm OR Esophagus Neoplasms OR Neoplasm, Esophagus OR Neoplasms, Esophagus OR Neoplasms, Esophageal OR Cancer of Esophagus OR Cancer of the Esophagus OR Esophagus Cancer OR Cancer, Esophagus OR Cancers, Esophagus OR Esophagus Cancers OR Esophageal Cancer OR Cancer, Esophageal OR Cancers, Esophageal OR Esophageal Cancers):ti,ab,kw | 5589 |
| #11 | #9 OR #10 | 5615 |
| #12 | #8 OR #11 | 8484 |
| #13 | (prognostic significance OR (predict* AND (respon* OR prognos* OR utility OR outcome )) OR remission OR treatment prediction OR therapy prediction OR therapy, radiation OR radiation):ti,ab,kw | 129843 |
| #14 | MeSH descriptor: [Radiation] explode all trees | 5895 |
| #15 | MeSH descriptor: [Prognosis] explode all trees | 165063 |
| #16 | #13 OR #14 OR #15 | 270617 |
| #17 | ((((endoscopic* AND (US OR ultrasonography OR ultrasound OR tri-modal imaging )) OR EUS OR endosonography OR endosonograph* OR (( curved array OR radial ) AND echoendoscop* )) OR (((contrast-enhanced OR spiral OR helical OR multidetector OR multisection OR multislice ) AND ( computerised tomography OR CT OR computed tomography )) OR 3D-CT ) OR (pet OR petscan OR PET-CT OR PET scan OR FDG-PET OR PET-CT OR (( Positron Emission Tomography OR PET ) AND (Computed OR Computerized ) AND Tomography )) OR (endoscopy OR endoscopic procedure )) OR Endosonography OR Endosonograph* OR Endoscopy OR endoscop* OR Positron-Emission Tomography OR PET OR Positron Emission Tomography Computed Tomography):ti,ab,kw | 41313 |
| #18 | MeSH descriptor: [Endosonography] explode all trees | 361 |
| #19 | MeSH descriptor: [Endoscopy] explode all trees | 18825 |
| #20 | MeSH descriptor: [Positron-Emission Tomography] explode all trees | 1106 |
| #21 | MeSH descriptor: [Positron Emission Tomography Computed Tomography] explode all trees | 137 |
| #22 | #17 OR #18 OR #19 OR #20 OR #21 | 53486 |
| #23 | #12 AND #16 AND #22 | 509 |
| #24 | #23 with Publication Year from 2019 to 2022, in Trials | 111 |

## Recherche 08



## 2.9 Recherche 09

| **Schlüsselfrage 9: Stellenwert der Operation nach Ansprechen auf eine Chemo(radio)therapie (Patienten mit klinisch kompletter Remission) beim Ösophaguskarzinom/ inklusive AEG** |
|---|
| P: 1)Pat. mit nicht fernmetastasiertem Plattenepithelkarzinom Ösophagus (Stadium Talle Nalle M0), 2) AEG (Stadium Talle Nalle M0)<br>I: Resektion<br>C: a) keine Resektion, b) definitive Radiochemotherapie, c) watch and wait<br>O: Patientenrelevante Endpunkte: Gesamtüberlebensrate, Überlebensrate nach 5 Jahren und 3 Jahren (ggfls. „Ableitung“ aus Überlebenskurven, wenn nicht im Text berichtet), medianes ÜL, Rate an R0 Resektionen, Rate an Lokal- und Fernrezidiven im Beobachtungszeitraum, Häufigkeit schwerer und lebensbedrohlicher NW durch die Radio- oder Chemotherapie in der präoperativen Phase |

Recherche in PubMed (04.02.2022)

| Nr. | Suchbegriff | Treffer |
|---|---|---|
| #1 | **Neoplasms[MeSH]** OR neoplasm*[tiab] OR carcinom*[tiab] OR adenocarcinom*[tiab] OR adeno-carcinom*[tiab] OR adenom*[tiab] OR malignan*[tiab] OR cancer[tiab] OR tumor[tiab] OR tumour[tiab] | 4.646.805 |
| #2 | **Esophagus[MeSH]** OR esophag*[tiab] OR oesophag*[tiab] OR gastro-esophag*[tiab] OR gastroesophag*[tiab] OR gastro-oesophag*[tiab] OR gastrooesophag*[tiab] OR **Cardia[MeSH]** OR cardia[tiab] | 211.996 |
| #3 | #1 AND #2 | 92.560 |
| #4 | **Esophageal Neoplasms[Mesh]** OR Esophageal Neoplasm[tiab] OR Neoplasm, Esophageal[tiab] OR Esophagus Neoplasm[tiab] OR Esophagus Neoplasms[tiab] OR Neoplasm, Esophagus[tiab] OR Neoplasms, Esophagus[tiab] OR Neoplasms, Esophageal[tiab] OR Cancer of Esophagus[tiab] OR Cancer of the Esophagus[tiab] OR Esophagus Cancer[tiab] OR Cancer, Esophagus[tiab] OR Cancers, Esophagus[tiab] OR Esophagus Cancers[tiab] OR Esophageal Cancer[tiab] OR Cancer, Esophageal[tiab] OR Cancers, Esophageal[tiab] OR Esophageal Cancers[tiab] | 61.768 |
| #5 | #3 OR #4 | 96.904 |
| #6 | resect*[tiab] OR operation[tiab] OR operat*[tiab] OR surgical[tiab] OR surgery[tiab] | 2.972.583 |
| #7 | preoperative[tiab] OR pre-operative[tiab] OR perioperative[tiab] OR peri-operative[tiab] OR remission[tiab] | 524.975 |

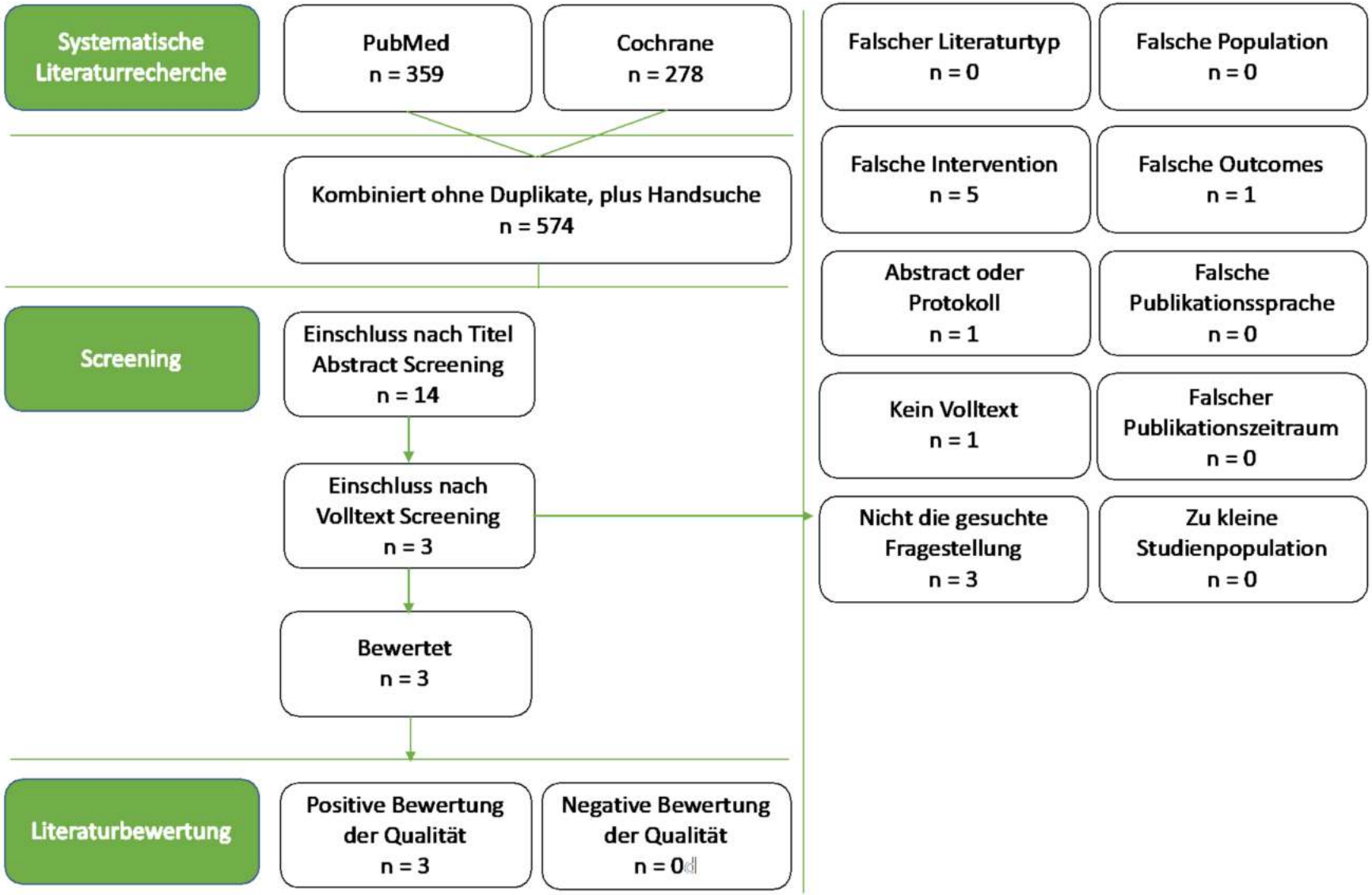
| | | |
|---|---|---|
| #8 | #5 AND #6 AND #7 | 6.329 |
| #9 | cohort studies[mesh:noexp] OR longitudinal studies[mesh:noexp] OR follow-up studies[mesh:noexp] OR prospective studies[mesh:noexp] OR cohort[tiab] OR longitudinal[tiab] OR prospective[tiab] | 2.240.015 |
| #10 | "Clinical Trial" [PT:NoExp] OR "clinical trial, phase i"[pt] OR "clinical trial, phase ii"[pt] OR "clinical trial, phase iii"[pt] OR "clinical trial, phase iv"[pt] OR "controlled clinical trial"[pt] OR "multicenter study"[pt] OR "randomized controlled trial"[pt] OR "Clinical Trials as Topic"[mesh:noexp] OR "clinical trials, phase i as topic"[MeSH Terms:noexp] OR "clinical trials, phase ii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iv as topic"[MeSH Terms:noexp] OR "controlled clinical trials as topic"[MeSH Terms:noexp] OR "randomized controlled trials as topic"[MeSH Terms:noexp] OR "early termination of clinical trials"[MeSH Terms:noexp] OR "multicenter studies as topic"[MeSH Terms:noexp] OR “Double-Blind Method”[Mesh] OR ((randomised[tiab] OR randomized[tiab]) AND (trial[tiab] OR trials[tiab])) OR ((single[tiab] OR double[tiab] OR doubled[tiab] OR triple[tiab] OR tripled[tiab] OR treble[tiab] OR treble[tiab]) AND (blind*[tiab] OR mask*[tiab])) OR ("4 arm"[tiab] OR "four arm"[tiab]) | 1.608.903 |
| #11 | #9 OR #10 | 3.426.414 |
| #12 | animals[mh] NOT humans[mh] | 4.953.882 |
| #13 | #11 NOT #12 | 3.350.120 |
| #14 | #8 AND #13 | 2.731 |
| #15 | **#14 Publication date from 09/2019 until date of search, English, German** | 359 |

Recherche in der Cochrane Library (04.22.2022)

| ID | Search | Treffer |
|---|---|---|
| #1 | MeSH descriptor: [Neoplasms] explode all trees | 86153 |
| #2 | (neoplasm* OR carcinom* OR adenocarcinom* OR adeno-carcinom* OR adenom* OR malignan* OR cancer OR tumor OR tumour):ti,ab,kw | 236065 |
| #3 | #1 OR #2 | 245738 |
| #4 | MeSH descriptor: [Esophagus] explode all trees | 1368 |
| #5 | MeSH descriptor: [Cardia] explode all trees | 53 |
| #6 | (esophag* OR oesophag* OR gastro-esophag* OR gastroesophag* OR gastro-oesophag* OR gastrooesophag* OR cardia):ti,ab,kw | 21273 |
| #7 | #4 OR #5 OR #6 | 21273 |
| #8 | #3 AND #7 | 8477 |

| | | |
|---|---|---|
| #9 | MeSH descriptor: [Esophageal Neoplasms] explode all trees | 1740 |
| #10 | (Esophageal Neoplasm OR Neoplasm, Esophageal OR Esophagus Neoplasm OR Esophagus Neoplasms OR Neoplasm, Esophagus OR Neoplasms, Esophagus OR Neoplasms, Esophageal OR Cancer of Esophagus OR Cancer of the Esophagus OR Esophagus Cancer OR Cancer, Esophagus OR Cancers, Esophagus OR Esophagus Cancers OR Esophageal Cancer OR Cancer, Esophageal OR Cancers, Esophageal OR Esophageal Cancers):ti,ab,kw | 5589 |
| #11 | #9 OR #10 | 5615 |
| #12 | #8 OR #11 | 8484 |
| #13 | (resect* OR operation OR operat* OR surgical OR surgery):ti,ab,kw | 306380 |
| #14 | (preoperative OR pre-operative OR perioperative OR peri-operative OR remission):ti,ab,kw | 92016 |
| #15 | #12 AND #13 AND #14 | 1238 |
| #16 | #15 with Publication Year from 2019 to 2022, in Trials | 278 |

## Recherche 09



## 2.10 Recherche 10

| **Schlüselfrage 10 Stellenwert der Kombination endoskopischer Resektion kleiner Tumore bei Ansprechen nach Radio/Chemo/Radiochemotherapie** |
|---|
| P: 1)Pat. mit Plattenepithelkarzinom des Ösophagus (Stadium bis T2N1M0 (UICC6th) bzw. bis T2N1-3M0 (UICC7th) separat von Stadium T3-4NalleM0 2)Pat mit Adenokarzinom des Ösophagus oder des ösophago-gastralen Übergangs (Stadium bis T2N1M0 (UICC6th) bzw. bis T2N1-3M0 (UICC7th) separat von Stadium T3-4NalleM0<br>I: Endoskopische Resektion<br>C: 1) keine endoskopische Resektion 2) chirurgische Resektion 3) Radiochemotherapie 4) watch and wait<br>O: Patientenrelevante Endpunkte: Gesamtüberlebensrate, Überlebensrate nach 5 Jahren und 3 Jahren (ggfls. „Ableitung“ aus Überlebenskurven, wenn nicht im Text berichtet), medianes ÜL, Rate an R0 Resektionen, Rate an Lokal- und Fernrezidiven im Beobachtungszeitraum, Häufigkeit schwerer und lebensbedrohlicher NW durch die Endoskopie |

Recherche in PubMed (04.02.2022)

| Nr. | Suchbegriff | Treffer |
|---|---|---|
| #1 | **Neoplasms[MeSH]** OR neoplasm*[tiab] OR carcinom*[tiab] OR adenocarcinom*[tiab] OR adeno-carcinom*[tiab] OR adenom*[tiab] OR malignan*[tiab] OR cancer[tiab] OR tumor[tiab] OR tumour[tiab] | 4.646.805 |
| #2 | **Esophagus[MeSH]** OR esophag*[tiab] OR oesophag*[tiab] OR gastro-esophag*[tiab] OR gastroesophag*[tiab] OR gastro-oesophag*[tiab] OR gastrooesophag*[tiab] OR **Cardia[MeSH]** OR cardia[tiab] | 211.996 |
| #3 | #1 AND #2 | 92.560 |
| #4 | **Esophageal Neoplasms[Mesh]** OR Esophageal Neoplasm[tiab] OR Neoplasm, Esophageal[tiab] OR Esophagus Neoplasm[tiab] OR Esophagus Neoplasms[tiab] OR Neoplasm, Esophagus[tiab] OR Neoplasms, Esophagus[tiab] OR Neoplasms, Esophageal[tiab] OR Cancer of Esophagus[tiab] OR Cancer of the Esophagus[tiab] OR Esophagus Cancer[tiab] OR Cancer, Esophagus[tiab] OR Cancers, Esophagus[tiab] OR Esophagus Cancers[tiab] OR Esophageal Cancer[tiab] OR Cancer, Esophageal[tiab] OR Cancers, Esophageal[tiab] OR Esophageal Cancers[tiab] | 61.768 |
| #5 | #3 OR #4 | 96.904 |

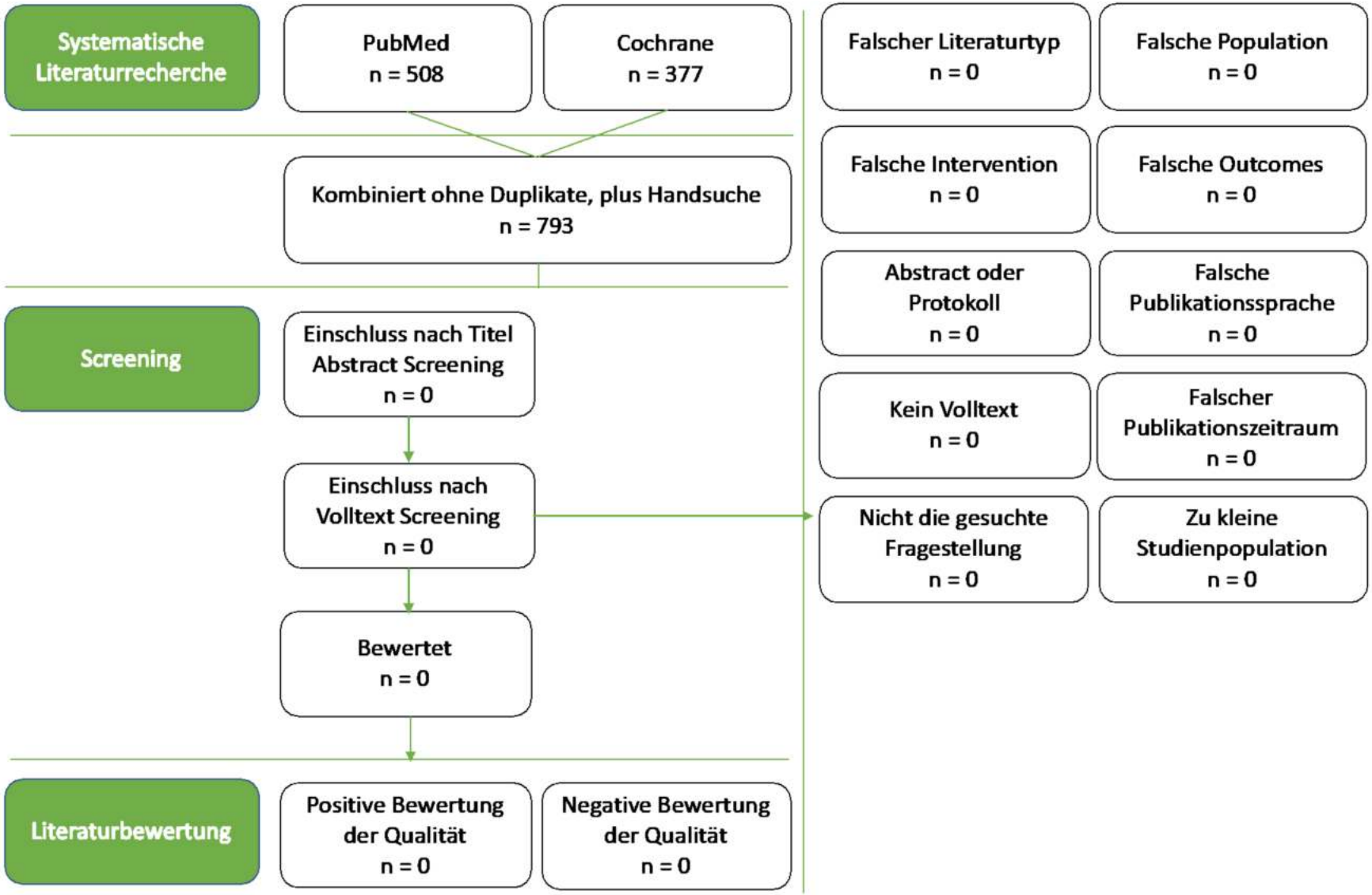
| | | |
|---|---|---|
| #6 | resect*[tiab] OR operation[tiab] OR operat*[tiab] OR surgical[tiab] OR surgery[tiab] OR **Endoscopy[Mesh]** OR endoscop*[tiab] OR Surgical Procedures, Endoscopic[tiab] OR Procedure, Endoscopic Surgical[tiab] OR Procedures, Endoscopic Surgical[tiab] OR Surgical Procedure, Endoscopic[tiab] OR Endoscopy, Surgical[tiab] OR Surgical Endoscopy[tiab] OR Endoscopic Surgical Procedure[tiab] OR Endoscopic Surgical Procedures[tiab] | 3.233.210 |
| #7 | **"Radiotherapy"[Mesh]** OR radiotherap*[tiab] OR radiation therapy[tiab] OR radiochemotherap*[tiab] OR chemoradiotherapy[tiab] OR **"Chemoradiotherapy"[Mesh]** OR chemoradiation[tiab] OR **"Radiation"[Mesh]** OR radiation[tiab] OR response[tiab] | 3.148.287 |
| #8 | #5 AND #6 AND #7 | 9.749 |
| #9 | cohort studies[mesh:noexp] OR longitudinal studies[mesh:noexp] OR follow-up studies[mesh:noexp] OR prospective studies[mesh:noexp] OR cohort[tiab] OR longitudinal[tiab] OR prospective[tiab] | 2.240.015 |
| #10 | "Clinical Trial" [PT:NoExp] OR "clinical trial, phase i"[pt] OR "clinical trial, phase ii"[pt] OR "clinical trial, phase iii"[pt] OR "clinical trial, phase iv"[pt] OR "controlled clinical trial"[pt] OR "multicenter study"[pt] OR "randomized controlled trial"[pt] OR "Clinical Trials as Topic"[mesh:noexp] OR "clinical trials, phase i as topic"[MeSH Terms:noexp] OR "clinical trials, phase ii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iv as topic"[MeSH Terms:noexp] OR "controlled clinical trials as topic"[MeSH Terms:noexp] OR "randomized controlled trials as topic"[MeSH Terms:noexp] OR "early termination of clinical trials"[MeSH Terms:noexp] OR "multicenter studies as topic"[MeSH Terms:noexp] OR “Double-Blind Method”[Mesh] OR ((randomised[tiab] OR randomized[tiab]) AND (trial[tiab] OR trials[tiab])) OR ((single[tiab] OR double[tiab] OR doubled[tiab] OR triple[tiab] OR tripled[tiab] OR treble[tiab] OR treble[tiab]) AND (blind*[tiab] OR mask*[tiab])) OR ("4 arm"[tiab] OR "four arm"[tiab]) | 1.608.903 |
| #11 | #9 OR #10 | 3.426.414 |
| #12 | animals[mh] NOT humans[mh] | 4.953.882 |
| #13 | #11 NOT #12 | 3.350.120 |
| #14 | #8 AND #13 | 3.540 |
| #15 | **#14 Publication date from 09/2019 until date of search, English, German** | 508 |

Recherche in der Cochrane Library (04.02.2022)

| ID | Search | Treffer |
|---|---|---|
| #1 | MeSH descriptor: [Neoplasms] explode all trees | 86153 |

| | | |
|---|---|---|
| #2 | (neoplasm* OR carcinom* OR adenocarcinom* OR adeno-carcinom* OR adenom* OR malignan* OR cancer OR tumor OR tumour):ti,ab,kw | 236065 |
| #3 | #1 OR #2 | 245738 |
| #4 | MeSH descriptor: [Esophagus] explode all trees | 1368 |
| #5 | MeSH descriptor: [Cardia] explode all trees | 53 |
| #6 | (esophag* OR oesophag* OR gastro-esophag* OR gastroesophag* OR gastro-oesophag* OR gastrooesophag* OR cardia):ti,ab,kw | 21273 |
| #7 | #4 OR #5 OR #6 | 21273 |
| #8 | #3 AND #7 | 8477 |
| #9 | MeSH descriptor: [Esophageal Neoplasms] explode all trees | 1740 |
| #10 | (Esophageal Neoplasm OR Neoplasm, Esophageal OR Esophagus Neoplasm OR Esophagus Neoplasms OR Neoplasm, Esophagus OR Neoplasms, Esophagus OR Neoplasms, Esophageal OR Cancer of Esophagus OR Cancer of the Esophagus OR Esophagus Cancer OR Cancer, Esophagus OR Cancers, Esophagus OR Esophagus Cancers OR Esophageal Cancer OR Cancer, Esophageal OR Cancers, Esophageal OR Esophageal Cancers):ti,ab,kw | 5589 |
| #11 | #9 OR #10 | 5615 |
| #12 | #8 OR #11 | 8484 |
| #13 | (resect* OR operation OR operat* OR surgical OR surgery OR endoscop* OR Surgical Procedures, Endoscopic OR Procedure, Endoscopic Surgical OR Procedures, Endoscopic Surgical OR Surgical Procedure, Endoscopic OR Endoscopy, Surgical OR Surgical Endoscopy OR Endoscopic Surgical Procedure OR Endoscopic Surgical Procedures):ti,ab,kw | 323841 |
| #14 | MeSH descriptor: [Endoscopy] explode all trees | 18825 |
| #15 | #13 OR #14 | 327090 |
| #16 | (Radiotherapy OR radiotherap* OR radiation therapy OR radiochemotherap* OR chemoradiotherapy OR Chemoradiotherapy OR chemoradiation OR Radiation OR radiation OR response):ti,ab,kw | 290398 |
| #17 | MeSH descriptor: [Radiotherapy] explode all trees | 6504 |
| #18 | MeSH descriptor: [Chemoradiotherapy] explode all trees | 1098 |
| #19 | MeSH descriptor: [Radiation] explode all trees | 5895 |
| #20 | #16 OR #17 OR #18 OR #19 | 292400 |
| #21 | #12 AND #15 AND #20 | 1826 |
| #22 | #21 with Publication Year from 2019 to 2022, in Trials | 377 |

## Recherche 10



## 2.11 Recherche 11

| **Schlüsselfrage 11.1 Stellenwert der palliativen Chemotherapie (Fragestellungen 2 und 3 für Evidenzbericht: Definition einer multidisziplinären Therapie in der Palliation und Indikation, Nutzen und Schaden der palliativen Chemotherapie** |
|---|
| P: Patienten im Stadium IV und mit lokoregionär fortgeschrittenen, primär inoperablen Plattenepithel- und Adenokarzinomen des Ösophagus und Adenokarzinomen des gastroösophagealen Übergangs 1-3<br>I: 1) palliative Chemotherapie, 2) Zweitlinienchemo therapie palliativ , 3) Radiotherapie palliativ, 4) Brachytherapie palliativ, 5) Radiochemotherapie palliativ, 6) Stentimplantation palliativ, 7) palliative OP 8) Immuntherapie (Pembrolizumab, Nivolumab, Tislelizumab, Cambrelizumab..)<br>C: Die jeweils anderen Verfahren<br>O: Patientenrelevante Endpunkte: Lebensqualität (QoL), Nutzen, Schaden (Therapienebenwirkungen/Toxizität), Perforation, Blutung, Todesfall), Remissionsrate, Progressionsfreies Überleben, symptomfreies Überleben (symptomfree survival) (time without signs and symptoms), Gesamtüberlebensrate/ Überlebenszeit, Speziell für 6) Stentimplantation zusätzlich: Dysphagiefreies Überleben ohne Stentverschluss, Dysphagieminderung |

| **Schlüsselfrage 11.2 Stellenwert der Immuntherapie - Erstlinie (PICO s.o.)** |
|---|
| P: Patienten im Stadium IV und mit lokoregionär fortgeschrittenen, primär inoperablen Plattenepithel- und Adenokarzinomen des Ösophagus und Adenokarzinomen des gastroösophagealen Übergangs 1-3<br>I: 1) palliative Chemotherapie, 2) Zweitlinienchemo therapie palliativ , 3) Radiotherapie palliativ, 4) Brachytherapie palliativ, 5) Radiochemotherapie palliativ, 6) Stentimplantation palliativ, 7) palliative OP 8) Immuntherapie (Pembrolizumab, Nivolumab, Tislelizumab, Cambrelizumab..)<br>C: Die jeweils anderen Verfahren<br>O: Patientenrelevante Endpunkte: Lebensqualität (QoL), Nutzen, Schaden (Therapienebenwirkungen/Toxizität), Perforation, Blutung, Todesfall), Remissionsrate, Progressionsfreies Überleben, symptomfreies Überleben (symptomfree survival) (time without signs and symptoms), Gesamtüberlebensrate/ Überlebenszeit, Speziell für 6) Stentimplantation zusätzlich: Dysphagiefreies Überleben ohne Stentverschluss, Dysphagieminderung |

| **Schlüsselfrage 11.3 Stellenwert HER2- gerichteter Therapieansätze nach Versagen der Erstlinie (in Kombination mit Chemo/Immuntherapie)** |
|---|

P: Patienten im Stadium IV und mit lokoregionär fortgeschrittenen, primär inoperablen Plattenepithel- und Adenokarzinomen des Ösophagus und Adenokarzinomen des gastroösophagealen Übergangs 1-3
I: 1) palliative Chemotherapie, 2) Zweitlinienchemo therapie palliativ , 3) Radiotherapie palliativ, 4) Brachytherapie palliativ, 5) Radiochemotherapie palliativ, 6) Stentimplantation palliativ, 7) palliative OP 8) Immuntherapie (Pembrolizumab, Nivolumab, Tislelizumab, Cambrelizumab..)
C: Die jeweils anderen Verfahren
O: Patientenrelevante Endpunkte: Lebensqualität (QoL), Nutzen, Schaden (Therapienebenwirkungen/Toxizität), Perforation, Blutung, Todesfall), Remissionsrate, Progressionsfreies Überleben, symptomfreies Überleben (symptomfree survival) (time without signs and symptoms), Gesamtüberlebensrate/ Überlebenszeit, Speziell für 6) Stentimplantation zusätzlich: Dysphagiefreies Überleben ohne Stentverschluss, Dysphagieminderung

Recherche in PubMed (03.02.2022)

| Nr. | Suchbegriff | Treffer |
|---|---|---|
| #1 | **Neoplasms[MeSH]** OR neoplasm*[tiab] OR carcinom*[tiab] OR adenocarcinom*[tiab] OR adeno-carcinom*[tiab] OR adenom*[tiab] OR malignan*[tiab] OR cancer[tiab] OR tumor[tiab] OR tumour[tiab] | 4.668.309 |
| #2 | **Esophagus[MeSH]** OR esophag*[tiab] OR oesophag*[tiab] OR gastro-esophag*[tiab] OR gastroesophag*[tiab] OR gastro-oesophag*[tiab] OR gastrooesophag*[tiab] OR **Cardia[MeSH]** OR cardia[tiab] | 212.781 |
| #3 | #1 AND #2 | 93.069 |
| #4 | **Esophageal Neoplasms[Mesh]** OR Esophageal Neoplasm[tiab] OR Neoplasm, Esophageal[tiab] OR Esophagus Neoplasm[tiab] OR Esophagus Neoplasms[tiab] OR Neoplasm, Esophagus[tiab] OR Neoplasms, Esophagus[tiab] OR Neoplasms, Esophageal[tiab] OR Cancer of Esophagus[tiab] OR Cancer of the Esophagus[tiab] OR Esophagus Cancer[tiab] OR Cancer, Esophagus[tiab] OR Cancers, Esophagus[tiab] OR Esophagus Cancers[tiab] OR Esophageal Cancer[tiab] OR Cancer, Esophageal[tiab] OR Cancers, Esophageal[tiab] OR Esophageal Cancers[tiab] | 61.768 |
| #5 | #3 OR #4 | 97.395 |

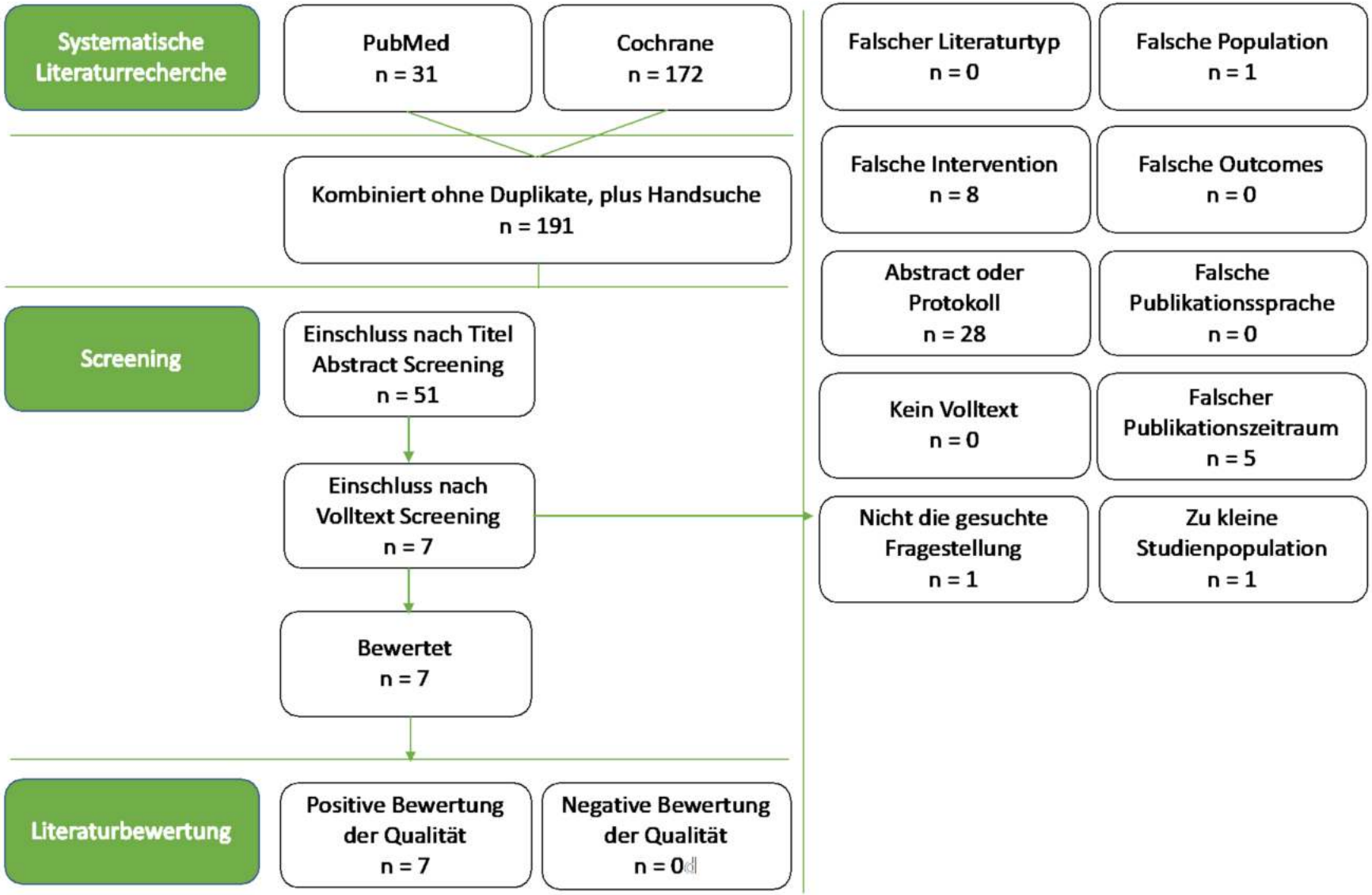
| | | |
|---|---|---|
| #6 | "Palliative Care"[Mesh] OR Palliat*[tiab] OR chemotherap*[tiab] OR chemo therap*[tiab] OR "Radiotherapy"[Mesh] OR radiotherap*[tiab] OR radiation therapy[tiab] OR "Immunotherapy"[Mesh] OR Immunotherap*[tiab] OR immune therapy[tiab] OR checkpoint[tiab] OR check point[tiab] OR **"Radiation"[Mesh]** OR radiation[tiab] OR HER2[tiab] OR HER-2[tiab] OR HER2/neu[tiab] OR HER-2neu[tiab] OR Neu, neu[tiab] OR neu neu[tiab] OR **"Trastuzumab"[Mesh]** OR Trastuzumab beta[tiab] OR beta, Trastuzumab[tiab] OR Herceptin[tiab] OR Trazimera[tiab] OR Trastuzumab-qyyp[tiab] OR Trastuzumab qyyp[tiab] | 1.792.915 |
| #7 | first line[tiab] OR firstline[tiab] OR first-line[tiab] OR 1st line[tiab] OR 1(st)line[tiab] OR naive[tiab] | 189.606 |
| #8 | #5 AND #6 AND #7 | 178 |
| #9 | cohort studies[mesh:noexp] OR longitudinal studies[mesh:noexp] OR follow-up studies[mesh:noexp] OR prospective studies[mesh:noexp] OR cohort[tiab] OR longitudinal[tiab] OR prospective[tiab] | 2.253.143 |
| #10 | "Clinical Trial" [PT:NoExp] OR "clinical trial, phase i"[pt] OR "clinical trial, phase ii"[pt] OR "clinical trial, phase iii"[pt] OR "clinical trial, phase iv"[pt] OR "controlled clinical trial"[pt] OR "multicenter study"[pt] OR "randomized controlled trial"[pt] OR "Clinical Trials as Topic"[mesh:noexp] OR "clinical trials, phase i as topic"[MeSH Terms:noexp] OR "clinical trials, phase ii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iv as topic"[MeSH Terms:noexp] OR "controlled clinical trials as topic"[MeSH Terms:noexp] OR "randomized controlled trials as topic"[MeSH Terms:noexp] OR "early termination of clinical trials"[MeSH Terms:noexp] OR "multicenter studies as topic"[MeSH Terms:noexp] OR “Double-Blind Method”[Mesh] OR ((randomised[tiab] OR randomized[tiab]) AND (trial[tiab] OR trials[tiab])) OR ((single[tiab] OR double[tiab] OR doubled[tiab] OR triple[tiab] OR tripled[tiab] OR treble[tiab] OR treble[tiab]) AND (blind*[tiab] OR mask*[tiab])) OR ("4 arm"[tiab] OR "four arm"[tiab]) | 1.616.176 |
| #11 | #9 OR #10 | 3.443.068 |
| #12 | animals[mh] NOT humans[mh] | 4.953.882 |
| #13 | #11 NOT #12 | 3.366.554 |
| #14 | #8 AND #13 | 123 |
| #15 | **#14 Publication date from 09/2019 until date of search, English, German** | 31 |

Recherche in der Cochrane Library (02.03.2022)

| ID | Search | Treffer |
|---|---|---|

| | | |
|---|---|---|
| #1 | MeSH descriptor: [Neoplasms] explode all trees | 86823 |
| #2 | (neoplasm* OR carcinom* OR adenocarcinom* OR adeno-carcinom* OR adenom* OR malignan* OR cancer OR tumor OR tumour):ti,ab,kw | 237744 |
| #3 | #1 OR #2 | 247514 |
| #4 | MeSH descriptor: [Esophagus] explode all trees | 1379 |
| #5 | MeSH descriptor: [Cardia] explode all trees | 53 |
| #6 | (esophag* OR oesophag* OR gastro-esophag* OR gastroesophag* OR gastro-oesophag* OR gastrooesophag* OR cardia):ti,ab,kw | 21478 |
| #7 | #4 OR #5 OR #6 | 21478 |
| #8 | #3 AND #7 | 8594 |
| #9 | MeSH descriptor: [Esophageal Neoplasms] explode all trees | 1766 |
| #10 | (Esophageal Neoplasm OR Neoplasm, Esophageal OR Esophagus Neoplasm OR Esophagus Neoplasms OR Neoplasm, Esophagus OR Neoplasms, Esophagus OR Neoplasms, Esophageal OR Cancer of Esophagus OR Cancer of the Esophagus OR Esophagus Cancer OR Cancer, Esophagus OR Cancers, Esophagus OR Esophagus Cancers OR Esophageal Cancer OR Cancer, Esophageal OR Cancers, Esophageal OR Esophageal Cancers):ti,ab,kw | 5660 |
| #11 | #9 OR #10 | 5687 |
| #12 | #8 OR #11 | 8601 |
| #13 | ( Palliative Care OR Palliat* OR chemotherap* OR chemo therap* OR Radiotherapy OR radiotherap* OR radiation therapy OR Immunotherapy OR Immunotherap* OR immune therapy OR checkpoint OR check point OR Radiation OR radiation OR HER2 OR HER-2 OR HER2/neu OR HER-2neu OR Neu, neu OR neu neu OR Trastuzumab OR beta, Trastuzumab OR Herceptin OR Trazimera OR Trastuzumab-qyyp OR Trastuzumab qyyp):ti,ab,kw | 148355 |
| #14 | MeSH descriptor: [Palliative Care] explode all trees | 1748 |
| #15 | MeSH descriptor: [Radiotherapy] explode all trees | 6545 |
| #16 | MeSH descriptor: [Radiation] explode all trees | 5920 |
| #17 | MeSH descriptor: [Immunotherapy] explode all trees | 8560 |
| #18 | MeSH descriptor: [Trastuzumab] explode all trees | 824 |
| #19 | #13 OR #14 OR #15 OR #16 OR #17 OR #18 | 155976 |
| #20 | (first line OR firstline OR first-line OR 1st line OR 1(st)line OR naive):ti,ab,kw | 47476 |
| #21 | #12 AND #19 AND #20 | 559 |
| #22 | #21 with Publication Year from 2019 to 2022, in Trials | 213 |
| #23 | #22 NOT (CT.gov OR ICTRP) | 172 |

## Recherche 11



## 2.12 Recherche 12

| **12.1 Stellenwert der Zweitlinienchemotherapie (PICO s.o.)** |
|---|
| P: Patienten im Stadium IV und mit lokoregionär fortgeschrittenen, primär inoperablen Plattenepithel- und Adenokarzinomen des Ösophagus und Adenokarzinomen des gastroösophagealen Übergangs 1-3<br>I: 1) palliative Chemotherapie, 2) Zweitlinienchemo therapie palliativ , 3) Radiotherapie palliativ, 4) Brachytherapie palliativ, 5) Radiochemotherapie palliativ, 6) Stentimplantation palliativ, 7) palliative OP 8) Immuntherapie (Pembrolizumab, Nivolumab, Tislelizumab, Cambrelizumab..)<br>C: Die jeweils anderen Verfahren<br>O: Patientenrelevante Endpunkte: Lebensqualität (QoL), Nutzen, Schaden (Therapienebenwirkungen/Toxizität), Perforation, Blutung, Todesfall), Remissionsrate, Progressionsfreies Überleben, symptomfreies Überleben (symptomfree survival) (time without signs and symptoms), Gesamtüberlebensrate/ Überlebenszeit, Speziell für 6) Stentimplantation zusätzlich: Dysphagiefreies Überleben ohne Stentverschluss, Dysphagieminderung |

| **12.2 Stellenwert der Immuntherapie - Zweitlinie (PICO s.o.)** |
|---|
| P: Patienten im Stadium IV und mit lokoregionär fortgeschrittenen, primär inoperablen Plattenepithel- und Adenokarzinomen des Ösophagus und Adenokarzinomen des gastroösophagealen Übergangs 1-3<br>I: 1) palliative Chemotherapie, 2) Zweitlinienchemo therapie palliativ , 3) Radiotherapie palliativ, 4) Brachytherapie palliativ, 5) Radiochemotherapie palliativ, 6) Stentimplantation palliativ, 7) palliative OP 8) Immuntherapie (Pembrolizumab, Nivolumab, Tislelizumab, Cambrelizumab..)<br>C: Die jeweils anderen Verfahren<br>O: Patientenrelevante Endpunkte: Lebensqualität (QoL), Nutzen, Schaden (Therapienebenwirkungen/Toxizität), Perforation, Blutung, Todesfall), Remissionsrate, Progressionsfreies Überleben, symptomfreies Überleben (symptomfree survival) (time without signs and symptoms), Gesamtüberlebensrate/ Überlebenszeit, Speziell für 6) Stentimplantation zusätzlich: Dysphagiefreies Überleben ohne Stentverschluss, Dysphagieminderung |

| **12.3 Stellenwert HER2- gerichteter Therapieansätze nach Versagen der Erstlinie (in Kombination mit Chemo/Immuntherapie)** |
|---|
| P: Patienten im Stadium IV und mit lokoregionär fortgeschrittenen, primär inoperablen Plattenepithel- und Adenokarzinomen des Ösophagus und Adenokarzinomen des gastroösophagealen Übergangs 1-3<br>I: 1) palliative Chemotherapie, 2) Zweitlinienchemo therapie palliativ , 3) Radiotherapie palliativ, 4) Brachytherapie palliativ, 5) Radiochemotherapie palliativ, 6) Stentimplantation palliativ, 7) palliative OP 8) Immuntherapie (Pembrolizumab, |

| |
|---|
| Nivolumab, Tislelizumab, Cambrelizumab..)<br>C: Die jeweils anderen Verfahren<br>O: Patientenrelevante Endpunkte: Lebensqualität (QoL), Nutzen, Schaden (Therapienebenwirkungen/Toxizität), Perforation, Blutung, Todesfall), Remissionsrate, Progressionsfreies Überleben, symptomfreies Überleben (symptomfree survival) (time without signs and symptoms), Gesamtüberlebensrate/ Überlebenszeit, Speziell für 6) Stentimplantation zusätzlich: Dysphagiefreies Überleben ohne Stentverschluss, Dysphagieminderung |

Recherche in PubMed (03.02.2022)

| Nr. | Suchbegriff | Treffer |
|---|---|---|
| #1 | **Neoplasms[MeSH]** OR neoplasm*[tiab] OR carcinom*[tiab] OR adenocarcinom*[tiab] OR adeno-carcinom*[tiab] OR adenom*[tiab] OR malignan*[tiab] OR cancer[tiab] OR tumor[tiab] OR tumour[tiab] | 4.668.309 |
| #2 | **Esophagus[MeSH]** OR esophag*[tiab] OR oesophag*[tiab] OR gastro-esophag*[tiab] OR gastroesophag*[tiab] OR gastro-oesophag*[tiab] OR gastrooesophag*[tiab] OR **Cardia[MeSH]** OR cardia[tiab] | 212.781 |
| #3 | #1 AND #2 | 93.069 |
| #4 | **Esophageal Neoplasms[Mesh]** OR Esophageal Neoplasm[tiab] OR Neoplasm, Esophageal[tiab] OR Esophagus Neoplasm[tiab] OR Esophagus Neoplasms[tiab] OR Neoplasm, Esophagus[tiab] OR Neoplasms, Esophagus[tiab] OR Neoplasms, Esophageal[tiab] OR Cancer of Esophagus[tiab] OR Cancer of the Esophagus[tiab] OR Esophagus Cancer[tiab] OR Cancer, Esophagus[tiab] OR Cancers, Esophagus[tiab] OR Esophagus Cancers[tiab] OR Esophageal Cancer[tiab] OR Cancer, Esophageal[tiab] OR Cancers, Esophageal[tiab] OR Esophageal Cancers[tiab] | 61.768 |
| #5 | #3 OR #4 | 97.395 |
| #6 | "Palliative Care"[Mesh] OR Palliat*[tiab] OR chemotherap*[tiab] OR chemo therap*[tiab] OR "Radiotherapy"[Mesh] OR radiotherap*[tiab] OR radiation therapy[tiab] OR "Immunotherapy"[Mesh] OR Immunotherap*[tiab] OR immune therapy[tiab] OR checkpoint[tiab] OR check point[tiab] OR **"Radiation"[Mesh]** OR radiation[tiab] OR HER2[tiab] OR HER-2[tiab] OR HER2/neu[tiab] OR HER-2neu[tiab] OR Neu, neu[tiab] OR neu neu[tiab] OR "Trastuzumab"[Mesh] OR Trastuzumab beta[tiab] OR beta, Trastuzumab[tiab] OR Herceptin[tiab] OR Trazimera[tiab] OR Trastuzumab-qyyp[tiab] OR Trastuzumab qyyp[tiab] | 1.792.915 |
| #7 | second line[tiab] OR secondline[tiab] OR second-line[tiab] OR 2nd line[tiab] OR 2(nd)line[tiab] OR refractor*[tiab] | 171.700 |

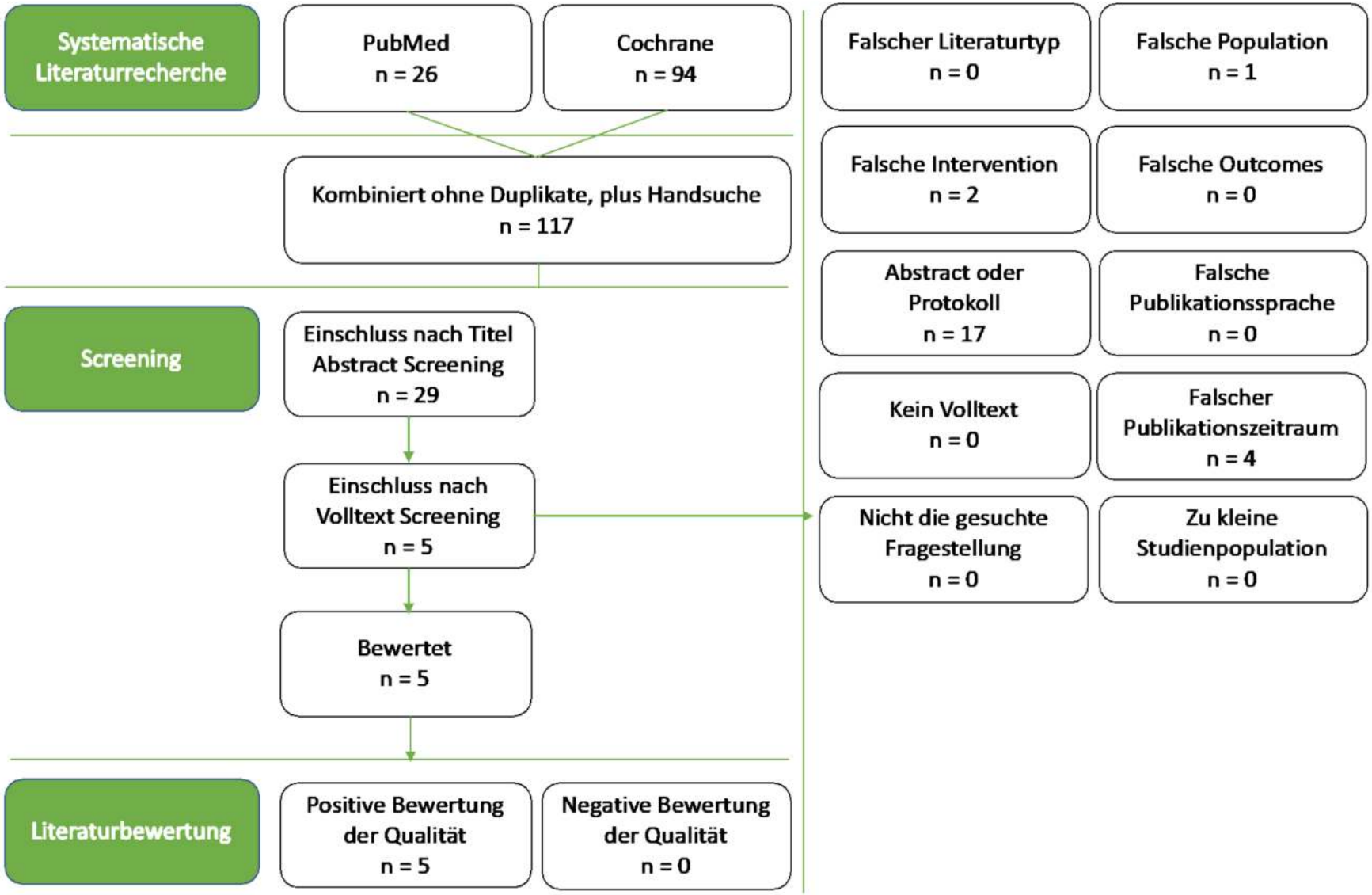
| | | |
|---|---|---|
| #8 | #5 AND #6 AND #7 | 287 |
| #9 | cohort studies[mesh:noexp] OR longitudinal studies[mesh:noexp] OR follow-up studies[mesh:noexp] OR prospective studies[mesh:noexp] OR cohort[tiab] OR longitudinal[tiab] OR prospective[tiab] | 2.253.143 |
| #10 | "Clinical Trial" [PT:NoExp] OR "clinical trial, phase i"[pt] OR "clinical trial, phase ii"[pt] OR "clinical trial, phase iii"[pt] OR "clinical trial, phase iv"[pt] OR "controlled clinical trial"[pt] OR "multicenter study"[pt] OR "randomized controlled trial"[pt] OR "Clinical Trials as Topic"[mesh:noexp] OR "clinical trials, phase i as topic"[MeSH Terms:noexp] OR "clinical trials, phase ii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iv as topic"[MeSH Terms:noexp] OR "controlled clinical trials as topic"[MeSH Terms:noexp] OR "randomized controlled trials as topic"[MeSH Terms:noexp] OR "early termination of clinical trials"[MeSH Terms:noexp] OR "multicenter studies as topic"[MeSH Terms:noexp] OR “Double-Blind Method”[Mesh] OR ((randomised[tiab] OR randomized[tiab]) AND (trial[tiab] OR trials[tiab])) OR ((single[tiab] OR double[tiab] OR doubled[tiab] OR triple[tiab] OR tripled[tiab] OR treble[tiab] OR treble[tiab]) AND (blind*[tiab] OR mask*[tiab])) OR ("4 arm"[tiab] OR "four arm"[tiab]) | 1.616.176 |
| #11 | #9 OR #10 | 3.443.068 |
| #12 | animals[mh] NOT humans[mh] | 4.953.882 |
| #13 | #11 NOT #12 | 3.366.554 |
| #14 | #11 AND #13 | 104 |
| #15 | **#14 Publication date from 09/2019 until date of search, English, German** | 26 |

Recherche in der Cochrane Library (02.03.2022)

| ID | Search | Treffer |
|---|---|---|
| #1 | MeSH descriptor: [Neoplasms] explode all trees | 86823 |
| #2 | (neoplasm* OR carcinom* OR adenocarcinom* OR adeno-carcinom* OR adenom* OR malignan* OR cancer OR tumor OR tumour):ti,ab,kw | 237744 |
| #3 | #1 OR #2 | 247514 |
| #4 | MeSH descriptor: [Esophagus] explode all trees | 1379 |
| #5 | MeSH descriptor: [Cardia] explode all trees | 53 |
| #6 | (esophag* OR oesophag* OR gastro-esophag* OR gastroesophag* OR gastro-oesophag* OR gastrooesophag* OR cardia):ti,ab,kw | 21478 |
| #7 | #4 OR #5 OR #6 | 21478 |
| #8 | #3 AND #7 | 8594 |
| #9 | MeSH descriptor: [Esophageal Neoplasms] explode all trees | 1766 |

| | | |
|---|---|---|
| #10 | (Esophageal Neoplasm OR Neoplasm, Esophageal OR Esophagus Neoplasm OR Esophagus Neoplasms OR Neoplasm, Esophagus OR Neoplasms, Esophagus OR Neoplasms, Esophageal OR Cancer of Esophagus OR Cancer of the Esophagus OR Esophagus Cancer OR Cancer, Esophagus OR Cancers, Esophagus OR Esophagus Cancers OR Esophageal Cancer OR Cancer, Esophageal OR Cancers, Esophageal OR Esophageal Cancers):ti,ab,kw | 5660 |
| #11 | #9 OR #10 | 5687 |
| #12 | #8 OR #11 | 8601 |
| #13 | ( Palliative Care OR Palliat* OR chemotherap* OR chemo therap* OR Radiotherapy OR radiotherap* OR radiation therapy OR Immunotherapy OR Immunotherap* OR immune therapy OR checkpoint OR check point OR Radiation OR radiation OR HER2 OR HER-2 OR HER2/neu OR HER-2neu OR Neu, neu OR neu neu OR Trastuzumab OR beta, Trastuzumab OR Herceptin OR Trazimera OR Trastuzumab-qyyp OR Trastuzumab qyyp):ti,ab,kw | 148355 |
| #14 | MeSH descriptor: [Palliative Care] explode all trees | 1748 |
| #15 | MeSH descriptor: [Radiotherapy] explode all trees | 6545 |
| #16 | MeSH descriptor: [Radiation] explode all trees | 5920 |
| #17 | MeSH descriptor: [Immunotherapy] explode all trees | 8560 |
| #18 | MeSH descriptor: [Trastuzumab] explode all trees | 824 |
| #19 | #13 OR #14 OR #15 OR #16 OR #17 OR #18 | 155976 |
| #20 | (second line OR secondline OR second-line OR 2nd line OR 2(nd)line OR refractor*):ti,ab,kw | 30192 |
| #21 | #12 AND #19 AND #20 | 305 |
| #22 | #21 with Publication Year from 2019 to 2022, in Trials | 114 |
| #23 | #22 NOT (CT.gov OR ICTRP) | 94 |

## Recherche 12



# 3 Evidenztabellen

## 3.1 Schlüsselfrage 1: Indikationen für EMR ESD RFA Ablation

**Schlüsselfrage:**

**01 Indikationen für EMR / ESD / RFA Ablation**
P: Pat mit Dysplasie, ESCC, AEG 1-3 (jeweils Mukosa und Submukosa)
I: EMR (endoskopischen Mukosaresektion)/ ESD (endoskopische Submukosadissektion) RFA (radio frequenzablation
C: konventionelle operative Verfahren
O: Patientenrelevante Endpunkte: Gesamtüberlebensrate, Überlebensrate nach 5 Jahren und 3 Jahren (ggfls. „Ableitung“ aus Überlebenskurven, wenn nicht im Text berichtet), medianes Überleben, Letalität, Rate an Lokalrezidiven im Beobachtungszeitraum, Fernmetastasen, Häufigkeit von Eingriffskomplikationen, (Perforation, Blutung, Striktur) Morbidität, LQ, QoL

***Inhalt:*** *3 Literaturstellen*

| Literaturstelle | Evidenzlevel | Studientyp |
|---|---|---|
| Dunn, J. M. 2021 | 3 | Retrospective cohort study |
| Gong, L. 2019 | 3 | retrospective study |
| Lee, H. D. 2020 | 3 | A Propensity Score-Matched Survival Analysis |

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

| **Dunn, J. M. et al. Transition from esophagectomy to endoscopic therapy for early esophageal cancer. Dis Esophagus. . . 2021** | | | |
|---|---|---|---|
| **Evidence level** | **Methodical Notes** | **Patient characteristics** | **Interventions** |
| **Evidence level:** 3<br>**Study type:** Retrospective cohort study | **Funding sources:**<br>**Conflict of Interests:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout rates:** | **Total no. patients:** 269<br>**Recruiting Phase:** 2000 till 2018<br>**Inclusion criteria:** e patients who had an EMR or an esophagectomy for HGD or EEC<br>**Exclusion criteria:** | **Interventions:** endoscopic eradication therapy<br><br>**Comparison:** esophagectomy |
| **Notes:** | Newcastle-Ottawa Scale (NOS) for Cohort studies: 8/9 stars<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment harms): 3 (Non-randomized controlled cohort / follow up study).<br>**Author's conclusion:** This series of patients treated during a transition period from surgery to EET, demonstrates a primary endoscopic approach does not compromise oncological outcomes with the benefit of fewer complications, shorter hospital stays, and lower costs compared to surgery. It should be available as the gold standard treatment for patients with early esophageal cancer. Those with adverse prognostic features may still benefit from esophagectomy. | | |
| **Outcome Measures/results** | **Primary** all-cause and disease-specific mortality assessed by multivariable Cox regression and a propensity score matching sub analysis, providing hazard ratios (HR) with 95% confidence intervals | **Results:** : Among 269 patients, 133 underwent esophagectomy and 136 received EET. Adjusted survival analysis showed no difference between groups regarding all-cause mortality (HR 1.85, 95% CI 0.73, 4.72) and disease-specific mortality (HR 1.10, 95% CI 0.26, 4.65). In-hospital and 30-day mortality was 0% in both groups. The surgical group had a | |

| | | |
|---|---|---|
| | (CI) adjusted for age, tumor grade (G1/2 vs. G3), tumor stage, and lymphovascular invasion<br>**Secondary** tumor recurrence, post procedure complications, hospital stay, and overall cost | significantly higher rate of complications (Clavien–Dindo ≥3 26.3% vs. endoscopic therapy 0.74%), longer in-patient stay (median 14 vs. 0 days endoscopic therapy) and higher hospital costs(£16 360 vs. £8786 per patient). |

**Gong, L. et al. Comparison of the therapeutic effects of endoscopic submucosal dissection and minimally invasive esophagectomy for T1 stage esophageal carcinoma. Thorac Cancer. 10. 2161-2167. 2019**

| Evidence level | Methodical Notes | Patient characteristics | Interventions |
|---|---|---|---|
| **Evidence level:** 3<br>**Study type:** retrospective study | **Funding sources:**<br>**Conflict of Interests:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout rates:** | **Total no. patients:** 206<br>**Recruiting Phase:** January2015 and December 2018<br>**Inclusion criteria:** Patients with stage T0, T1a, and T1b ESCC<br>**Exclusion criteria:** | **Interventions:** endoscopic submucosal dissection for T1 stage esophageal carcinoma<br><br>**Comparison:** minimally invasive esophagectomy for T1 stage esophageal carcinoma |
| **Notes:** | Newcastle-Ottawa Scale (NOS) for Cohort studies: 7/9 stars<br>Unclear confounder adjustment<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 3 (Cohort study / Non-randomized controlled cohort)<br>**Author's conclusion:** For early-stage cases, lymph node metastasis and positive margins are risk factors affecting long-term survival. Efficient predictive factors mentioned in our study would provide a proper indication for treatment strategy selection. | | |

| | | |
|---|---|---|
| **Outcome Measures/results** | **Primary** predictors for lymph node metastasis<br>**Secondary** | **Results:** In the ESD group, 76.92% of the patients were stage T1a, while 34.38% in the MIE group were stage T1a. The lymph node metastasis rate was 16.41% in the MIE group (6.98% in T1a stage), which related to tumor differentiation, tumor length (≥37.5 mm), depth of invasion, and angiolymphatic invasion. However, the R0 resection rate was only 73.08% in the ESD group. Comprehensive analysis of all T1 patients in the two groups revealed that the positive margin was related to tumor differentiation, tumor width (≥13.5 mm), and depth of invasion (≥3.25 mm). |

**Lee, H. D. et al. Endoscopic Submucosal Dissection Versus Surgery for Superficial Esophageal Squamous Cell Carcinoma: A Propensity Score-Matched Survival Analysis. Clin Transl Gastroenterol. 11. e00193. 2020**

| Evidence level | Methodical Notes | Patient characteristics | Interventions |
|---|---|---|---|
| **Evidence level:** 3<br>**Study type:** A Propensity Score-Matched Survival Analysis | **Funding sources:**<br>**Conflict of Interests:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout rates:** | **Total no. patients:** 184<br>**Recruiting Phase:** January 2011 to December 2017<br>**Inclusion criteria:** (i) patients who were pathologically staged N0 (pN0) and clinically staged M0 (cM0) for the surgery group and (ii) patients who were clinically staged N0M0 (cN0M0) for the ESD group<br>**Exclusion criteria:** : (i) patients with previous treatment history of malignancy within 5 years, (ii) patients with second primary malignancy, (iii) patients with neoadjuvant therapy (neoadjuvant chemotherapy or radiation therapy), and (iv) patients who underwent endoscopic treatment for previous esophageal neoplasm | **Interventions:** surgery of superficial esophageal squamous cell carcinoma<br><br>**Comparison:** Endoscopic submucosal dissection of superficial esophageal squamous cell carcinoma |

| | | |
|---|---|---|
| **Notes:** | Newcastle-Ottawa Scale (NOS) for Cohort studies: 8/9 stars<br>Unclear number of patients lost to follow-up<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 3 (Cohort study / Non-randomized controlled cohort).<br>**Author's conclusion:** Long-term outcomes of ESD are comparable with surgical outcomes in patients with SESCC. ESD is related to lower early major complication rates and shorter hospital stay. Thus, ESD is a better treatment option for SESCC than radical surgery. | |
| **Outcome Measures/results** | **Primary** overall survival (OS), recurrence-free survival<br>**Secondary** complication rates | **Results:** In the matching study, the ESD group (n 5 34) showed comparable survival outcomes with the surgery group (n 5 34). The 5-year OS rates were 89.4% vs 87.8% for the ESD and the surgery groups, respectively; similarly, the 5-year recurrence-free survival rates were 90.9% and 91.6%, respectively. The<br>ESD group showed a lower early major complication rate (2.9% [1 of 34] vs 23.5% [8 of 34], P < 0.001) and shorter hospital stay (median, 3.0 days vs 16.5 days, P < 0.001) than the surgery group. In the tumor in situ (Tis)-subgroup, ESD showed better OS than esophagectomy (P 5 0.030). Between-group comparisons of survival outcomes in the T1a and T1b subgroups revealed no significant differences. |

## 3.2 Schlüsselfrage 3.1: Art des operativen Zugangs

**Schlüsselfrage:**

**03.1 Art des operativen Zugangs**
P: 1) Pat. mit gesichertem Plattenepithel- oder Adenokarzinom des Ösophagus in Abhängigkeit von der Tumorhöhe (zervikal, thorakal suprabifurkal, thorakalinfrabifurkal, abdominell bzw. nur supra-/infrabifurkal) 2)bzw. Pat. mit gesichertem AEG 1-3
I: offen-thorakal / offen-abdominalzervikal / offen-abdominaltranshiatal
C: Standard: offenabdominothora rakal/thorakoabdominal
O: Patientenrelevante Endpunkte: Gesamtüberlebensrate, Überlebensrate nach 5 Jahren und 3 Jahren (ggfls. „Ableitung“ aus Überlebenskurven, wenn nicht im Text berichtet), medianes ÜL, Morbidität, LQ, 30 Tage Hospitalletalität, Rate an Lokalrezidiven im Beobachtungszeitraum, Fernmetastasierung, Häufigkeit der Komplikationen (v.a. pulmonal)

***Inhalt:*** *4 Literaturstellen*

| Literaturstelle | Evidenzlevel | Studientyp |
|---|---|---|
| De Pasqual, C. A. 2021 | 3 | a multicenter retrospective cohort study |
| Mertens, A. C. 2021 | 3 | A Nationwide Propensity Score-Matched Cohort Analysis |
| Mine, S. 2021 | 4 | Prospective nationwide multicenter study |
| Verstegen, M. H. P. 2021 | 3 | A Nationwide Cohort Study |

***NEWCASTLE - OTTAWA Checklist: Cohort:*** *4 Bewertung(en)*

| **De Pasqual, C. A. et al. Transthoracic esophagectomy compared to transhiatal extended gastrectomy for adenocarcinoma of the esophagogastric junction: a multicenter retrospective cohort study. Dis Esophagus. . . 2021** | | | |
|---|---|---|---|
| **Evidence level** | **Methodical Notes** | **Patient characteristics** | **Interventions** |
| **Evidence level:** 3<br>**Study type:** a multicenter retrospective cohort study | **Funding sources:**<br>**Conflict of Interests:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout rates:** | **Total no. patients:** 159<br>**Recruiting Phase:** 2014 till 2019<br>**Inclusion criteria:** patients with EGJ adenocarcinoma Siewert type II (tumor epicenter within 1 proximal and 2 cm distal of the Z line) submitted to either TTE or TEG with curative intent<br>**Exclusion criteria:** obstructive lesions in which a complete description of tumor length was not provided | **Interventions:** Transthoracic esophagectomy for adenocarcinoma of the esophagogastric junction<br><br>**Comparison:** transhiatal extended gastrectomy for adenocarcinoma of the esophagogastric junction |
| **Notes:** | Newcastle-Ottawa Scale (NOS) for Cohort studies: 8/9 stars<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits/harms): 3 (Cohort study / Non-randomized controlled cohort).<br><br>**Author's conclusion:** Siewert type II tumors can be treated with TEG or TTE, provided that an appropriate patient selection is performed. Even so, TEG exposes the patient to an increased risk of a positive proximal resection margin. | | |

| | | |
|---|---|---|
| **Outcome Measures/results** | **Primary** compare the surgical and oncological outcomes of TTE and total extended gastrectomy in patients with Siewert type II tumors<br>**Secondary** | **Results:** Post-operative morbidity was comparable (P = 0.88), while 90-day mortality was higher after TEG (90-day mortality 10.0% in TEG group vs. 2.0% in TTE group P = 0.01). R0 resection was achieved in 83.3% of patients after TEG and in 97.9% after TTE (P < 0.01), with the proximal resection margin involved in 16.6% of patients after TEG versus 0 in TTE group (P < 0.01). The 3-year overall survival was comparable (TEG: 36.5%, TTE: 48.4%, P = 0.12). At multivariable analysis, (y)pT category was an independent risk factor for 3-year recurrence. After matching, TEG was still associated with an increased risk of incomplete tumor resection (P = 0.03) and proximal margin involvement (P < 0.01), while there were no differences in postoperative morbidity (P = 0.56) and mortality (P = 0.31). |

**Mertens, A. C. et al. Transthoracic Versus Transhiatal Esophagectomy for Esophageal Cancer: A Nationwide Propensity Score-Matched Cohort Analysis. Ann Surg Oncol. 28. 175-183. 2021**

| Evidence level | Methodical Notes | Patient characteristics | Interventions |
|---|---|---|---|
| **Evidence level:** 3<br>**Study type:** A Nationwide Propensity Score-Matched Cohort Analysis | **Funding sources:**<br>**Conflict of Interests:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout rates:** | **Total no. patients:** After propensity score matching, 1532 of 4143 patients were included for analysis.<br>**Recruiting Phase:** 2011 to 2016<br>**Inclusion criteria:** All patients undergoing surgery with curative intent for mid to distal esophageal or junction carcinoma (cT1-4aN0-3M0), including cTxNx, from 2011 through 2016 were retrieved from the database. Patients undergoing a three-stage McKeown (cervical anastomosis), a two-stage Ivor Lewis (thoracic anastomosis), or a transhiatal (cervical | **Interventions:** Transthoracic Esophagectomy for Esophageal Cancer<br><br>**Comparison:** Transhiatal Esophagectomy for Esophageal Cancer |

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| | | anastomosis) procedure with gastric tube reconstruction were included.<br>**Exclusion criteria:** Patients with missing baseline data and patients undergoing emergency surgery were excluded. Patients undergoing a hybrid resection were excluded due to the heterogeneity of this group; there was no possibility to discern between a laparoscopy combined with a thoracotomy or a laparotomy combined with thoracoscopy. | |
| **Notes:** | Newcastle-Ottawa Scale (NOS) for Cohort studies: 7/9 stars<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 3 (Cohort study / Non-randomized controlled cohort).<br>**Author's conclusion:** Our analysis showed that, even after correction for baseline characteristics, a transthoracic approach provides a higher lymph node yield, at the cost of increased morbidity and short-term mortality. The lower lymph node yield after a transhiatal resection could indicate positive lymph nodes left in situ. Although results in high-volume centers and RCTs often are superior, these data reflect the national performance. We believe future research should investigate further whether long-term survival differs between a transthoracic and transhiatal resection in the era of (neo)adjuvant therapy, minimally invasive surgery, and increasingly centralized care. | | |
| **Outcome Measures/results** | **Primary**<br>**Secondary** | **Results:** After propensity score matching, 1532 of 4143 patients were included for analysis. The transthoracic approach yielded more lymph nodes (transthoracic median 19, transhiatal median 14; $p < 0.001$). There was no difference in the number of positive lymph nodes, however, the median (y)pN-stage was higher in the transthoracic group ($p = 0.044$). The transthoracic group experienced more chyle leakage (9.7% vs. 2.7%, $p < 0.001$), more pulmonary complications (35.5% vs. 26.1%, $p < 0.001$), and more cardiac complications (15.4% vs. 10.3%, $p = 0.003$). The transthoracic group required a longer hospital stay (median 14 vs. 11 days, $p < 0.001$), ICU stay | |

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| | | (median 3 vs. 1 day, p < 0.001), and had a higher 30-day/in-hospital mortality rate (4.0% vs. 1.7%, p = 0.009). |

**Mine, S. et al. Postoperative complications after a transthoracic esophagectomy or a transhiatal gastrectomy in patients with esophagogastric junctional cancers: a prospective nationwide multicenter study. Gastric Cancer. . . 2021**

| Evidence level | Methodical Notes | Patient characteristics | Interventions |
|---|---|---|---|
| **Evidence level:** 4<br>**Study type:** Prospective nationwide multicenter study | **Funding sources:**<br>**Conflict of Interests:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout rates:** | **Total no. patients:** 345<br>**Recruiting Phase:** April 2014 to September 2017<br>**Inclusion criteria:** (1) tumor epicenter located within 2.0 cm of the EGJ; (2) histologically proven adenocarcinoma, squamous cell carcinoma (SCC), or adenosquamous carcinoma; (3) cT2–T4; (4) tumor deemed to be resectable; (5) patient age≥20 years; (6) Eastern Cooperative Oncology Group performance status of 0, 1, or 2; (7) no prior history of gastrectomy; (8) adequate organ function; and (9) provision of written informed consent. The location of the EGJ was defned as the lower margin of palisading small vessels on endoscopy according to the Japanese Classifcation of Esophageal Cancer (11th edition)<br>**Exclusion criteria:** In addition, the patients who could not undergo the surgical treatment specifed in the protocol were excluded from this study regarding postoperative complications | **Interventions:** Postoperative complications after transthoracic esophagectomy in patients with esophagogastric junctional cancers<br><br>**Comparison:** Postoperative complications after transhiatal gastrectomy in patients with esophagogastric junctional cancers |

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| **Notes:** | Newcastle-Ottawa Scale (NOS) for Cohort studies: 5/9 stars<br>Downgrade due to 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain.<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 3 (Cohort study / Non-randomized controlled cohort).<br>Downgrade to evidence level 4 due to high risk of bias.<br>**Author's conclusion:** For patients with EGJ cancers, both transhiatal gastrectomy and transthoracic esophagectomy could be performed safely even when lymphadenectomy around the left renal vein area was performed. However, over 30% of the patients in our cohort had postoperative but non-fatal complications (≥Grade II). Male sex and a longer esophageal invasion in the transhiatal gastrectomy group, as well as a high BMI in the transthoracic esophagectomy group were signifcantly correlated with postoperative complications. Of all complications, anastomotic leakages were the most common and were observed more frequently than expected. Therefore, we should perform anastomoses with utmost care in obese patients undergoing transthoracic esophagectomy, and in patients with larger tumors undergoing transhiatal gastrectomy. In addition, a transhiatal esophagojejunostomy should be performed very carefully because leakage from the anastomosis can lead to a critical condition. | |
| **Outcome Measures/results** | **Primary** incidence of nodal metastasis in each nodal station for EGJ cancers<br>**Secondary** R0 resection rate, survival, postoperative complications | **Results:** A total of 345 patients were eligible for this study. TTE and THG were performed in 120 and 225 patients, respectively. Complications of Clavien-Dindo ≥ Grade II were found in 115/345 (33.3%) patients. Recurrent laryngeal nerve palsy was found only in the TTE group ($p < 0.001$). The incidence of other complications was not significantly different between the two groups. High body mass index (BMI) in the TTE group, male sex, and longer esophageal invasion in the THG group were significantly correlated with complications ≥ Grade II ($p = 0.049$, 0.037, and 0.019, respectively). Anastomotic leakage was most frequently observed (12.2%). Tumor size in the THG group ($p = 0.02$) was significantly associated with leakage. All six patients with ≥ Grade IV leakage underwent THG, whereas, none of the patients in the TTE group had leakage ≥ Grade IV (2.7% vs. 0%, $p = 0.096$). |

| Verstegen, M. H. P. et al. Outcomes of Patients with Anastomotic Leakage After Transhiatal, McKeown or Ivor Lewis Esophagectomy: A Nationwide Cohort Study. World J Surg. 45. 3341-3349. 2021 | | | |
|---|---|---|---|
| **Evidence level** | **Methodical Notes** | **Patient characteristics** | **Interventions** |
| **Evidence level:** 3<br>**Study type:** A Nationwide Cohort Study | **Funding sources:**<br>**Conflict of Interests:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout rates:** | **Total no. patients:** 1030<br>**Recruiting Phase:** 2011 till 2019<br>**Inclusion criteria:** All patients with anastomotic leakage after primary esophagectomy with gastric tube reconstruction for intrathoracic esophageal cancer or junctional cancer. Patients undergoing open or minimally invasive transhiatal esophagectomy or esophagectomy with 2 field lymphadenectomy (McKeown or Ivor Lewis) were included. Regarding junctional tumors, patients with a Siewert I or II tumor who underwent an esophagectomy were included in this study<br>**Exclusion criteria:** Patients younger than 18 years, patients undergoing palliative or emergency resection and patients with missing data regarding the inclusion or exclusion criteria were excluded | **Interventions:** anastomotic leakage after different types of esophagectomy<br><br>**Comparison:** |

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| **Notes:** | Newcastle-Ottawa Scale (NOS) for Cohort studies: 8/9 stars<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 3 (Cohort study / Non-randomized controlled cohort).<br>**Author's conclusion:** This study in patients with anastomotic leakage confirms a strong association between severity of clinical consequences and different types of esophagectomy. It supports the hypothesis that cervical leakage is generally less severe than intrathoracic leakage. The clinical impact of anastomotic leakage should be taken into account, in addition to its incidence, when different types of esophagectomy are compared by clinicians or researchers. | |
| **Outcome Measures/results** | **Primary** 30-day/in-hospital mortality (defined as mortality from any cause during admission for esophagectomy or within 30-days after esophagectomy)<br>**Secondary** pulmonary complications, cardiac complications, gastric tube necrosis<br>(defined as a distinct outcome parameter), chyle leakage, re-intervention rate (radiologic, endoscopic or surgical) and re-operation rate<br>(defined as for any complication during admission for esophagectomy) and ICU and hospital length of stay | **Results:** Data from 1030 patients with anastomotic leakage after transhiatal (n=287), McKeown (n=397) and Ivor Lewis esophagectomy (n=346) were evaluated. The 30-day/in-hospital mortality rate was 4.5% in patients with leakage after transhiatal esophagectomy, 8.1% after McKeown and 8.1% after Ivor Lewis esophagectomy (P=0.139). After correction for confounders, leakage after transhiatal resection was associated with lower mortality (OR 0.152-0.699, P=0.004), but mortality after McKeown and Ivor Lewis esophagectomy was similar. Re-operation rate was 24.0% after transhiatal, 40.6% after McKeown and 41.3% after Ivor Lewis esophagectomy (P |

## 3.3 Schlüsselfrage 3.2: Wertung thorakoskopischer laparoskopischer Techniken Robotertechnik

**Schlüsselfrage:**

**03.2 Wertung thorakoskopischer/ laparoskopischer Techniken / Robotertechnik**
P: 1)Pat. mit gesichertem Plattenepithel- oder Adenokarzinom des Ösophagus in Abhängigkeit von der Tumorhöhe (zervikal, thorakal suprabifurkal, thorakalinfrabifurkal, abdominell bzw. nur supra-/infrabifurkal) 2)bzw. Pat. mit gesichertem AEG 1-3
I: OP-Zugang / Technik: a)thorakoskopisch, b)laparoskopisch, c)thorakoskopisch und laparoskopisch d)Hybridverfahren, (laparoskopisch/offen chir)
C: OP-Zugang / Technik offenthorakoabdominal
O: Patientenrelevante Endpunkte: Gesamtüberlebensrate, Überlebensrate nach 5 Jahren und 3 Jahren (ggfls. „Ableitung“ aus Überlebenskurven, wenn nicht im Text berichtet), medianes ÜL, Morbidität, LQ, 30 Tage Hospitalletalität, Rate an Lokalrezidiven im Beobachtungszeitraum, Fernmetastasierung, Häufigkeit der Komplikationen (v.a. pulmonal)

***Inhalt:*** *16 Literaturstellen*

| Literaturstelle | Evidenzlevel | Studientyp |
|---|---|---|
| Carroll, P. A. 2020 | 3 | Benchmarking |
| de Groot, E. M. 2020 | 2 | long-term follow-up of a randomized clinical trial |
| Helminen, O. 2019 | 3 | Population-based study from nationwide registries in Finland and Sweden |
| Kalff, M. C. 2020 | 4 | NATIONWIDE PROPENSITY-SCORE MATCHED ANALYSIS |
| Kamarajah, S. K. 2021 | 3 | |

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| Klevebro, F. 2021 | 4 | a population-based cohort study |
| Li, Z. 2021 | 4 | retrospective study |
| Mariette, C. 2020 | 2 | Multicenter, Open-label, Randomized Phase III Controlled Trial |
| Markar, S. R. 2020 | 3 | Implementation of a Randomized Controlled trial setting to National Practice |
| Sarkaria, I. S. 2019 | n/a | prospective, nonrandomized trial |
| Veenstra, M. M. K. 2021 | 3 | prospective study |
| Vimolratana, M. 2021 | 4 | a prospective, nonrandomized trial |
| Yang, Y. 2020 | 3 | A propensity score-matched study |
| Yoshimura, S. 2021 | 3 | a prospective study |
| Zhang, T. 2020 | 3 | A multicentre, non-interventional, retrospective, observational study |
| Zheng, Y. 2021 | 4 | A Retrospective Study |

***Cochrane Risk of Bias Tool 1 (RCT):*** *3 Bewertung(en)*

| **de Groot, E. M. et al. Robot-assisted minimally invasive thoracolaparoscopic esophagectomy versus open esophagectomy: long-term follow-up of a randomized clinical trial. Dis Esophagus. 33. . 2020** | | | |
|---|---|---|---|
| **Population** | **Intervention / Comparison** | **Outcomes/Results** | **Methodical Notes** |
| **Evidence level:** 2<br>**Study type:** long-term follow-up of a randomized clinical trial<br>**Number of Patients:** 112<br>**Recruiting Phase:** January 2012 till August 2016<br>**Inclusion Criteria:** All patients included in the ROBOT trial were included in the present study. Inclusion criteria for the ROBOT trial were patients (age ≥18 and â‰¤80 years) with histologically proven, surgically resectable esophageal cancer (cT1-4a, N0–3, M0).<br>**Exclusion Criteria:** | **Intervention:** Robot-assisted thoraco-laparoscopic esophagectomy<br>**Comparison:** Open transthoracic esophagectomy | **Primary:** 5-year overall survival<br>**Secondary:** disease-free survival and recurrence patterns<br>**Results:** The combined 5-year overall survival rates for RAMIE and OTE were 41% (95% CI 27–55) and 40% (95% CI 26–53), respectively (log rank test P = 0.827). The 5-year disease-free survival rate was 42% (95% CI 28–55) in the RAMIE group and 43% (95% CI 29–57) in the OTE group (log rank test P = 0.749). Out of 104 patients, 57 (55%) developed recurrent disease detected at a median of 10 months (range 0–56) after surgery. No statistically difference in recurrence rate nor recurrence pattern was observed between both groups.<br>**Author's Conclusion:** Overall survival and disease-free survival of RAMIE are comparable to OTE. These results continue to support the use of robotic surgery for esophageal cancer. In case a robotic system is available and the | **Funding Sources:**<br>**COI:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout Rate/ITT-Analysis:**<br>**Notes:** Cochrane risk of bias tool 1 (RoB 1):<br>(2 unclear risks of bias were observed)<br>Overall risk of bias: Low<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 2 (Randomized trial). |

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| | | surgical team has acquired proficiency with the procedure, RAMIE should be preferred over open transthoracic esophagectomy for patients with esophageal cancer. | |

| **Mariette, C. et al. Health-related Quality of Life Following Hybrid Minimally Invasive Versus Open Esophagectomy for Patients With Esophageal Cancer, Analysis of a Multicenter, Open-label, Randomized Phase III Controlled Trial: The MIRO Trial. Ann Surg. 271. 1023-1029. 2020** | | | |
|---|---|---|---|
| **Population** | **Intervention / Comparison** | **Outcomes/Results** | **Methodical Notes** |
| **Evidence level:** 2<br>**Study type:** Multicenter, Open-label, Randomized Phase III Controlled Trial<br>**Number of Patients:** 207<br>**Recruiting Phase:** October 2009 to April 2012<br>**Inclusion Criteria:** patients with squamous cell carcinoma (SCC) or adenocarcinoma of the middle or lower third of the esophagus and was eligible for surgical resection, clinically staged I, II, or III (T1, T2, T3, N0 or N1, M0), aged 18 to 75 years and with WHO performance status 0 to 2.<br>**Exclusion Criteria:** The surgical | **Intervention:** Hybrid Minimally Invasive Esophagectomy for Patients With Esophageal Cancer<br>**Comparison:** Open Esophagectomy for Patients With Esophageal Cancer | **Primary:** Comparison of short- and long-term health-related quality of life (HRQOL) following HMIE and OE. To decrease postoperative major 30-days morbidity from 45% in the open arm to 25% in the laparoscopically-assisted arm. [ Time Frame: 30 days ]<br>**Secondary:** overall morbidity [Time Frame: 30 days]; disease free survival [Time Frame: 2 years]; overall survival [Time Frame: 2 years]; quality of life [Time Frame: 2 years]; economical interest of the surgical technique apprehended through a hospital point of view [Time Frame: 6 months]<br>**Results:** The short-term reduction in global HRQOL at 30 days specifically role functioning [33.33 (HMIE) vs 46.3 (OE); P Â¼ 0.0407] and social functioning [16.88 (HMIE) vs 35.74 (OE); P | **Funding Sources:**<br>**COI:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout Rate/ITT-Analysis:**<br>**Notes:** Cochrane risk of bias tool 1 (RoB 1):<br>(2 unclear risks of bias were observed)<br>Overall risk of bias: Low<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 2 |

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| technique–associated exclusion criteria were (1) contraindication for laparoscopy and (2) a previous history of supraumbilical laparotomy. | | Â¼ 0.0003] was less substantial in the HMIE group. At 2 years, social functioning had improved following HMIE to beyond baseline (Ã¾5.37) but remained reduced in the OE group (8.33) (P Â¼ 0.0303). At 2 years, increases in pain were similarly reduced in the HMIE compared with the OE group [Ã¾6.94 (HMIE) vs Ã¾14.05 (OE); P Â¼ 0.018]. Postoperative complications in multivariate analysis were associated with role functioning, pain, and dysphagia.<br>**Author's Conclusion:** Esophagectomy has substantial effects upon short-term HRQOL. These effects for some specific parameters are, however, reduced with HMIE, with persistent differences up to 2 years, and maybe mediated by a reduction in postoperative complications. | (Randomized trial). |

**Markar, S. R. et al. Implementation of Minimally Invasive Esophagectomy From a Randomized Controlled Trial Setting to National Practice. J Clin Oncol. 38. 2130-2139. 2020**

| Population | Intervention / Comparison | Outcomes/Results | Methodical Notes |
|---|---|---|---|
| **Evidence level:** 3<br>**Study type:** Implementation of a Randomized Controlled trial setting to National Practice<br>**Number of Patients:** 4720 | **Intervention:**<br>**Comparison:** | **Primary:** external validity of the randomized TIME trial<br>**Secondary:**<br>**Results:** One hundred fifteen patients from the TIME trial (59 MIE v 56 open) and 4,605 patients | **Funding Sources:**<br>**COI:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout Rate/ITT-** |

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| **Recruiting Phase:**<br>**Inclusion Criteria:** patients receiving transthoracic esophagectomy for the treatment of esophageal cancer<br>**Exclusion Criteria:** excluded from the DUCA database those patients who received only minimally invasive abdominal surgeries (n = 653), only minimally invasive thoracic surgeries (n = 129), or unknown interventions (n = 2) | | from the DUCA dataset (2,652 MIE v 1,953 open) were included. In the TIME trial, univariate analysis showed that MIE reduced pulmonary complications and length of hospital stay. On the contrary, in the DUCA dataset, MIE was associated with increased total and pulmonary complications and reoperations; however, benefits included increased proportion of R0 margin and lymph nodes harvested, and reduced 30-day mortality. Multivariate analysis from the TIME trial showed that MIE reduced pulmonary complications (odds ratio [OR], 0.19; 95% CI, 0.06 to 0.61). In the DUCA dataset, MIE was associated with increased total complications (OR, 1.36;<br>95% CI, 1.19 to 1.57), pulmonary complications (OR, 1.50; 95% CI, 1.29 to 1.74), reoperations (OR, 1.74;<br>95% CI, 1.42 to 2.14), and length of hospital stay. Multivariate analysis of the combined and MIE datasets showed that inclusion in the TIME trial was associated with a reduction in reoperations, Clavien-Dindo grade > 1<br>complications, and length of hospital stay.<br>**Author's Conclusion:** In conclusion, this study has shown that the benefits of MIE demonstrated in the TIME RCT lacked external validity when the practice of MIE was studied nationally in the | **Analysis:**<br>**Notes:** Cochrane risk of bias tool 1 (RoB 1):<br>(3 unclear risks of bias were observed)<br>Overall risk of bias:<br>Unclear<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 3 (Randomized trial).<br>Downgrade to evidence level 3 due to high risk of bias. |

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| | | Netherlands. After adjustment for patient and tumor factors, inclusion in the TIME trial was associated with substantial reductions in reoperations and Clavien-Dindo grade . 1 complications compared with national practice from DUCA, suggesting a high level of expertise in the centers included in the TIME trial. The inference from this present study is that the implementation of a new complex surgical technique outside of an RCT must be carefully introduced nationally through competency-based training programs, and additional surgical RCTs may also seek external validity with different study designs, including registrybased RCTs. | |

***NEWCASTLE - OTTAWA Checklist: Cohort:*** *13 Bewertung(en)*

| **Carroll, P. A. et al. Using Benchmarking Standards to Evaluate Transition to Minimally Invasive Esophagectomy. Ann Thorac Surg. 109. 383-388. 2020** | | | |
|---|---|---|---|
| **Evidence level** | **Methodical Notes** | **Patient characteristics** | **Interventions** |
| **Evidence level:** 3<br>**Study type:** Benchmarking | **Funding sources:**<br>**Conflict of Interests:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout rates:** | **Total no. patients:** 383<br>**Recruiting Phase:** 2007 to 2017<br>**Inclusion criteria:** patients diagnosed with cancer of the esophagus and gastroesophageal junction<br>**Exclusion criteria:** | **Interventions:** Minimally invasive esophagectomy<br><br>**Comparison:** open esophagectomy |
| **Notes:** | Newcastle-Ottawa Scale (NOS) for Cohort studies: 8/9 stars<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment harms): 3 (Randomized trial Cohort study / Non-randomized controlled cohort).<br>**Author's conclusion:** These results compare favorably to those reported by ECCG. MIE can be the standard approach for surgical management of esophageal cancer. Introduction of the approach in each surgeonâ€™s practice should be benchmarked to international standards. | | |
| **Outcome Measures/results** | **Primary**<br>**Secondary** | **Results:** Of 383 patients, 299 (76%) were men with a median age of 64.5 years (range, 56-72 years). MIE was performed in 49.6%. No differences were found in age, histologic finding (P = .222), pT stage (P = .136), or nodal positivity (P = .918). Stage 3 cancers accounted for 42.0% of OEs and 47.9% of MIEs. A thoracic anastomosis was more frequent in MIEs (156 of 190; 82.1%) than in OEs (113 of 193; 58.5%; P = .001). Frequency, severity (Clavien-Dindo), and complexity (comprehensive complication index) of complications were better in the MIE group, without compromising operative outcomes. No differences were identified in individual complication | |

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| | | groupings or grade in MIEs compared with OEs (pneumonia: 19.5% versus 26.9% ([P = .09]; intensive care unit readmission: 7.4% versus 9.3% [P = .519]; atrial fibrillation: 11.1% versus 6.7% [P = .082], or grade of leak [P = .99]). |

**Helminen, O. et al. Population-based study of anastomotic stricture rates after minimally invasive and open oesophagectomy for cancer. BJS Open. 3. 634-640. 2019**

| Evidence level | Methodical Notes | Patient characteristics | Interventions |
|---|---|---|---|
| **Evidence level:** 3<br>**Study type:** Population-based study from nationwide registries in Finland and Sweden | **Funding sources:**<br>**Conflict of Interests:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout rates:** | **Total no. patients:** 1669<br>**Recruiting Phase:** 2007 till 2014<br>**Inclusion criteria:** patients who had MIO or OO for oesophageal cancer<br>**Exclusion criteria:** | **Interventions:** minimally invasive oesophagectomy of anastomotic stricture<br><br>**Comparison:** open oesophagectomy of anastomotic stricture |
| **Notes:** | Newcastle-Ottawa Scale (NOS) for Cohort studies: 8/9 stars<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment harms): 3 (Cohort study / Non-randomized controlled cohort).<br>**Author's conclusion:** The need for endoscopic anastomotic dilatation after oesophagectomy was common, and the need for repeated dilatation was higher after MIO than following OO. The increased risk after MIO may reflect a learning curve. | | |
| **Outcome Measures/results** | **Primary** overall rate of anastomotic stricture and need for single or repeated (3 or more) dilatations for stricture | **Results:** Some 239 patients underwent MIO and 1430 had an open procedure. The incidence of strictures requiring one dilatation was 16â‹…7 per cent, and that for strictures requiring three or more dilatations was 6â‹…6 per cent. The HR for strictures requiring one dilatation was not increased after MIO compared with that after OO (HR 1â‹…19, 95 per cent c.i. 0â‹…66 to 2â‹…12), | |

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| | within the first year after surgery<br>**Secondary** | but was threefold higher for repeated dilatations (HR 3â‹…25, 1â‹…43 to 7â‹…36). Of 18 strictures following MIO, 14 (78 per cent) occurred during the first 2 years after initiating this approach. |

**Kalff, M. C. et al. Long-Term Survival After Minimally Invasive Versus Open Esophagectomy for Esophageal Cancer: A Nationwide Propensity-Score Matched Analysis. Ann Surg. Publish Ahead of Print. . 2020**

| Evidence level | Methodical Notes | Patient characteristics | Interventions |
|---|---|---|---|
| **Evidence level:** 4<br>**Study type:** NATIONWIDE PROPENSITY-SCORE MATCHED ANALYSIS | **Funding sources:**<br>**Conflict of Interests:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout rates:** | **Total no. patients:** 3096<br>**Recruiting Phase:** 2011-2015<br>**Inclusion criteria:** Patients undergoing minimally invasive or open, transthoracic or transhiatal esophagectomy for primary esophageal cancer<br>**Exclusion criteria:** Patients with missing data on in- or exclusion criteria, patients that<br>underwent a salvage procedure, hybrid procedure and patients with histology other than adeno or squamous cell carcinoma. | **Interventions:** minimally invasive esophagectomy<br><br>**Comparison:** open esophagectomy |
| **Notes:** | Newcastle-Ottawa Scale (NOS) for Cohort studies: 6/9 stars<br>Downgrade due to 0 stars in comparability.<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 3 (Cohort study / Non-randomized controlled cohort).<br>Downgrade to evidence level 4, due to risk of bias. | | |

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| | **Author's conclusion:** Long-term survival after minimally invasive esophagectomy was equivalent to open in both propensity-score matched cohorts of patients undergoing transthoracic or transhiatal esophageal resections. Transhiatal minimally invasive esophagectomy was accompanied with more post-operative morbidity. Both transthoracic and transhiatal minimally invasive esophagectomy resulted in a more extended lymphadenectomy. | |
| **Outcome Measures/results** | **Primary** long-term survival<br>**Secondary** short-term morbidity and mortality, and oncological outcomes including the complete microscopic resection (R0) rate and (positive) lymph node yield were compared between minimally invasive and open esophagectomy | **Results:** A total of 1036 transthoracic MIE and OE patients, and 582 transhiatal MIE and OE patients were matched. Long-term survival was comparable for MIE and OE for both transthoracic and transhiatal procedures (5-year overall survival: transthoracic MIE 49.2% vs. OE 51.1%, p 0.695; transhiatal MIE 48.4% vs. OE 50.7%, p 0.832). For both procedures, MIE yielded more lymph nodes (transthoracic median 21 vs. 18, p |

**Kamarajah, S. K. et al. Robotic Techniques in Esophagogastric Cancer Surgery: An Assessment of Short- and Long-Term Clinical Outcomes. Ann Surg Oncol. . . 2021**

| Evidence level | Methodical Notes | Patient characteristics | Interventions |
|---|---|---|---|
| **Evidence level:** 3<br>**Study type:** | **Funding sources:**<br>**Conflict of Interests:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout rates:** | **Total no. patients:**<br>**Recruiting Phase:**<br>**Inclusion criteria:**<br>**Exclusion criteria:** | **Interventions:**<br><br>**Comparison:** |
| **Notes:** | Newcastle-Ottawa Scale (NOS) for Cohort studies: 8/9 stars<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 3 (Cohort | | |

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| | study / Non-randomized controlled cohort).<br><br>**Author's conclusion:** | |
| **Outcome Measures/results** | **Primary**<br>**Secondary** | **Results:** |

**Klevebro, F. et al. Health-related quality of life following total minimally invasive, hybrid minimally invasive or open oesophagectomy: a population-based cohort study. Br J Surg. 108. 702-708. 2021**

| Evidence level | Methodical Notes | Patient characteristics | Interventions |
|---|---|---|---|
| **Evidence level:** 4<br>**Study type:** a population-based cohort study | **Funding sources:**<br>**Conflict of Interests:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout rates:** | **Total no. patients:** 246<br>**Recruiting Phase:** January 2013 to April 2018<br>**Inclusion criteria:** patients who had survived 1 year after surgical resection for oesophageal or gastro-oesophageal junction cancer in Sweden between 2013 and 2018<br>**Exclusion criteria:** | **Interventions:** total or hybrid minimally invasive oesophagectomy<br><br>**Comparison:** open surgery |
| **Notes:** | Newcastle-Ottawa Scale (NOS) for Cohort studies: 7/9 stars<br>Downgrade due to 0 or 1 stars in outcome/exposure domain.<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 4 (Cohort study / Non-randomized controlled cohort).<br>Downgrade to evidence level 4 due to high risk of bias.<br>**Author's conclusion:** In this population-based nationwide Swedish study, longitudinal HRQoL after minimally invasive oesophagectomy was similar to that of the open surgical approach. The study showed that functional outcomes after oesophagectomy need to be improved and that the introduction of a minimally invasive surgical technique does not | | |

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| | seem to solve this problem. Providing adequate information to patients before and during treatment, and developing specific treatments aimed at decreasing the lasting symptoms of the operation are areas that could improve future outcomes. | |
| **Outcome Measures/results** | **Primary** Health-related quality of life<br>**Secondary** effects of postoperative complications in the exposure groups on HRQoL | **Results:** Of the 246 patients recruited, 153 underwent minimally invasive oesophagectomy, of which 75 were hybrid minimally invasive and 78 were total minimally invasive procedures. After adjustment for age, sex, Charlson Co-morbidity Index score, pathological tumour stage and neoadjuvant therapy, there were no clinically and statistically significant differences in overall or disease-specific HRQoL after oesophagectomy between hybrid minimally invasive and total minimally invasive surgical technique versus open surgery. All groups had a relatively high level of problems with postoperative symptoms. |

**Li, Z. et al. Comparison of up-front minimally invasive esophagectomy versus open esophagectomy on quality of life for esophageal squamous cell cancer. Current oncology (Toronto, Ont.). 28. 693?701. 2021**

| Evidence level | Methodical Notes | Patient characteristics | Interventions |
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| **Evidence level:** 4<br>**Study type:** retrospective study | **Funding sources:**<br>**Conflict of Interests:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout rates:** | **Total no. patients:** 104 Chinese patients<br>**Recruiting Phase:** January 2013 to March 2014<br>**Inclusion criteria:** patients with esophageal cancer<br>**Exclusion criteria:** patients with distant metastases, patients with operational contraindications, and patients who received radiotherapy or chemotherapy beforehand. Operational contraindications included (1) patients with severe cardiopulmonary insufficiency or serious diseases who could not tolerate surgery; (2) patients with tumor invaded surrounding important | **Interventions:** Up-Front Minimally Invasive Esophagectomy of Esophageal Squamous Cell Cancer<br><br>**Comparison:** Open Esophagectomy of Esophageal Squamous Cell Cancer |

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| | | tissues and organs shown by preoperative imaging examinations that could not be removed by surgery; (3) patients with distant metastases shown by preoperative imaging examinations, such as hepatic metastases, pulmonary metastasis and bone metastases; (4) patients first diagnosed with esophageal small cell carcinoma; and (5) patients who underwent chest or abdominal surgery in the past who could not undergo surgery again. | |
| **Notes:** | Newcastle-Ottawa Scale (NOS) for Cohort studies: 5/9 stars<br>Downgrade due to 0 stars in comparability domain and 0 or 1 stars in outcome/exposure domain.<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 4 (Cohort study / Non-randomized controlled cohort).<br>Downgrade to evidence level 4 due to high risk of bias.<br>**Author's conclusion:** MIE had a better effect on quality of life of Chinese esophagus cancer patients | | |
| **Outcome Measures/results** | **Primary** short-term quality of life (QOL) before the operation and at the first, third, sixth and twelfth months after MIE or OE<br>**Secondary** | **Results:** The MIE group was higher than the OE group in one-year survival rate (92.54% vs. 72.00%). Significant differences between the two groups were observed in intraoperative bleeding volume (158.53 Â± 91.07 mL vs. 228.97 Â± 109.33 mL, p = 0.001), and the incidence of postoperative pneumonia (33.33% vs. 58.62%, p = 0.018). The KPS of MIE group was significantly higher than the OE group at the first (80 vs. 70, p = 0.004 < 0.05), third (90 vs. 80, p = 0.006 < 0.05), sixth (90 vs. 80, p = 0.007 < 0.05) and twelfth months (90 vs. 80, p = 0.004 < 0.05) after surgery. The QLQC-30 score of MIE group was better than OE group at first and twelfth months after the operation. The OES-18 score of MIE group was | |

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| | | significantly better than OE group at first, sixth and twelfth months after surgery. The short-term quality of life in MIE group was better than OE group. |

| **Sarkaria, I. S. et al. Early Quality of Life Outcomes After Robotic-Assisted Minimally Invasive and Open Esophagectomy. Ann Thorac Surg. 108. 920-928. 2019** | | | |
|---|---|---|---|
| **Evidence level** | **Methodical Notes** | **Patient characteristics** | **Interventions** |
| **Evidence level:** n/a<br>**Study type:** prospective, nonrandomized trial | **Funding sources:**<br>**Conflict of Interests:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout rates:** | **Total no. patients:** 150<br>**Recruiting Phase:** March 2012 till August 2014<br>**Inclusion criteria:** All patients aged 18 years or older with a diagnosis of clinical stage I to IIIC esophageal cancer who were scheduled to undergo surgical resection via a transthoracic approach (Ivor Lewis, thoracoabdominal, or McKeown) were considered for inclusion<br>**Exclusion criteria:** Exclusion criteria included inability to give informed consent, presence of tumors requiring laryngectomy or colon interposition, and scleroderma | **Interventions:** Minimally Invasive esophagectomy: Quality of Life instruments, FACT-E, Symptom Assessment Scale, Brief Pain Inventory and Daily Analgesic Log<br><br>**Comparison:** Open esophagectomy: Quality of Life instruments, FACT-E, Symptom Assessment Scale, Brief Pain Inventory and Daily Analgesic Log |
| **Notes:** | Newcastle-Ottawa Scale (NOS) for Cohort studies: 6/9 stars<br>Downgrade due to 0 or 1 star in selection domain.<br>Unclear wether exposed and non-exposed were recruited.<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 3 (Cohort study / Non- | | |

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| | randomized controlled cohort).<br>Downgrade to evidence level 4 due to high risk of bias.<br>**Author's conclusion:** RAMIE is associated with lower immediate postoperative pain severity and interference and decreased pulmonary and infectious complications. Ongoing data accrual will assess mid-term and long-term outcomes in this cohort. | |
| **Outcome Measures/results** | **Primary** short-term pain [Time Frame: 4 months]; short-term quality of life (QOL) [Time Frame: 4 months]<br>**Secondary** long-term pain [Time Frame: 2 years]; long time quality of life (QOL) [Time Frame: 2 years]; differences in surgical outcomes [Time Frame: 90 days]; Complications [Time Frame: 90 days] | **Results:** In total, 106 patients underwent open esophagectomy; 64 underwent minimally invasive esophagectomy (98% RAMIE). The groups did not differ in age, sex, comorbidities, histologic subtype, stage, or induction treatment (P = .42 to P > .95). Total Functional Assessment of Cancer Therapy-Esophageal scores were lower at 1 month (P < .001), returned to near baseline by 4 months, and did not differ between groups (P = .83). Brief Pain Inventory average pain severity (P = .007) and interference (P = .004) were lower for RAMIE. RAMIE had lower estimated blood loss (250 vs 350 cm3; P < .001), shorter length of stay (9 vs 11 days; P < .001), fewer intensive care unit admissions (8% vs 20%; P = .033), more lymph nodes harvested (25 vs 22; P = .05), and longer surgical time (6.4 vs 5.4 hours; P < .001). Major complications (39% for RAMIE vs 52% for open esophagectomy; P > .95), anastomotic leak (3% vs 9%; P = .41), and 90-day mortality (2% vs 4%; P = .85) did not differ between groups. Pulmonary (14% vs 34%; P = .014) and infectious (17% vs 36%; P = .029) complications were lower for RAMIE. |

**Veenstra, M. M. K. et al. Complications and survival after hybrid and fully minimally invasive oesophagectomy. BJS Open. 5. . 2021**

| Evidence level | Methodical Notes | Patient characteristics | Interventions |
|---|---|---|---|
| **Evidence level:** 3<br>**Study** | **Funding sources:**<br>**Conflict of Interests:**<br>**Randomization:** | **Total no. patients:** 828<br>**Recruiting Phase:** August 1993 and September 2019 | **Interventions:** Minimally invasive oesophagectomy |

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| **type:** prospective study | **Blinding:**<br>**Dropout rates:** | **Inclusion criteria:** Patients were included in this study if they had either a threephase (McKeown) MIO or HMIO (open abdomen) with cervical anastomosis<br>**Exclusion criteria:** Patients were excluded if they underwent twophase (Ivor Lewis) oesophagectomy or had undergone salvage surgery following definitive chemoradiotherapy | **Comparison:** Hybrid Minimally invasive oesophagectomy |
| **Notes:** | Newcastle-Ottawa Scale (NOS) for Cohort studies: 9/9 stars<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 3 (Cohort study / Non-randomized controlled cohort).<br><br>**Author's conclusion:** MIO had a small benefit in terms of blood loss and hospital stay, but not in operating time. Oncological outcomes were similar in the two groups. Postoperative complications were associated with pre-existing cardiorespiratory co-morbidities rather than operative approach. | | |
| **Outcome Measures/results** | **Primary** postoperative complications<br>**Secondary** Duration of operation, blood transfusion requirement, duration of hospital stay, overall survival | **Results:** There were 828 patients, of whom 722 had HMIO and 106 MIO, without significant baseline differences. Median duration of operation was longer for MIO (325 versus 289 min; $P < 0.001$), but with less blood loss (median 250 versus 300 ml; $P < 0.001$) and a shorter hospital stay (median 12 versus 13 days; $P = 0.006$). Respiratory complications were not associated with operative approach (31.1 versus 35.2 per cent for MIO and HMIO respectively; $P = 0.426$). Anastomotic leak rates (10.4 versus 10.2 per cent) and 90-day mortality (1.0 versus 1.7 per cent) did not differ. Cardiac co-morbidity was associated with more medical and surgical complications. Overall survival was associated with AJCC stage and co-morbidities, but not operative approach. | |

| **Vimolratana, M. et al. Two-Year Quality of Life Outcomes After Robotic-Assisted Minimally Invasive and Open Esophagectomy. Ann Thorac Surg. 112. 880-889. 2021** | | | |
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| **Evidence level** | **Methodical Notes** | **Patient characteristics** | **Interventions** |
| **Evidence level:** 4<br>**Study type:** a prospective, nonrandomized trial | **Funding sources:**<br>**Conflict of Interests:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout rates:** | **Total no. patients:** 170<br>**Recruiting Phase:** March 2012 till August 2014<br>**Inclusion criteria:** Diagnosis of esophageal cancer, stages I-IIIC, with no prior esophageal resection. Neoadjuvant therapy given prior to presentation at MSKCC. Anticipated to undergo surgical resection (Ivor Lewis, Trans Hiatal, thoracoabdominal, or McKeown procedure) of esophageal cancer either by open or minimally invasive methods.<br>**Exclusion criteria:** Patients requiring laryngectomy or colon interposition were excluded | **Interventions:** Robotic-Assisted Minimally Invasive Esophagectomy<br><br>**Comparison:** Open Esophagectomy |
| **Notes:** | Newcastle-Ottawa Scale (NOS) for Cohort studies: 5/9 stars<br>Downgrade due 0 or 1 stars in outcome/exposure domain.<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 3 (Cohort study / Non-randomized controlled cohort).<br>Downgrade to evidence level 4 due to high risk of bias.<br>**Author's conclusion:** during 2 years of follow-up, RAMIE was associated with improved patient-reported QOL, compared with OE, especially in esophageal symptoms and emotional well-being. RAMIE was also associated with decreased postoperative pain. However, pain interference did not differ between surgical groups. Taken together, these findings suggest that RAMIE may offer HRQOL benefits to patients undergoing curative resection for esophageal cancer and should receive consideration as a minimally invasive alternative to OE. | | |

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| **Outcome Measures/results** | **Primary** patient-reported QOL, measured by the Functional Assessment of Cancer Therapy–Esophageal (FACT-E), and pain, measured by the Brief Pain Inventory (BPI)<br>**Secondary** complications and perioperative outcomes | **Results:** Esophagectomy was performed in 170 patients (106 OE and 64 RAMIE). The groups did not differ significantly by any measured clinicopathologic variables. After covariates were controlled for, FACT-E scores were higher in the RAMIE cohort than in the OE cohort (parameter estimate [PE], 6.13; P-adj = .051). RAMIE was associated with higher esophageal cancer subscale (PE, 2.72; P-adj = .022) and emotional well-being (PE, 1.25; P-adj = .016) scores. BPI pain severity scores were lower in the RAMIE cohort than in the OE cohort (PE, -0.56; P-adj = .005), but pain interference scores did not differ significantly between groups (P-adj = .11). |

**Yang, Y. et al. Short- and mid-term outcomes of robotic versus thoraco-laparoscopic McKeown esophagectomy for squamous cell esophageal cancer: a propensity score-matched study. Dis Esophagus. 33. . 2020**

| Evidence level | Methodical Notes | Patient characteristics | Interventions |
|---|---|---|---|
| **Evidence level:** 3<br>**Study type:** A propensity score-matched study | **Funding sources:**<br>**Conflict of Interests:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout rates:** | **Total no. patients:** 652<br>**Recruiting Phase:** November 2015 to June 2018<br>**Inclusion criteria:** histologically proven surgically resectable (cT1b-3, N0-2, M0) squamous cell carcinoma of the intrathoracic esophagus with European Clinical Oncology Group performance status 0, 1 or 2.<br>**Exclusion criteria:** | **Interventions:** robotic McKeown esophagectomy for squamous cell esophageal cancer<br><br>**Comparison:** thoraco-laparoscopic McKeown esophagectomy for squamous cell esophageal cancer |
| **Notes:** | Newcastle-Ottawa Scale (NOS) for Cohort studies: 7/9 stars<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 3 (Cohort study / Non-randomized controlled cohort). | | |

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| | **Author's conclusion:** RME is demonstrated to be feasible and safe, with satisfying short- and mid-term outcomes in the treatment of patients with ESCC and compared favorably in a propensity-score-matched analysis with TLME. Based on these results, the robot-assisted technique should be considered as an alternative option for MIE. | |
| **Outcome Measures/results** | **Primary** 5-year overall survival rate<br>**Secondary** 5-year disease free survival, 3-year overall survival rate, 3-year disease free survival, (in hospital) mortality within 30 and 60 days, R0 resections, operation related events, postoperative recovery, lymph nodes status, quality of life | **Results:** RME was associated with similar intraoperative blood loss (P = 0.895), but with shorter surgical duration (244.5 vs. 276.0 min, P < 0.001), shorter thoracic duration (85.0 vs. 102.9 min, P < 0.001) and lower thoracic conversions (0.7% vs. 5.9%, P = 0.001). In spite of the similar results on total and thoracic lymph nodes dissection, RME yielded more lymph nodes along recurrent laryngeal nerve (4.8 vs. 4.1, P = 0.012), as well as the higher incidence of recurrent nerve injury (29.2% vs. 15.1%, P < 0.001) when compared to TLME. Tumor recurrence occurred in 30 patients and was locoregional only in 9 (3.5%) patients, systemic only in 17 (6.7%) patients, and combined in 4 (1.6%) patients in RME, while in 26 patients and was locoregional only in 10 (10.6%) patients, systemic only in 7 (2.8%) patients, and combined in 9 (3.6%) patients in TLME. RME was associated with a lower rate of mediastinal lymph nodes recurrence (2.0% vs. 5.3%, P = 0.044). Overall and disease-free survival was not different between the two cohorts (P = 0.097 and P = 0.248, respectively). RME was shown to be a safe and oncologically effective approach with favorable short- and mid-term outcomes in the treatment of patients with ESCC. |
| **Yoshimura, S. et al. Comparison of short-term outcomes between transthoracic and robot-assisted transmediastinal radical surgery for esophageal cancer: a prospective study. BMC Cancer. 21. 338. 2021** | | |

| Evidence level | Methodical Notes | Patient characteristics | Interventions |
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| **Evidence level:** 3<br>**Study type:** a prospective study | **Funding sources:**<br>**Conflict of Interests:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout rates:** | **Total no. patients:** 78<br>**Recruiting Phase:** April 2015 till March 2017<br>**Inclusion criteria:** (1) histologically proven esophageal cancer; (2) a T0–3â€‰N0–2 M0 stage tumor according to the TNM Classification of Malignant Tumors, 7th edition; (3) age 20â€‰years or older to 85â€‰years or younger; (4) European Clinical Oncology Group Performance Status (ECOG-PS) â‰¦1; (5) good enough general health to tolerate a conventional open esophagectomy; (6) no concomitant malignancies; and (7) no preoperative radiotherapy<br>**Exclusion criteria:** Patients with a history of surgery for other malignancies were excluded | **Interventions:** transthoracic surgery for esophageal cancer<br><br>**Comparison:** robot-assisted transmediastinal radical surgery for esophageal cancer |
| **Notes:** | Newcastle-Ottawa Scale (NOS) for Cohort studies: 7/9 stars<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits/harms): 3 (Cohort study / Non-randomized controlled cohort).<br>**Author's conclusion:** The present, prospective study indicated that TME might be a minimally invasive surgical procedure providing more, short-term benefits than TTE. However, additional studies should be conducted to evaluate the benefits of TME for patients with advanced esophageal cancer. Moreover, the present study did not compare TME with video-assisted thoracoscopic esophagectomy and included more confounding factors than a randomized trial. | | |
| **Outcome Measures/results** | **Primary** Comparison of postoperative cytokine | **Results:** Sixty patients with esophageal cancer were enrolled. The transmediastinal esophagectomy group had a significantly lower incidence of postoperative pneumonia ($p = 0.002$) and a significantly shorter postoperative hospital stay ($p < 0.0002$). The serum IL-6 | |

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| | level and quality of life<br>**Secondary** | levels on postoperative days 1, 3, 5, and 7 were significantly lower in the transmediastinal esophagectomy group (p = 0.005, 0.0007, 0.022, 0.020, respectively). In the latter group, the serum IL-8 level was significantly lower immediately after surgery and on postoperative day 1 (p = 0.003, 0.001, respectively) while the serum IL-10 level was significantly lower immediately after surgery (p = 0.041). The reduction in vital capacity, percent vital capacity, forced vital capacity, and forced expiratory volume at 1.0 s 6 months after surgery was significantly greater in the transthoracic esophagectomy group (p < 0.0001 for all four measurements). |

**Zhang, T. et al. Effectiveness and safety of minimally invasive Ivor Lewis and McKeown oesophagectomy in Chinese patients with stage IA-IIIB oesophageal squamous cell cancer: a multicentre, non-interventional and observational study. Interact Cardiovasc Thorac Surg. 30. 812-819. 2020**

| Evidence level | Methodical Notes | Patient characteristics | Interventions |
|---|---|---|---|
| **Evidence level:** 3<br>**Study type:** A multicentre, non-interventional, retrospective, observational study | **Funding sources:**<br>**Conflict of Interests:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout rates:** | **Total no. patients:** 1540<br>**Recruiting Phase:** 1 January 2010 till 30 June 2017<br>**Inclusion criteria:** Patients with pathologically confirmed stage IA–IIIB middle or lower thoracic oesophageal cancer who underwent an Ivor Lewis or McKeown procedure during the study period were included. These patients had also undergone tubular gastro-oesophageal and oesophageal reconstruction.<br>**Exclusion criteria:** The exclusion | **Interventions:** oesophageal squamous cell cancer treated with minimally invasive McKeown oesophagectomy.<br><br>**Comparison:** oesophageal squamous cell cancer treated with minimally invasive Ivor Lewis oesophagectomy. |

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| | | criteria included a history of prior antireflux or gastric surgery, prior right thoracic surgery and the presence of a second primary tumour. Patients with comorbidities such as severe arrhythmia or heart, lung, liver or renal dysfunction were also excluded. Patients who underwent hybrid procedures that included thoracotomy with laparoscopy or laparotomy with video-assisted thoracoscopic surgery were excluded. | |
| **Notes:** | Newcastle-Ottawa Scale (NOS) for Cohort studies: 8/9 stars<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 3 (Cohort study / Non-randomized controlled cohort).<br>**Author's conclusion:** the Ivor Lewis procedure may be optimal for the surgical treatment of OSCC patients with stage T1 and stage T2 tumours to minimize associated postoperative morbidity. Conversely, in OSCC patients with stage T3 tumours, the McKeown technique may represent the preferred surgical technique for improved long-term survival. | | |
| **Outcome Measures/results** | **Primary** overall survival and cancer recurrence, defined as the time (months) from the date of MIO to the date of death (any cause) or recurrence (tumour recurrence, metastasis or lymph node recurrence), respectively. Patients who died within 30 days following MIO or lost to follow-up were excluded from the | **Results:** A total of 1540 patients were included (950 McKeown, 590 Ivor Lewis). The mean age was 61.6 years, and 1204 were male. The mean number of lymph nodes removed during the McKeown procedure was 21.2 Â± 11.4 compared with 14.8 Â± 8.9 in Ivor Lewis patients (P < 0.001). The 5-year overall survival rates were 67.9% (McKeown) and 55.0% (Ivor Lewis). McKeown oesophagectomy was associated with improved overall survival (Ivor Lewis versus McKeown hazard ratio 1.36, 95% confidence interval 1.11-1.66; P = 0.003), particularly in patients with stage T3 tumours (middle | |

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| | overall survival analysis.<br>**Secondary** number of lymph nodes dissected, 30-day postoperative mortality and incidence of postoperative complications. | thoracic oesophagus). However, postoperative complications occurred more frequently following McKeown oesophagectomy (42.2% vs 17.6% Ivor Lewis; P < 0.001). |

**Zheng, Y. et al. Minimally Invasive Versus Open McKeown for Patients with Esophageal Cancer: A Retrospective Study. Ann Surg Oncol. 28. 6329-6336. 2021**

| Evidence level | Methodical Notes | Patient characteristics | Interventions |
|---|---|---|---|
| **Evidence level:** 4<br>**Study type:** A Retrospective Study | **Funding sources:**<br>**Conflict of Interests:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout rates:** | **Total no. patients:** 502<br>**Recruiting Phase:** 1 January 2015 to 6 January 2018c<br>**Inclusion criteria:** consecutive thoracic EC patients, pathological T stage 3 according to the 2009 American Joint Committee on Cancer (AJCC) TNM staging criteria; surgically resected EC via either McKeownMIE or McKeown-OE; and more than 14 lymph nodes harvested during the operation (at least two-field lymphadenectomy)<br>**Exclusion criteria:** missing information on follow-up | **Interventions:** McKeown minimally invasive esophagectomy<br><br>**Comparison:** McKeown open esophagectomy |
| **Notes:** | Newcastle-Ottawa Scale (NOS) for Cohort studies: 6/9 stars<br>Downgrade due 0 stars in comparability domain.<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 3 (Cohort study / Non-randomized controlled cohort).<br>Downgrade to evidence level 4 due to high risk of bias. | | |

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| | **Author's conclusion:** These results showed that McKeown-MIE was associated with better long-term survival than McKeown-OE for patients with resectable EC. | |
| **Outcome Measures/results** | **Primary** longterm survival<br>**Secondary** | **Results:** We included 502 patients who underwent McKeown-MIE (n = 306) or McKeown-OE (n = 196) for EC. The median age in the total patient population was 63 years. All baseline characteristics were well-balanced between the two groups. There was a significantly shorter mean operative time (269.76 min vs. 321.14 min, $p < 0.001$) in the OE group. The 30-day and in-hospital mortality rates were 0, and there was no difference in 90-day mortality ($p = 0.053$) between the groups. The postoperative stay was shorter in the MIE group and was 14 days and 18 days in the MIE and OE groups, respectively ($p < 0.001$). The OS at 60 months was 58.8% and 41.6% in the MIE and OE groups, respectively ($p < 0.001$) [hazard ratio 1.783, 95% confidence interval 1.347-2.359]. |

## 3.4 Schlüsselfrage 3.3: Stellenwert der limitierten Resektion proximaler Tumore

**Schlüsselfrage:**

**03.3 Stellenwert der limitierten Resektion proximaler Tumore**
P: 1)Pat. mit AEG (Stadium Talle Nalle M0)
I: limitierte Resektion
C: a) offene Resektion
O: Patientenrelevante Endpunkte: Gesamtüberlebensrate, Überlebensrate nach 5 Jahren und 3 Jahren (ggfls. „Ableitung“ aus Überlebenskurven, wenn nicht im Text berichtet), medianes ÜL, Morbidität, LQ, 30 Tage Hospitalletalität, Rate an Lokalrezidiven im Beobachtungszeitraum, Fernmetastasierung, Häufigkeit der Komplikationen (v.a. pulmonal)

***Inhalt:*** *13 Literaturstellen*

| Literaturstelle | Evidenzlevel | Studientyp |
|---|---|---|
| Carroll, P. A. 2020 | 3 | Benchmarking |
| de Groot, E. M. 2020 | 2 | long-term follow-up of a randomized clinical trial |
| Helminen, O. 2019 | 3 | Population-based study from nationwide registries in Finland and Sweden |
| Kalff, M. C. 2020 | 4 | NATIONWIDE PROPENSITY-SCORE MATCHED ANALYSIS |
| Kamarajah, S. K. 2021 | 3 | |
| Klevebro, F. 2021 | 4 | a population-based cohort study |

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| Li, Z. 2021 | 4 | retrospective study |
| Mariette, C. 2020 | 2 | Multicenter, Open-label, Randomized Phase III Controlled Trial |
| Markar, S. R. 2020 | 3 | Implementation of a Randomized Controlled trial setting to National Practice |
| Sarkaria, I. S. 2019 | n/a | prospective, nonrandomized trial |
| Veenstra, M. M. K. 2021 | 3 | prospective study |
| Vimolratana, M. 2021 | 4 | a prospective, nonrandomized trial |
| Zheng, Y. 2021 | 4 | A Retrospective Study |

***Cochrane Risk of Bias Tool 1 (RCT):*** *3 Bewertung(en)*

| **de Groot, E. M. et al. Robot-assisted minimally invasive thoracolaparoscopic esophagectomy versus open esophagectomy: long-term follow-up of a randomized clinical trial. Dis Esophagus. 33. . 2020** | | | |
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| **Population** | **Intervention / Comparison** | **Outcomes/Results** | **Methodical Notes** |
| **Evidence level:** 2<br>**Study type:** long-term follow-up of a randomized clinical trial<br>**Number of Patients:** 112<br>**Recruiting Phase:** January 2012 till August 2016<br>**Inclusion Criteria:** All patients included in the ROBOT trial were included in the present study. Inclusion criteria for the ROBOT trial were patients (age ≥18 and â‰¤80 years) with histologically proven, surgically resectable esophageal cancer (cT1-4a, N0–3, M0).<br>**Exclusion Criteria:** | **Intervention:** Robot-assisted thoraco-laparoscopic esophagectomy<br>**Comparison:** Open transthoracic esophagectomy | **Primary:** 5-year overall survival<br>**Secondary:** disease-free survival and recurrence patterns<br>**Results:** The combined 5-year overall survival rates for RAMIE and OTE were 41% (95% CI 27–55) and 40% (95% CI 26–53), respectively (log rank test P = 0.827). The 5-year disease-free survival rate was 42% (95% CI 28–55) in the RAMIE group and 43% (95% CI 29–57) in the OTE group (log rank test P = 0.749). Out of 104 patients, 57 (55%) developed recurrent disease detected at a median of 10 months (range 0–56) after surgery. No statistically difference in recurrence rate nor recurrence pattern was observed between both groups.<br>**Author's Conclusion:** Overall survival and disease-free survival of RAMIE are comparable to OTE. These results continue to support the use of robotic surgery for esophageal cancer. In case a robotic system is available and the | **Funding Sources:**<br>**COI:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout Rate/ITT-Analysis:**<br>**Notes:** Cochrane risk of bias tool 1 (RoB 1):<br>(2 unclear risks of bias were observed)<br>Overall risk of bias: Low<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 2 (Randomized trial). |

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| | | surgical team has acquired proficiency with the procedure, RAMIE should be preferred over open transthoracic esophagectomy for patients with esophageal cancer. | |

| **Mariette, C. et al. Health-related Quality of Life Following Hybrid Minimally Invasive Versus Open Esophagectomy for Patients With Esophageal Cancer, Analysis of a Multicenter, Open-label, Randomized Phase III Controlled Trial: The MIRO Trial. Ann Surg. 271. 1023-1029. 2020** | | | |
|---|---|---|---|
| **Population** | **Intervention / Comparison** | **Outcomes/Results** | **Methodical Notes** |
| **Evidence level:** 2<br>**Study type:** Multicenter, Open-label, Randomized Phase III Controlled Trial<br>**Number of Patients:** 207<br>**Recruiting Phase:** October 2009 to April 2012<br>**Inclusion Criteria:** patients with squamous cell carcinoma (SCC) or adenocarcinoma of the middle or lower third of the esophagus and was eligible for surgical resection, clinically staged I, II, or III (T1, T2, T3, N0 or N1, M0), aged 18 to 75 years and with WHO performance status 0 to 2.<br>**Exclusion Criteria:** The surgical | **Intervention:** Hybrid Minimally Invasive Esophagectomy for Patients With Esophageal Cancer<br>**Comparison:** Open Esophagectomy for Patients With Esophageal Cancer | **Primary:** Comparison of short- and long-term health-related quality of life (HRQOL) following HMIE and OE. To decrease postoperative major 30-days morbidity from 45% in the open arm to 25% in the laparoscopically-assisted arm. [ Time Frame: 30 days ]<br>**Secondary:** overall morbidity [Time Frame: 30 days]; disease free survival [Time Frame: 2 years]; overall survival [Time Frame: 2 years]; quality of life [Time Frame: 2 years]; economical interest of the surgical technique apprehended through a hospital point of view [Time Frame: 6 months]<br>**Results:** The short-term reduction in global HRQOL at 30 days specifically role functioning [33.33 (HMIE) vs 46.3 (OE); P Â¼ 0.0407] and social functioning [16.88 (HMIE) vs 35.74 (OE); P | **Funding Sources:**<br>**COI:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout Rate/ITT-Analysis:**<br>**Notes:** Cochrane risk of bias tool 1 (RoB 1):<br>(2 unclear risks of bias were observed)<br>Overall risk of bias: Low<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 2 |

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| technique–associated exclusion criteria were (1) contraindication for laparoscopy and (2) a previous history of supraumbilical laparotomy. | | Â¼ 0.0003] was less substantial in the HMIE group. At 2 years, social functioning had improved following HMIE to beyond baseline (Ã¾5.37) but remained reduced in the OE group (8.33) (P Â¼ 0.0303). At 2 years, increases in pain were similarly reduced in the HMIE compared with the OE group [Ã¾6.94 (HMIE) vs Ã¾14.05 (OE); P Â¼ 0.018]. Postoperative complications in multivariate analysis were associated with role functioning, pain, and dysphagia.<br>**Author's Conclusion:** Esophagectomy has substantial effects upon short-term HRQOL. These effects for some specific parameters are, however, reduced with HMIE, with persistent differences up to 2 years, and maybe mediated by a reduction in postoperative complications. | (Randomized trial). |

**Markar, S. R. et al. Implementation of Minimally Invasive Esophagectomy From a Randomized Controlled Trial Setting to National Practice. J Clin Oncol. 38. 2130-2139. 2020**

| Population | Intervention / Comparison | Outcomes/Results | Methodical Notes |
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| **Evidence level:** 3<br>**Study type:** Implementation of a Randomized Controlled trial setting to National Practice<br>**Number of Patients:** 4720 | **Intervention:**<br>**Comparison:** | **Primary:** external validity of the randomized TIME trial<br>**Secondary:**<br>**Results:** One hundred fifteen patients from the TIME trial (59 MIE v 56 open) and 4,605 patients | **Funding Sources:**<br>**COI:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout Rate/ITT-** |

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| **Recruiting Phase:**<br>**Inclusion Criteria:** patients receiving transthoracic esophagectomy for the treatment of esophageal cancer<br>**Exclusion Criteria:** excluded from the DUCA database those patients who received only minimally invasive abdominal surgeries (n = 653), only minimally invasive thoracic surgeries (n = 129), or unknown interventions (n = 2) | | from the DUCA dataset (2,652 MIE v 1,953 open) were included. In the TIME trial, univariate analysis showed that MIE reduced pulmonary complications and length of hospital stay. On the contrary, in the DUCA dataset, MIE was associated with increased total and pulmonary complications and reoperations; however, benefits included increased proportion of R0 margin and lymph nodes harvested, and reduced 30-day mortality. Multivariate analysis from the TIME trial showed that MIE reduced pulmonary complications (odds ratio [OR], 0.19; 95% CI, 0.06 to 0.61). In the DUCA dataset, MIE was associated with increased total complications (OR, 1.36;<br>95% CI, 1.19 to 1.57), pulmonary complications (OR, 1.50; 95% CI, 1.29 to 1.74), reoperations (OR, 1.74;<br>95% CI, 1.42 to 2.14), and length of hospital stay. Multivariate analysis of the combined and MIE datasets showed that inclusion in the TIME trial was associated with a reduction in reoperations, Clavien-Dindo grade > 1<br>complications, and length of hospital stay.<br>**Author's Conclusion:** In conclusion, this study has shown that the benefits of MIE demonstrated in the TIME RCT lacked external validity when the practice of MIE was studied nationally in the | **Analysis:**<br>**Notes:** Cochrane risk of bias tool 1 (RoB 1):<br>(3 unclear risks of bias were observed)<br>Overall risk of bias:<br>Unclear<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 3 (Randomized trial).<br>Downgrade to evidence level 3 due to high risk of bias. |

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| | | Netherlands. After adjustment for patient and tumor factors, inclusion in the TIME trial was associated with substantial reductions in reoperations and Clavien-Dindo grade . 1 complications compared with national practice from DUCA, suggesting a high level of expertise in the centers included in the TIME trial. The inference from this present study is that the implementation of a new complex surgical technique outside of an RCT must be carefully introduced nationally through competency-based training programs, and additional surgical RCTs may also seek external validity with different study designs, including registrybased RCTs. | |

***NEWCASTLE - OTTAWA Checklist: Cohort:*** *10 Bewertung(en)*

| **Carroll, P. A. et al. Using Benchmarking Standards to Evaluate Transition to Minimally Invasive Esophagectomy. Ann Thorac Surg. 109. 383-388. 2020** | | | |
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| **Evidence level** | **Methodical Notes** | **Patient characteristics** | **Interventions** |
| **Evidence level:** 3<br>**Study type:** Benchmarking | **Funding sources:**<br>**Conflict of Interests:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout rates:** | **Total no. patients:** 383<br>**Recruiting Phase:** 2007 to 2017<br>**Inclusion criteria:** patients diagnosed with cancer of the esophagus and gastroesophageal junction<br>**Exclusion criteria:** | **Interventions:** Minimally invasive esophagectomy<br><br>**Comparison:** open esophagectomy |
| **Notes:** | Newcastle-Ottawa Scale (NOS) for Cohort studies: 8/9 stars<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment harms): 3 (Randomized trial Cohort study / Non-randomized controlled cohort).<br>**Author's conclusion:** These results compare favorably to those reported by ECCG. MIE can be the standard approach for surgical management of esophageal cancer. Introduction of the approach in each surgeonâ€™s practice should be benchmarked to international standards. | | |
| **Outcome Measures/results** | **Primary**<br>**Secondary** | **Results:** Of 383 patients, 299 (76%) were men with a median age of 64.5 years (range, 56-72 years). MIE was performed in 49.6%. No differences were found in age, histologic finding (P = .222), pT stage (P = .136), or nodal positivity (P = .918). Stage 3 cancers accounted for 42.0% of OEs and 47.9% of MIEs. A thoracic anastomosis was more frequent in MIEs (156 of 190; 82.1%) than in OEs (113 of 193; 58.5%; P = .001). Frequency, severity (Clavien-Dindo), and complexity (comprehensive complication index) of complications were better in the MIE group, without compromising operative outcomes. No differences were identified in individual complication | |

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| | | groupings or grade in MIEs compared with OEs (pneumonia: 19.5% versus 26.9% ([P = .09]; intensive care unit readmission: 7.4% versus 9.3% [P = .519]; atrial fibrillation: 11.1% versus 6.7% [P = .082], or grade of leak [P = .99]). |

**Helminen, O. et al. Population-based study of anastomotic stricture rates after minimally invasive and open oesophagectomy for cancer. BJS Open. 3. 634-640. 2019**

| Evidence level | Methodical Notes | Patient characteristics | Interventions |
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| **Evidence level:** 3<br>**Study type:** Population-based study from nationwide registries in Finland and Sweden | **Funding sources:**<br>**Conflict of Interests:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout rates:** | **Total no. patients:** 1669<br>**Recruiting Phase:** 2007 till 2014<br>**Inclusion criteria:** patients who had MIO or OO for oesophageal cancer<br>**Exclusion criteria:** | **Interventions:** minimally invasive oesophagectomy of anastomotic stricture<br><br>**Comparison:** open oesophagectomy of anastomotic stricture |
| **Notes:** | Newcastle-Ottawa Scale (NOS) for Cohort studies: 8/9 stars<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment harms): 3 (Cohort study / Non-randomized controlled cohort).<br>**Author's conclusion:** The need for endoscopic anastomotic dilatation after oesophagectomy was common, and the need for repeated dilatation was higher after MIO than following OO. The increased risk after MIO may reflect a learning curve. | | |
| **Outcome Measures/results** | **Primary** overall rate of anastomotic stricture and need for single or repeated (3 or more) dilatations for stricture | **Results:** Some 239 patients underwent MIO and 1430 had an open procedure. The incidence of strictures requiring one dilatation was 16â‹…7 per cent, and that for strictures requiring three or more dilatations was 6â‹…6 per cent. The HR for strictures requiring one dilatation was not increased after MIO compared with that after OO (HR 1â‹…19, 95 per cent c.i. 0â‹…66 to 2â‹…12), | |

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| | within the first year after surgery<br>**Secondary** | but was threefold higher for repeated dilatations (HR 3â‹…25, 1â‹…43 to 7â‹…36). Of 18 strictures following MIO, 14 (78 per cent) occurred during the first 2 years after initiating this approach. |

**Kalff, M. C. et al. Long-Term Survival After Minimally Invasive Versus Open Esophagectomy for Esophageal Cancer: A Nationwide Propensity-Score Matched Analysis. Ann Surg. Publish Ahead of Print. . 2020**

| Evidence level | Methodical Notes | Patient characteristics | Interventions |
|---|---|---|---|
| **Evidence level:** 4<br>**Study type:** NATIONWIDE PROPENSITY-SCORE MATCHED ANALYSIS | **Funding sources:**<br>**Conflict of Interests:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout rates:** | **Total no. patients:** 3096<br>**Recruiting Phase:** 2011-2015<br>**Inclusion criteria:** Patients undergoing minimally invasive or open, transthoracic or transhiatal esophagectomy for primary esophageal cancer<br>**Exclusion criteria:** Patients with missing data on in- or exclusion criteria, patients that<br>underwent a salvage procedure, hybrid procedure and patients with histology other than adeno or squamous cell carcinoma. | **Interventions:** minimally invasive esophagectomy<br><br>**Comparison:** open esophagectomy |
| **Notes:** | Newcastle-Ottawa Scale (NOS) for Cohort studies: 6/9 stars<br>Downgrade due to 0 stars in comparability.<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 3 (Cohort study / Non-randomized controlled cohort).<br>Downgrade to evidence level 4, due to risk of bias. | | |

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| | **Author's conclusion:** Long-term survival after minimally invasive esophagectomy was equivalent to open in both propensity-score matched cohorts of patients undergoing transthoracic or transhiatal esophageal resections. Transhiatal minimally invasive esophagectomy was accompanied with more post-operative morbidity. Both transthoracic and transhiatal minimally invasive esophagectomy resulted in a more extended lymphadenectomy. | |
| **Outcome Measures/results** | **Primary** long-term survival<br>**Secondary** short-term morbidity and mortality, and oncological outcomes including the complete microscopic resection (R0) rate and (positive) lymph node yield were compared between minimally invasive and open esophagectomy | **Results:** A total of 1036 transthoracic MIE and OE patients, and 582 transhiatal MIE and OE patients were matched. Long-term survival was comparable for MIE and OE for both transthoracic and transhiatal procedures (5-year overall survival: transthoracic MIE 49.2% vs. OE 51.1%, p 0.695; transhiatal MIE 48.4% vs. OE 50.7%, p 0.832). For both procedures, MIE yielded more lymph nodes (transthoracic median 21 vs. 18, p |

**Kamarajah, S. K. et al. Robotic Techniques in Esophagogastric Cancer Surgery: An Assessment of Short- and Long-Term Clinical Outcomes. Ann Surg Oncol. . . 2021**

| Evidence level | Methodical Notes | Patient characteristics | Interventions |
|---|---|---|---|
| **Evidence level:** 3<br>**Study type:** | **Funding sources:**<br>**Conflict of Interests:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout rates:** | **Total no. patients:**<br>**Recruiting Phase:**<br>**Inclusion criteria:**<br>**Exclusion criteria:** | **Interventions:**<br><br>**Comparison:** |
| **Notes:** | Newcastle-Ottawa Scale (NOS) for Cohort studies: 8/9 stars<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 3 (Cohort | | |

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| | study / Non-randomized controlled cohort).<br><br>**Author's conclusion:** | |
| **Outcome Measures/results** | **Primary**<br>**Secondary** | **Results:** |

**Klevebro, F. et al. Health-related quality of life following total minimally invasive, hybrid minimally invasive or open oesophagectomy: a population-based cohort study. Br J Surg. 108. 702-708. 2021**

| Evidence level | Methodical Notes | Patient characteristics | Interventions |
|---|---|---|---|
| **Evidence level:** 4<br>**Study type:** a population-based cohort study | **Funding sources:**<br>**Conflict of Interests:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout rates:** | **Total no. patients:** 246<br>**Recruiting Phase:** January 2013 to April 2018<br>**Inclusion criteria:** patients who had survived 1 year after surgical resection for oesophageal or gastro-oesophageal junction cancer in Sweden between 2013 and 2018<br>**Exclusion criteria:** | **Interventions:** total or hybrid minimally invasive oesophagectomy<br><br>**Comparison:** open surgery |
| **Notes:** | Newcastle-Ottawa Scale (NOS) for Cohort studies: 7/9 stars<br>Downgrade due to 0 or 1 stars in outcome/exposure domain.<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 4 (Cohort study / Non-randomized controlled cohort).<br>Downgrade to evidence level 4 due to high risk of bias.<br>**Author's conclusion:** In this population-based nationwide Swedish study, longitudinal HRQoL after minimally invasive oesophagectomy was similar to that of the open surgical approach. The study showed that functional outcomes after oesophagectomy need to be improved and that the introduction of a minimally invasive surgical technique does not | | |

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| | seem to solve this problem. Providing adequate information to patients before and during treatment, and developing specific treatments aimed at decreasing the lasting symptoms of the operation are areas that could improve future outcomes. | |
| **Outcome Measures/results** | **Primary** Health-related quality of life<br>**Secondary** effects of postoperative complications in the exposure groups on HRQoL | **Results:** Of the 246 patients recruited, 153 underwent minimally invasive oesophagectomy, of which 75 were hybrid minimally invasive and 78 were total minimally invasive procedures. After adjustment for age, sex, Charlson Co-morbidity Index score, pathological tumour stage and neoadjuvant therapy, there were no clinically and statistically significant differences in overall or disease-specific HRQoL after oesophagectomy between hybrid minimally invasive and total minimally invasive surgical technique versus open surgery. All groups had a relatively high level of problems with postoperative symptoms. |

**Li, Z. et al. Comparison of up-front minimally invasive esophagectomy versus open esophagectomy on quality of life for esophageal squamous cell cancer. Current oncology (Toronto, Ont.). 28. 693?701. 2021**

| Evidence level | Methodical Notes | Patient characteristics | Interventions |
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| **Evidence level:** 4<br>**Study type:** retrospective study | **Funding sources:**<br>**Conflict of Interests:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout rates:** | **Total no. patients:** 104 Chinese patients<br>**Recruiting Phase:** January 2013 to March 2014<br>**Inclusion criteria:** patients with esophageal cancer<br>**Exclusion criteria:** patients with distant metastases, patients with operational contraindications, and patients who received radiotherapy or chemotherapy beforehand. Operational contraindications included (1) patients with severe cardiopulmonary insufficiency or serious diseases who could not tolerate surgery; (2) patients with tumor invaded surrounding important | **Interventions:** Up-Front Minimally Invasive Esophagectomy of Esophageal Squamous Cell Cancer<br><br>**Comparison:** Open Esophagectomy of Esophageal Squamous Cell Cancer |

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| | | tissues and organs shown by preoperative imaging examinations that could not be removed by surgery; (3) patients with distant metastases shown by preoperative imaging examinations, such as hepatic metastases, pulmonary metastasis and bone metastases; (4) patients first diagnosed with esophageal small cell carcinoma; and (5) patients who underwent chest or abdominal surgery in the past who could not undergo surgery again. | |
| **Notes:** | Newcastle-Ottawa Scale (NOS) for Cohort studies: 5/9 stars<br>Downgrade due to 0 stars in comparability domain and 0 or 1 stars in outcome/exposure domain.<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 4 (Cohort study / Non-randomized controlled cohort).<br>Downgrade to evidence level 4 due to high risk of bias.<br>**Author's conclusion:** MIE had a better effect on quality of life of Chinese esophagus cancer patients | | |
| **Outcome Measures/results** | **Primary** short-term quality of life (QOL) before the operation and at the first, third, sixth and twelfth months after MIE or OE<br>**Secondary** | **Results:** The MIE group was higher than the OE group in one-year survival rate (92.54% vs. 72.00%). Significant differences between the two groups were observed in intraoperative bleeding volume (158.53 Â± 91.07 mL vs. 228.97 Â± 109.33 mL, p = 0.001), and the incidence of postoperative pneumonia (33.33% vs. 58.62%, p = 0.018). The KPS of MIE group was significantly higher than the OE group at the first (80 vs. 70, p = 0.004 < 0.05), third (90 vs. 80, p = 0.006 < 0.05), sixth (90 vs. 80, p = 0.007 < 0.05) and twelfth months (90 vs. 80, p = 0.004 < 0.05) after surgery. The QLQC-30 score of MIE group was better than OE group at first and twelfth months after the operation. The OES-18 score of MIE group was | |

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| | | significantly better than OE group at first, sixth and twelfth months after surgery. The short-term quality of life in MIE group was better than OE group. |

**Sarkaria, I. S. et al. Early Quality of Life Outcomes After Robotic-Assisted Minimally Invasive and Open Esophagectomy. Ann Thorac Surg. 108. 920-928. 2019**

| Evidence level | Methodical Notes | Patient characteristics | Interventions |
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| **Evidence level:** n/a<br>**Study type:** prospective, nonrandomized trial | **Funding sources:**<br>**Conflict of Interests:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout rates:** | **Total no. patients:** 150<br>**Recruiting Phase:** March 2012 till August 2014<br>**Inclusion criteria:** All patients aged 18 years or older with a diagnosis of clinical stage I to IIIC esophageal cancer who were scheduled to undergo surgical resection via a transthoracic approach (Ivor Lewis, thoracoabdominal, or McKeown) were considered for inclusion<br>**Exclusion criteria:** Exclusion criteria included inability to give informed consent, presence of tumors requiring laryngectomy or colon interposition, and scleroderma | **Interventions:** Minimally Invasive esophagectomy: Quality of Life instruments, FACT-E, Symptom Assessment Scale, Brief Pain Inventory and Daily Analgesic Log<br><br>**Comparison:** Open esophagectomy: Quality of Life instruments, FACT-E, Symptom Assessment Scale, Brief Pain Inventory and Daily Analgesic Log |
| **Notes:** | Newcastle-Ottawa Scale (NOS) for Cohort studies: 6/9 stars<br>Downgrade due to 0 or 1 star in selection domain.<br>Unclear wether exposed and non-exposed were recruited.<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 3 (Cohort study / Non- | | |

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| | randomized controlled cohort).<br>Downgrade to evidence level 4 due to high risk of bias.<br>**Author's conclusion:** RAMIE is associated with lower immediate postoperative pain severity and interference and decreased pulmonary and infectious complications. Ongoing data accrual will assess mid-term and long-term outcomes in this cohort. | |
| **Outcome Measures/results** | **Primary** short-term pain [Time Frame: 4 months]; short-term quality of life (QOL) [Time Frame: 4 months]<br>**Secondary** long-term pain [Time Frame: 2 years]; long time quality of life (QOL) [Time Frame: 2 years]; differences in surgical outcomes [Time Frame: 90 days]; Complications [Time Frame: 90 days] | **Results:** In total, 106 patients underwent open esophagectomy; 64 underwent minimally invasive esophagectomy (98% RAMIE). The groups did not differ in age, sex, comorbidities, histologic subtype, stage, or induction treatment (P = .42 to P > .95). Total Functional Assessment of Cancer Therapy-Esophageal scores were lower at 1 month (P < .001), returned to near baseline by 4 months, and did not differ between groups (P = .83). Brief Pain Inventory average pain severity (P = .007) and interference (P = .004) were lower for RAMIE. RAMIE had lower estimated blood loss (250 vs 350 cm3; P < .001), shorter length of stay (9 vs 11 days; P < .001), fewer intensive care unit admissions (8% vs 20%; P = .033), more lymph nodes harvested (25 vs 22; P = .05), and longer surgical time (6.4 vs 5.4 hours; P < .001). Major complications (39% for RAMIE vs 52% for open esophagectomy; P > .95), anastomotic leak (3% vs 9%; P = .41), and 90-day mortality (2% vs 4%; P = .85) did not differ between groups. Pulmonary (14% vs 34%; P = .014) and infectious (17% vs 36%; P = .029) complications were lower for RAMIE. |

**Veenstra, M. M. K. et al. Complications and survival after hybrid and fully minimally invasive oesophagectomy. BJS Open. 5. . 2021**

| Evidence level | Methodical Notes | Patient characteristics | Interventions |
|---|---|---|---|
| **Evidence level:** 3<br>**Study** | **Funding sources:**<br>**Conflict of Interests:**<br>**Randomization:** | **Total no. patients:** 828<br>**Recruiting Phase:** August 1993 and September 2019 | **Interventions:** Minimally invasive oesophagectomy |

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| **type:** prospective study | **Blinding:**<br>**Dropout rates:** | **Inclusion criteria:** Patients were included in this study if they had either a threephase (McKeown) MIO or HMIO (open abdomen) with cervical anastomosis<br>**Exclusion criteria:** Patients were excluded if they underwent twophase (Ivor Lewis) oesophagectomy or had undergone salvage surgery following definitive chemoradiotherapy | **Comparison:** Hybrid Minimally invasive oesophagectomy |
| **Notes:** | Newcastle-Ottawa Scale (NOS) for Cohort studies: 9/9 stars<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 3 (Cohort study / Non-randomized controlled cohort).<br><br>**Author's conclusion:** MIO had a small benefit in terms of blood loss and hospital stay, but not in operating time. Oncological outcomes were similar in the two groups. Postoperative complications were associated with pre-existing cardiorespiratory co-morbidities rather than operative approach. | | |
| **Outcome Measures/results** | **Primary** postoperative complications<br>**Secondary** Duration of operation, blood transfusion requirement, duration of hospital stay, overall survival | **Results:** There were 828 patients, of whom 722 had HMIO and 106 MIO, without significant baseline differences. Median duration of operation was longer for MIO (325 versus 289 min; P < 0.001), but with less blood loss (median 250 versus 300 ml; P < 0.001) and a shorter hospital stay (median 12 versus 13 days; P = 0.006). Respiratory complications were not associated with operative approach (31.1 versus 35.2 per cent for MIO and HMIO respectively; P = 0.426). Anastomotic leak rates (10.4 versus 10.2 per cent) and 90-day mortality (1.0 versus 1.7 per cent) did not differ. Cardiac co-morbidity was associated with more medical and surgical complications. Overall survival was associated with AJCC stage and co-morbidities, but not operative approach. | |

| **Vimolratana, M. et al. Two-Year Quality of Life Outcomes After Robotic-Assisted Minimally Invasive and Open Esophagectomy. Ann Thorac Surg. 112. 880-889. 2021** | | | |
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| **Evidence level** | **Methodical Notes** | **Patient characteristics** | **Interventions** |
| **Evidence level:** 4<br>**Study type:** a prospective, nonrandomized trial | **Funding sources:**<br>**Conflict of Interests:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout rates:** | **Total no. patients:** 170<br>**Recruiting Phase:** March 2012 till August 2014<br>**Inclusion criteria:** Diagnosis of esophageal cancer, stages I-IIIC, with no prior esophageal resection. Neoadjuvant therapy given prior to presentation at MSKCC. Anticipated to undergo surgical resection (Ivor Lewis, Trans Hiatal, thoracoabdominal, or McKeown procedure) of esophageal cancer either by open or minimally invasive methods.<br>**Exclusion criteria:** Patients requiring laryngectomy or colon interposition were excluded | **Interventions:** Robotic-Assisted Minimally Invasive Esophagectomy<br><br>**Comparison:** Open Esophagectomy |
| **Notes:** | Newcastle-Ottawa Scale (NOS) for Cohort studies: 5/9 stars<br>Downgrade due 0 or 1 stars in outcome/exposure domain.<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 3 (Cohort study / Non-randomized controlled cohort).<br>Downgrade to evidence level 4 due to high risk of bias.<br>**Author's conclusion:** during 2 years of follow-up, RAMIE was associated with improved patient-reported QOL, compared with OE, especially in esophageal symptoms and emotional well-being. RAMIE was also associated with decreased postoperative pain. However, pain interference did not differ between surgical groups. Taken together, these findings suggest that RAMIE may offer HRQOL benefits to patients undergoing curative resection for esophageal cancer and should receive consideration as a minimally invasive alternative to OE. | | |

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| **Outcome Measures/results** | **Primary** patient-reported QOL, measured by the Functional Assessment of Cancer Therapy–Esophageal (FACT-E), and pain, measured by the Brief Pain Inventory (BPI)<br>**Secondary** complications and perioperative outcomes | **Results:** Esophagectomy was performed in 170 patients (106 OE and 64 RAMIE). The groups did not differ significantly by any measured clinicopathologic variables. After covariates were controlled for, FACT-E scores were higher in the RAMIE cohort than in the OE cohort (parameter estimate [PE], 6.13; P-adj = .051). RAMIE was associated with higher esophageal cancer subscale (PE, 2.72; P-adj = .022) and emotional well-being (PE, 1.25; P-adj = .016) scores. BPI pain severity scores were lower in the RAMIE cohort than in the OE cohort (PE, -0.56; P-adj = .005), but pain interference scores did not differ significantly between groups (P-adj = .11). |

**Zheng, Y. et al. Minimally Invasive Versus Open McKeown for Patients with Esophageal Cancer: A Retrospective Study. Ann Surg Oncol. 28. 6329-6336. 2021**

| Evidence level | Methodical Notes | Patient characteristics | Interventions |
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| **Evidence level:** 4<br>**Study type:** A Retrospective Study | **Funding sources:**<br>**Conflict of Interests:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout rates:** | **Total no. patients:** 502<br>**Recruiting Phase:** 1 January 2015 to 6 January 2018c<br>**Inclusion criteria:** consecutive thoracic EC patients, pathological T stage 3 according to the 2009 American Joint Committee on Cancer (AJCC) TNM staging criteria; surgically resected EC via either McKeownMIE or McKeown-OE; and more than 14 lymph nodes harvested during the operation (at least two-field lymphadenectomy)<br>**Exclusion criteria:** missing information on follow-up | **Interventions:** McKeown minimally invasive esophagectomy<br><br>**Comparison:** McKeown open esophagectomy |
| **Notes:** | Newcastle-Ottawa Scale (NOS) for Cohort studies: 6/9 stars<br>Downgrade due 0 stars in comparability domain.<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 3 (Cohort study / Non- | | |

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| | randomized controlled cohort).<br>Downgrade to evidence level 4 due to high risk of bias.<br>**Author's conclusion:** These results showed that McKeown-MIE was associated with better long-term survival than McKeown-OE for patients with resectable EC. | |
| **Outcome Measures/results** | **Primary** longterm survival<br>**Secondary** | **Results:** We included 502 patients who underwent McKeown-MIE (n = 306) or McKeown-OE (n = 196) for EC. The median age in the total patient population was 63 years. All baseline characteristics were well-balanced between the two groups. There was a significantly shorter mean operative time (269.76 min vs. 321.14 min, p < 0.001) in the OE group. The 30-day and in-hospital mortality rates were 0, and there was no difference in 90-day mortality (p = 0.053) between the groups. The postoperative stay was shorter in the MIE group and was 14 days and 18 days in the MIE and OE groups, respectively (p < 0.001). The OS at 60 months was 58.8% and 41.6% in the MIE and OE groups, respectively (p < 0.001) [hazard ratio 1.783, 95% confidence interval 1.347-2.359]. |

## 3.5 Schlüsselfrage 4: Stellenwert der standardisierten Nachsorge nach kurativer Ösophagus-Karzinom Therapie

**Schlüsselfrage:**

**04 Stellenwert der standardisierten Nachsorge nach kurativer Ösophagus-Karzinom Therapie**
P: 1)Pat. mit gesichertem Plattenepithel- oder Adenokarzinom des Ösophagus, 2) Pat mit AEG 1-3, 1) und 2) nach kurativer Resektion, oder definitiver Radiochemotherapie, oder watch and wait nach kompletter Remission
I: strukturierte Nachsorge
C: a) keine Nachsorge, b) symptomorientierte Nachsorge
O: Patientenrelevante Endpunkte: Gesamtüberlebensrate, Überlebensrate nach 5 Jahren und 3 Jahren (ggfls. „Ableitung“ aus Überlebenskurven, wenn nicht im Text berichtet), medianes ÜL, Morbidität, LQ, Rate an Lokal- und Fernrezidiven im Beobachtungszeitraum, Fernmetastasierung

***Inhalt:*** *3 Literaturstellen*

| Literaturstelle | Evidenzlevel | Studientyp |
|---|---|---|
| Bjerring, O. S. 2019 | 2 | Phase II randomized clinical trial |
| Bjerring, O. S. 2021 | 2 | Phase II randomized clinical trial |
| Jiang, D. M. 2020 | 3 | A single-site, retrospective cohort study |

***Cochrane Risk of Bias Tool 1 (RCT):*** *2 Bewertung(en)*

| **Bjerring, O. S. et al. Phase II randomized clinical trial of endosonography and PET/CT versus clinical assessment only for follow-up after surgery for upper gastrointestinal cancer (EUFURO study). Br J Surg. 106. 1761-1768. 2019** | | | |
|---|---|---|---|
| **Population** | **Intervention / Comparison** | **Outcomes/Results** | **Methodical Notes** |
| **Evidence level:** 2<br>**Study type:** Phase II randomized clinical trial<br>**Number of Patients:** 183<br>**Recruiting Phase:** March 2011 till April 2014<br>**Inclusion Criteria:** R0-resection for primary adenocarcinoma or squamous cell carcinoma of the esophagus, stomach or pancreas.<br>**Exclusion Criteria:** | **Intervention:** clinical assessment only for follow-up after surgery for upper gastrointestinal cancer<br>**Comparison:** endosonography and PET/CT for follow-up after surgery for upper gastrointestinal cancer | **Primary:** number of patients receiving oncological treatment for recurrence<br>**Secondary:** overall and progression-free survival, survival after recurrence detection of isolated locoregional recurrences and risk factors affecting survival<br>**Results:** In total, 183 patients were enrolled, including 93 who underwent standard follow-up and 90 who had follow-up plus imaging. A recurrence was detected in 84 patients within 2 years after surgery (42 in each group), including 33 of 42 patients in the imaging group who were asymptomatic. Some 25 of 42 patients in the imaging group and 14 of 42 in the standard group received chemotherapy (P = 0Â·028). Although survival after detection of recurrence in asymptomatic patients was significantly longer than that for symptomatic patients (P < 0Â·001), overall survival from date of surgery in the two treatment groups was comparable. | **Funding Sources:**<br>**COI:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout Rate/ITT-Analysis:**<br>**Notes:** Cochrane risk of bias tool 1 (RoB 1):<br>(1 unclear risks of bias (#6 reporting bias) was observed)<br>Overall risk of bias: Low<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits / Prognosis): 2 (Randomized trial). |

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| | | **Author's Conclusion:** Follow-up after surgery for upper gastrointestinal cancer with EUS and PET/CT leads to detection of more asymptomatic cancer recurrences and patients referred for treatment without prolonging overall survival. | |

**Bjerring, O. S. et al. Value of regular endosonography and [18F]fluorodeoxyglucose PET-CT after surgery for gastro-oesophageal junction, stomach or pancreatic cancer. BJS Open. 5. . 2021**

| Population | Intervention / Comparison | Outcomes/Results | Methodical Notes |
|---|---|---|---|
| **Evidence level:** 2<br>**Study type:** Phase II randomized clinical trial<br>**Number of Patients:** 191<br>**Recruiting Phase:** March 2011 till April 2014<br>**Inclusion Criteria:** All patients who had undergone radical resection for adenocarcinomas in the GOJ, stomach or pancreas in the Department of Surgery, Odense University Hospital, Denmark, and who were eligible for oncological treatment at the time of assessment 1 month after surgery<br>**Exclusion Criteria:** | **Intervention:** Standard outpatient follow-up<br>**Comparison:** PET/CT and EUS at 3,6,9,12,18 and 24 months after surgery | **Primary:**<br>**Secondary:**<br>**Results:** During the scheduled follow-up, 42 of 89 patients developed recurrence; PET-CT and EUS in combination detected 38 of these recurrences. EUS detected 23 of the 42 patients with recurrent disease during follow-up and correctly diagnosed 17 of 19 locoregional recurrences. EUS was able to detect isolated locoregional recurrence in 11 of 13 patients. In five patients, EUS was false-positive for isolated locoregional recurrence owing to missed distant metastases. PET-CT detected locoregional recurrence in only 12 of 19 patients, and isolated locoregional recurrence in only 7 of 13. False-positive PET- | **Funding Sources:**<br>**COI:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout Rate/ITT-Analysis:**<br>**Notes:** Cochrane risk of bias tool 1 (RoB 1):<br>(1 unclear risks of bias (#6 reporting bias) were observed)<br>Overall risk of bias: Low<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits / |

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| | | CT results in 23 patients led to a total of 44 futile procedures.<br>**Author's Conclusion:** Accuracy in detecting recurrences by concomitant use of PET-CT and EUS was high (90 per cent). PET-CT had moderate to high sensitivity for overall recurrence detection, but low specificity. EUS was superior to PET-CT in the detection of locoregional and isolated locoregional recurrences. | Prognosis): 2 (Randomized trial). |

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

| **Jiang, D. M. et al. Surveillance and outcomes after curative resection for gastroesophageal adenocarcinoma. Cancer Med. 9. 3023-3032. 2020** | | | |
|---|---|---|---|
| **Evidence level** | **Methodical Notes** | **Patient characteristics** | **Interventions** |
| **Evidence level:** 3<br>**Study type:** A single-site, retrospective cohort study | **Funding sources:**<br>**Conflict of Interests:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout rates:** | **Total no. patients:** 210<br>**Recruiting Phase:** 2011 till 2016<br>**Inclusion criteria:** patients with esophageal, gastroesophageal junction (GEJ), and gastric adenocarcinoma who had curative resection<br>**Exclusion criteria:** | **Interventions:**<br><br>**Comparison:** |
| **Notes:** | Newcastle-Ottawa Scale (NOS) for Cohort studies: 8/9 stars<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits/ Prognosis): 3 (Cohort study / Non-randomized controlled cohort).<br>**Author's conclusion:** Among patients surveyed, 96% of recurrences were distant, and salvage therapy was successful in only 1.9% of patients. Longer OS in patients with surveillance-detected compared to symptomatic recurrences was not associated with significant earlier disease detection, and may be contributed by differences in disease biology. Further prospective data are warranted to establish the benefit of surveillance testing in gastroesophageal adenocarcinoma. | | |
| **Outcome Measures/results** | **Primary** (a) recurrence patterns<br>(b) frequency of successful salvage therapy<br>(c) outcomes for patients with asymptomatic recurrence detected by surveillance testing compared to those | **Results:** Between 2011 and 2016, 210 consecutive patients were reviewed. Esophageal (14%), gastroesophageal junction (40%), and gastric adenocarcinomas (45%) were treated with surgery alone (29%) or multimodality therapy (71%). Adjuvant therapy was administered in 35%. At median follow-up of 38.3 months, 5-year overall survival (OS) rate was 56%. Among 97 recurrences, 53% were surveillance-detected, and 46% were | |

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| | with symptomatic recurrence<br>**Secondary** | symptomatic. None was detected by surveillance endoscopy. Median time-to-recurrence (TTR) was 14.8 months. Recurrences included locoregional only (4%), distant (86%), and both (10%). Salvage therapy was attempted in 15 patients, 4 were successful. Compared to symptomatic recurrences, patients with surveillance-detected recurrences had longer median OS (36.2 vs 23.7 months, P = .004) and postrecurrence survival (PRS, 16.5 vs 4.6 months, P < .001), but similar TTR (16.2 vs 13.3 months, P = .40) and duration of palliative chemotherapy (3.9 vs 3.3 months, P = .64). |

## 3.6 Schlüsselfrage 5: Stellenwert multimodaler incl. chirurgischer Therapiestrategien bei oligometastasierten Tumoren

**Schlüsselfrage:**

**05 Stellenwert multimodaler incl. chirurgischer Therapiestrategien bei oligometastasierten Tumoren**
P: 1)Pat. mit gesichertem Plattenepithel- oder Adenokarzinom des Ösophagus in Abhängigkeit von der Tumorhöhe (zervikal, thorakal suprabifurkal, thorakalinfrabifurkal, abdominell bzw. nur supra-/infrabifurkal) 2)bzw. Pat. mit gesichertem AEG 1-3, 1) und 2) mit Lungen und/oder Lebermetastasen
I: a) Metastasenresektion, b) Radiotherapie (stereotaktische Bestrahlung)
C: a) keine Metastasenresektion, b) palliative Chemotherapie, c) Immuntherapie, d) Radio(chemo)therapie
O: Patientenrelevante Endpunkte: Gesamtüberlebensrate, Überlebensrate nach 5 Jahren und 3 Jahren (ggfls. „Ableitung“ aus Überlebenskurven, wenn nicht im Text berichtet), medianes ÜL, Rate an Lokal- und Fernrezidiven im Beobachtungszeitraum, Häufigkeit schwerer und lebensbedrohlicher NW bzw. Letalität durch die OP/ Radio/ Chemotherapie im Vergleich zu anderen Therapieverfahren

***Inhalt:*** *2 Literaturstellen*

| Literaturstelle | Evidenzlevel | Studientyp |
|---|---|---|
| Li, B. 2020 | 4 | retrospective |
| Ohkura, Y. 2020 | 4 | database, prospectively |

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

| **Li, B. et al. Development and validation of a nomogram prognostic model for esophageal cancer patients with oligometastases. Sci Rep. 10. 11259. 2020** | | | |
|---|---|---|---|
| **Evidence level** | **Methodical Notes** | **Patient characteristics** | **Interventions** |
| **Evidence level:** 4<br>**Study type:** retrospective | **Funding sources:**<br>**Conflict of Interests:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout rates:** | **Total no. patients:** 273 oligometastatic EC patients<br>**Recruiting Phase:** March 2013 till December 2018<br>**Inclusion criteria:** (1) pathological diagnosis of EC<br>(2) newly diagnosed inoperable metastatic EC<br>(3) oligometastatic tumor that was defned as 1–5 metastases<br>(4) available medical records<br>**Exclusion criteria:** | **Interventions:** local treatment for metastases and local radiotherapy for esophageal cancer with oligometastases<br><br>**Comparison:** |
| **Notes:** | Newcastle-Ottawa Scale (NOS) for Cohort studies: 4/9 stars<br>Downgrade due to 0 or 1 star in selection domain and 0 stars in comparability domain.<br>Unclear if the cohort is representative how exposed and non-exposed are selected and ajdustments were made in the statistical model<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 3 (Cohort study or control arm of randomized trial).<br>Downgrade to evidence level 4 due to high risk of bias. | | |

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| | **Author's conclusion:** Oligometastatic EC patients with history of alcohol consumption, longer tumor had inferior PFS. And male patients with esophageal fstula, multiple metastatic organs were found to have inferior OS. Furthermore, local treatment for metastases and local radiotherapy for EC were demonstrated to be benefcial to the survival of oligometastatic EC patients. Te prognostic nomograms were able to predict individual survival and provide evidence for clinical decision-making. | |
| **Outcome Measures/results** | **Primary** prognostic factors for progression-free survival (PFS) and overall survival (OS)<br>**Secondary** | **Results:** In this study, characteristics of 273 oligometastatic EC patients were analyzed using univariate and multivariate Cox models to determine the independent prognostic factors for progression-free survival (PFS) and overall survival (OS). The result showed that history of alcohol consumption, longer tumor, no local radiotherapy for EC, and no local treatment for metastases were independent factors for PFS. Sex, esophageal fistula, number of metastatic organs, and local radiotherapy for EC were independent prognostic factors for OS. On the basis of Cox models, the respective nomogram for prediction of PFS and OS was established with the corrected concordance index of 0.739 and 0.696 after internal cross-validation. |

**Ohkura, Y. et al. Clinicopathologic Characteristics of Oligometastases from Esophageal Cancer and Long-Term Outcomes of Resection. Ann Surg Oncol. 27. 651-659. 2020**

| Evidence level | Methodical Notes | Patient characteristics | Interventions |
|---|---|---|---|
| **Evidence level:** 4<br>**Study type:** database, prospectively | **Funding sources:**<br>**Conflict of Interests:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout rates:** | **Total no. patients:** 206<br>**Recruiting Phase:** January 2011 till June 2017<br>**Inclusion criteria:** patients | **Interventions:** surgical resection of recurrence after radical therapy for esophageal cancer<br><br>**Comparison:** |

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|---|---|---|---|
| | | with esophageal cancer<br>**Exclusion criteria:** | |
| **Notes:** | Newcastle-Ottawa Scale (NOS) for Cohort studies: 6/9 stars<br>Downgrade due to 0 stars in comparability domain.<br>Unclear wether adjustment for confounding was applied.<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Prognosis ): 3 4 (Cohort study / Control arm of randomized trial).<br>Downgrade to evidence level 4 due to high risk of bias.<br>**Author's conclusion:** In this study, the overall survival rate was significantly better for the patients who underwent resection of oligometastases than for those who did not. Recurrence of esophageal cancer in the form of oligometastases could be an independent predictor of overall survival for patients who have undergone radical treatment. | | |
| **Outcome Measures/results** | **Primary** long-term outcomes for patients with oligometastases from esophageal cancer after radical therapy and the effectiveness of resection in oligometastic disease.<br>**Secondary** | **Results:** In the multivariate analysis, oligometastatic presentation was the only factor associated with survival after recurrence (hazard ratio 6.29; 95% confidence interval, 4.10-9.71). The actuarial survival rates for the patients with oligometastases were 59.5% at 3 years and 51.7% at 5 years. The survival rates at 3 and 5 years were significantly higher for the patients who underwent resection (64.3% and 55.6%, respectively) than for those who did not (both 100%) and for the patients with multiple metastases (9.8% and 0%, respectively). The survival rates for the patients who had oligometastases without resection were comparably lower than for the patients with multiple metastases. | |

## 3.7 Schlüsselfrage 6.1: Verbessert eine adjuvante Radio- oder Radio chemotherapie das Überleben?

**Schlüsselfrage:**

**06.1 Verbessert eine adjuvante Radio- oder Radio chemotherapie das Überleben?**
P: 1)Pat. mit Plattenepithelkarzinom des Ösophagus (pN0 separat von pN1 (UICC 6th) bzw. pN1-3 (7th Edition) 2)Pat mit Adenokarzinom des Ösophagus oder des ösophago-gastralen Übergangs pN0 separat von pN1 (UICC 6th) bzw. pN1-3 (7th Edition)
I: Postoperative adjuvante Radio- oder Radiochemotherapie (für RCT simultan; unabhängig von der Dosierung der Radiotherapie und der gewählten Chemotherapie
C: a)keine postoperative adjuvante Radio- oder Radiochemotherapie
O: Patientenrelevante Endpunkte: Gesamtüberlebensrate, Überlebensrate nach 5 Jahren und 3 Jahren (ggfls. „Ableitung“ aus Überlebenskurven, wenn nicht im Text berichtet), medianes ÜL, Rate an Lokalrezidiven und Rezidiven im Beobachtungszeitraum, Häufigkeit schwerer und lebensbedrohlicher NW durch adjuvante Therapie

***Inhalt:*** *4 Literaturstellen*

| Literaturstelle | Evidenzlevel | Studientyp |
|---|---|---|
| Deng, W. 2020 | 2 | Prospective, Phase III, Randomized Controlled Study |
| Ni, W. 2021 | 2 | A Phase III Randomized Controlled Trial |
| Park, S. R. 2019 | 2 | single-center, open-label, randomized, phase III trial |
| Semenkovich, T. R. 2019 | 3 | retrospective cohort study |

***Cochrane Risk of Bias Tool 1 (RCT):*** *3 Bewertung(en)*

| **Deng, W. et al. Postoperative Radiotherapy in Pathological T2-3N0M0 Thoracic Esophageal Squamous Cell Carcinoma: Interim Report of a Prospective, Phase III, Randomized Controlled Study. Oncologist. 25. e701-e708. 2020** | | | |
|---|---|---|---|
| **Population** | **Intervention / Comparison** | **Outcomes/Results** | **Methodical Notes** |
| **Evidence level:** 2<br>**Study type:** Prospective, Phase III, Randomized Controlled Study<br>**Number of Patients:** 167<br>**Recruiting Phase:** October 2012 to February 2018<br>**Inclusion Criteria:** Patients who received R0 esophagectomy and at least twofield lymphadenectomy (resection of mediastinal and abdominal lymph nodes) as their first treatment and who were pathologically confirmed as having T2–3N0 thoracic esophageal squamous cell carcinoma, according to the Union for International Cancer Control (UICC) 7th tumor-node-metastasis (TNM) classification<br>**Exclusion Criteria:** Patients with residual diseases, recurrences, or | **Intervention:** Postoperative Radiotherapy in Pathological T2–3N0M0 Thoracic Esophageal Squamous Cell Carcinoma<br>**Comparison:** | **Primary:** disease-free survival<br>**Secondary:** ocal-regional recurrence rate, overall survival, and radiation-related toxicities<br>**Results:** From October 2012 to February 2018, 167 patients were enrolled in this study. We analyzed 157 patients whose follow-up time was more than 1 year or who had died. The median follow-up time was 45.6 months. The 3-year disease-free survival rates were 75.1% (95% confidence interval [CI] 65.9-85.5) in the postoperative radiotherapy group and 58.7% (95% CI 48.2-71.5) in the surgery group (hazard ratio 0.53, 95% CI 0.30-0.94, p = .030). Local-regional recurrence rate decreased significantly in the radiotherapy group (10.0% vs. 32.5% in the surgery group, p = .001). The overall survival and distant metastasis rates were not significantly different | **Funding Sources:**<br>**COI:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout Rate/ITT-Analysis:**<br>**Notes:** Cochrane risk of bias tool 1 (RoB 1):<br>(1 high risk of bias (#2 Selection bias), 1 unclear risks of bias (#6 Reporting bias) were observed)<br>Overall risk of bias: Low<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 2 (Randomized trial). |

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| distant metastases before randomization; severe postoperative complications or comorbidities that ruled them out for receiving radiotherapy; or a history of other secondary malignancies | | between two groups. Grade 3 toxicity rate related to radiotherapy was 12.5%. **Author's Conclusion:** This study suggested that postoperative radiotherapy in pathological T2–3N0M0 thoracic esophageal squamous cell carcinoma could potentially increase DFS and reduce local-regional recurrence with low-grade toxicities. However, further enrollment and long-term follow-up are needed to validate the efficacy and safety of this treatment strategy | |

**Ni, W. et al. Postoperative Adjuvant Therapy Versus Surgery Alone for Stage IIB-III Esophageal Squamous Cell Carcinoma: A Phase III Randomized Controlled Trial. Oncologist. 26. e2151-e2160. 2021**

| Population | Intervention / Comparison | Outcomes/Results | Methodical Notes |
|---|---|---|---|
| **Evidence level:** 2<br>**Study type:** A Phase III Randomized Controlled Trial<br>**Number of Patients:** 172<br>**Recruiting Phase:** October 2014 till December 2019<br>**Inclusion Criteria:** (a) age 18–68 years<br>(b) pathologically proven stage IIB–III esophageal | **Intervention:** Postoperative Adjuvant Therapy for Stage IIB–III Esophageal Squamous Cell Carcinoma<br>**Comparison:** Surgery Alone for Stage IIB–III Esophageal Squamous Cell Carcinoma | **Primary:** disease-free survival<br>**Secondary:** overall survival<br>**Results:** A total of 172 patients were enrolled (SA, n = 54; PORT, n = 54; POCRT, n = 64). The 3-year DFS was significantly better in PORT/POCRT patients than in SA patients (53.8% vs. 36.7%; p = .020); the 3-year OS was also better in PORT/POCRT patients (63.9% vs. 48.0%; p = .025). The 3-year DFS for SA, PORT, and POCRT patients were 36.7%, 50.0%, | **Funding Sources:**<br>**COI:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout Rate/ITT-Analysis:**<br>**Notes:** Cochrane risk of bias tool 1 (RoB 1):<br>(2 unclear risks of bias (#2 Selection bias: Allocation |

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| squamous cell carcinoma (according to Union for International Cancer Control [UICC] criteria, 7th edition)<br>(c) undergoing radical resection (R0 indicates no evidence of residual tumor at circumferential margins as well as the proximal and distal margins)<br>(d) no history of other treatment before recruitment<br>(e) Karnofsky performance status score ≥70<br>(f) normal hematology and blood biochemistry<br>(g) fit for intensity-modulated radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT)<br>(h) willing to attend regular follow-up after treatment<br>**Exclusion Criteria:** (a) uncontrolled diabetes mellitus | | 57.3%, respectively (p = .048). The 3-year OS for SA, PORT, and POCRT patients were 48.0%, 60.8%, 66.5%, respectively (p = .048).<br>**Author's Conclusion:** This study is the first randomized controlled trial to explore the effect of postoperative adjuvant therapy for patients with pathological stage IIB–III esophageal cancer. The findings suggest that postoperative treatment (PORT/POCRT) may significantly improve survival in these patients. Postoperative radiotherapy with a reduced radiation field combined with chemotherapy appears to be an effective and safe treatment, with potential for being accepted as a standard treatment option for patients with pathological stage IIB–III esophageal squamous cell carcinoma after radical surgery. | concealment, #6 Reporting bias: Selective reporting) were observed) Overall risk of bias: Low Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 2 (Randomized trial). |

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| (b) interval between the surgical procedure and adjuvant therapy >3 months<br>(c) signs of recurrence on computed tomography (CT), ultrasound, or positron emission tomography (PET)-CT<br>(d) concurrent malignancy or previous malignancy (other than basal cell skin cancer or carcinoma in situ of the cervix) within the past 5 years<br>(e) pregnancy | | | |

**Park, S. R. et al. A Randomized Phase III Trial on the Role of Esophagectomy in Complete Responders to Preoperative Chemoradiotherapy for Esophageal Squamous Cell Carcinoma (ESOPRESSO). Anticancer Res. 39. 5123-5133. 2019**

| Population | Intervention / Comparison | Outcomes/Results | Methodical Notes |
|---|---|---|---|
| **Evidence level:** 2<br>**Study type:** single-center, open-label, randomized, phase III trial<br>**Number of Patients:** 86<br>**Recruiting Phase:** November 2012 till March 2016<br>**Inclusion Criteria:** histologically | **Intervention:** Esophagectomy in Complete Responders to Preoperative Chemoradiotherapy for Esophageal Squamous Cell Carcinoma<br>**Comparison:** | **Primary:** disease-free survival<br>**Secondary:** progression-free survival (PFS; the time between initiation of chemotherapy and progression or death), time to progression (TTP; the time between initiation of chemotherapy and progression), OS | **Funding Sources:**<br>**COI:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout Rate/ITT-Analysis:**<br>**Notes:** Cochrane risk |

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| confirmed, resectable cT3-T4a/anyN/M0 or anyT/N+/M0 (the 7th edition of the AJCC staging system) thoracic ESCC, age 20-75 years, Eastern Cooperative Oncology Group performance status 0-2, adequate major organs function, and no history of other cancers within 5 years. Pre-treatment staging work-up included esophago-gastroduodenoscopy with biopsy, thoracic/abdominal/pelvic computed tomography (CT), endoscopic ultrasonography, bone scan, 18F-fluorodeoxyglucose (FDG)-positron emission tomography (PET), and bronchoscopy when needed.<br>**Exclusion Criteria:** | | (the time between initiation of chemotherapy and death), the failure pattern, the pCR rate, treatment outcomes according to metabolic or clinical response, safety, and quality of life<br>**Results:** Among 86 patients, 38 (44.2%) achieved cCR after chemoradiotherapy; 37 were randomized to surgery (n=19) or observation (n=18). Although there were trends of better disease-free survival (DFS) toward the surgery arm in the intent-to-treat analysis (2-year DFS, 66.7% vs. 42.7%; p=0.262) or as-treated analysis (66.7% vs. 50.2%; p=0.273), overall survival was not different between the two arms in the intent-to-treat (HR=1.48; p=0.560) or as-treated analysis (HR=1.09; p=0.903). Among the 11 patients having recurrence during observation, 8 underwent surgery (n=7) or endoscopic dissection (n=1).<br>**Author's Conclusion:** our study suggests that close observation with salvage surgery as appropriate might | of bias tool 1 (RoB 1): (2 unclear risks of bias (#2 Selection bias: Allocation concealment, #6 Reporting bias: Selective reporting) were observed)<br>Overall risk of bias: Low<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 2 (Randomized trial). |

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| | | be a reasonable option in patients with thoracic ESCC achieving a cCR to chemoradiation. Further large-scale prospective studies are necessary to confirm our results and optimize the treatment decision in individual patients. | |

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

| **Semenkovich, T. R. et al. Adjuvant Therapy for Node-Positive Esophageal Cancer After Induction and Surgery: A Multisite Study. Ann Thorac Surg. 108. 828-836. 2019** | | | |
|---|---|---|---|
| **Evidence level** | **Methodical Notes** | **Patient characteristics** | **Interventions** |
| **Evidence level:** 3<br>**Study type:** retrospective cohort study | **Funding sources:**<br>**Conflict of Interests:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout rates:** | **Total no. patients:**<br>**Recruiting Phase:** 2000–2014<br>**Inclusion criteria:** patients who received neoadjuvant treatment, underwent esophagectomy, and had positive lymph nodes on pathology<br>**Exclusion criteria:** underwent total gastrectomy, had unknown adjuvant treatment status, died prior to eligibility (â‰¤90 days) for adjuvant therapy, had pathologic M1 disease, had clinical M1 disease with missing pathologic M staging, or had a documented recurrence of cancer prior to administration of adjuvant therapy | **Interventions:** Adjuvant Therapy for Node Positive Esophageal Cancer after Induction and Surgery<br><br>**Comparison:** |
| **Notes:** | Newcastle-Ottawa Scale (NOS) for Cohort studies: 8/9 stars<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 3 (Cohort study / Non-randomized controlled cohort).<br><br>**Author's conclusion:** Adjuvant therapy was associated with improved overall survival. Therefore, consideration should be given to administration of adjuvant therapy to esophageal cancer patients who have persistent node positive disease after induction therapy and esophagectomy, and are able to tolerate additional treatment. | | |

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| **Outcome Measures/results** | **Primary** overall survival **Secondary** | **Results:** 1,082 patients were analyzed with node positive cancer following induction therapy and esophagectomy. 209 (19.3%) received adjuvant therapy and 873 (80.7%) did not. Administration of adjuvant treatment varied significantly from 3.2% to 50.0% between sites (p |

## 3.8 Schlüsselfrage 6.2: Verbessert eine adjuvante Chemotherapie das Überleben?

**Schlüsselfrage:**

**06.2 Verbessert eine adjuvante Chemotherapie das Überleben?**
P: 1)Pat. mit Plattenepithelkarzinom des Ösophagus (pN0 separat von pN1 (UICC 6th) bzw. pN1-3 (7th Edition) 2)Pat mit Adenokarzinom des Ösophagus oder des ösophago-gastralen Übergangs pN0 separat von pN1 (UICC 6th) bzw. pN1-3 (7th Edition) nach R0 Resektion
I: Postoperative Chemotherapie
C: keine postoperative Chemotherapie
O: Patientenrelevante Endpunkte: Gesamtüberlebensrate, Überlebensrate nach 5 Jahren und 3 Jahren (ggfls. „Ableitung“ aus Überlebenskurven, wenn nicht im Text berichtet), medianes ÜL, Rate an Lokalrezidiven und Rezidiven im Beobachtungszeitraum, Häufigkeit schwerer und lebensbedrohlicher NW durch adjuvante Therapie

***Inhalt:*** *2 Literaturstellen*

| Literaturstelle | Evidenzlevel | Studientyp |
|---|---|---|
| Ni, W. 2021 | 2 | A Phase III Randomized Controlled Trial |
| Semenkovich, T. R. 2019 | 3 | retrospective cohort study |

***Cochrane Risk of Bias Tool 1 (RCT):*** *1 Bewertung(en)*

| **Ni, W. et al. Postoperative Adjuvant Therapy Versus Surgery Alone for Stage IIB-III Esophageal Squamous Cell Carcinoma: A Phase III Randomized Controlled Trial. Oncologist. 26. e2151-e2160. 2021** | | | |
|---|---|---|---|
| **Population** | **Intervention / Comparison** | **Outcomes/Results** | **Methodical Notes** |
| **Evidence level:** 2<br>**Study type:** A Phase III Randomized Controlled Trial<br>**Number of Patients:** 172<br>**Recruiting Phase:** October 2014 till December 2019<br>**Inclusion Criteria:** (a) age 18–68 years<br>(b) pathologically proven stage IIB–III esophageal squamous cell carcinoma (according to Union for International Cancer Control [UICC] criteria, 7th edition)<br>(c) undergoing radical resection (R0 indicates no evidence of residual tumor at circumferential margins as well as the proximal and distal margins)<br>(d) no history of other | **Intervention:** Postoperative Adjuvant Therapy for Stage IIB–III Esophageal Squamous Cell Carcinoma<br>**Comparison:** Surgery Alone for Stage IIB–III Esophageal Squamous Cell Carcinoma | **Primary:** disease-free survival<br>**Secondary:** overall survival<br>**Results:** A total of 172 patients were enrolled (SA, n = 54; PORT, n = 54; POCRT, n = 64). The 3-year DFS was significantly better in PORT/POCRT patients than in SA patients (53.8% vs. 36.7%; p = .020); the 3-year OS was also better in PORT/POCRT patients (63.9% vs. 48.0%; p = .025). The 3-year DFS for SA, PORT, and POCRT patients were 36.7%, 50.0%, 57.3%, respectively (p = .048). The 3-year OS for SA, PORT, and POCRT patients were 48.0%, 60.8%, 66.5%, respectively (p = .048).<br>**Author's Conclusion:** This study is the first randomized controlled trial to explore the effect of postoperative adjuvant therapy for patients with pathological stage IIB–III esophageal cancer. The findings suggest that postoperative treatment (PORT/POCRT) may significantly improve survival in these patients. Postoperative radiotherapy with a | **Funding Sources:**<br>**COI:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout Rate/ITT-Analysis:**<br>**Notes:** Cochrane risk of bias tool 1 (RoB 1):<br>(2 unclear risks of bias (#2 Selection bias: Allocation concealment, #6 Reporting bias: Selective reporting) were observed)<br>Overall risk of bias: Low<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 2 (Randomized trial). |

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| treatment before recruitment<br>(e) Karnofsky performance status score ≥70<br>(f) normal hematology and blood biochemistry<br>(g) fit for intensity-modulated radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT)<br>(h) willing to attend regular follow-up after treatment<br>**Exclusion Criteria:** (a) uncontrolled diabetes mellitus<br>(b) interval between the surgical procedure and adjuvant therapy >3 months<br>(c) signs of recurrence on computed tomography (CT), ultrasound, or positron emission tomography (PET)-CT<br>(d) concurrent malignancy or previous malignancy (other than basal cell skin cancer or | | reduced radiation field combined with chemotherapy appears to be an effective and safe treatment, with potential for being accepted as a standard treatment option for patients with pathological stage IIB–III esophageal squamous cell carcinoma after radical surgery. | |

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| carcinoma in situ of the cervix) within the past 5 years<br>(e) pregnancy | | | |

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

| **Semenkovich, T. R. et al. Adjuvant Therapy for Node-Positive Esophageal Cancer After Induction and Surgery: A Multisite Study. Ann Thorac Surg. 108. 828-836. 2019** | | | |
|---|---|---|---|
| **Evidence level** | **Methodical Notes** | **Patient characteristics** | **Interventions** |
| **Evidence level:** 3<br>**Study type:** retrospective cohort study | **Funding sources:**<br>**Conflict of Interests:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout rates:** | **Total no. patients:**<br>**Recruiting Phase:** 2000–2014<br>**Inclusion criteria:** patients who received neoadjuvant treatment, underwent esophagectomy, and had positive lymph nodes on pathology<br>**Exclusion criteria:** underwent total gastrectomy, had unknown adjuvant treatment status, died prior to eligibility (â‰¤90 days) for adjuvant therapy, had pathologic M1 disease, had clinical M1 disease with missing pathologic M staging, or had a documented recurrence of cancer prior to administration of adjuvant therapy | **Interventions:** Adjuvant Therapy for Node Positive Esophageal Cancer after Induction and Surgery<br><br>**Comparison:** |
| **Notes:** | Newcastle-Ottawa Scale (NOS) for Cohort studies: 8/9 stars<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 3 (Cohort study / Non-randomized controlled cohort).<br><br>**Author's conclusion:** Adjuvant therapy was associated with improved overall survival. Therefore, consideration should be given to administration of adjuvant therapy to esophageal cancer patients who have persistent node positive disease after induction therapy and esophagectomy, and are able to tolerate additional treatment. | | |

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| **Outcome Measures/results** | **Primary** overall survival **Secondary** | **Results:** 1,082 patients were analyzed with node positive cancer following induction therapy and esophagectomy. 209 (19.3%) received adjuvant therapy and 873 (80.7%) did not. Administration of adjuvant treatment varied significantly from 3.2% to 50.0% between sites (p |

## 3.9 Schlüsselfrage 6.4: Verbessert eine präoperative bzw. prä- und) postoperative (fortgesetzte Chemotherapie das Überleben?

**Schlüsselfrage:**

**06.4 Verbessert eine präoperative bzw. prä- und) postoperative (fortgesetzte Chemotherapie das Überleben? (Fragestellung 1 für Evidenzbericht: "Indikation, Nutzen und Schaden neoadjuvanter Therapieverfahren")**
P: 1)Pat. mit Plattenepithelkarzinom des Ösophagus (Stadium bis T2N1M0 (UICC6th) bzw. bis T2N1-3M0 (UICC7th) separat von Stadium T3-4NalleM0 2)Pat mit Adenokarzinom des Ösophagus oder des ösophago-gastralen Übergangs (Stadium bis T2N1M0 (UICC6th) bzw. bis T2N1-3M0 (UICC7th) separat von Stadium T3-4NalleM0
I: neoadjuvante Chemotherapie unabhängig von Art und Dauer
C: keine neoadjuvante Therapie=chirurgische Therapie
O: Patientenrelevante Endpunkte: Gesamtüberlebensrate, Überlebensrate nach 5 Jahren und 3 Jahren (ggfls. „Ableitung" aus Überlebenskurven, wenn nicht im Text berichtet), medianes ÜL, Rate an R0 Resektionen, Rate an Fernrezidiven im Beobachtungszeitraum, Häufigkeit schwerer und lebensbedrohlicher NW durch die Chemotherapie in der präoperativen und postoperativen Phase

***Inhalt:*** *3 Literaturstellen*

| Literaturstelle | Evidenzlevel | Studientyp |
|---|---|---|
| Kamarajah, S. K. 2022 | 3 | international, multicenter prospective cohort study |
| Park, S. R. 2019 | 2 | single-center, open-label, randomized, phase III trial |
| Steber, C. 2021 | 3 | retrospective analysis of a prospectively maintained database |

***Cochrane Risk of Bias Tool 1 (RCT):*** *1 Bewertung(en)*

| **Park, S. R. et al. A Randomized Phase III Trial on the Role of Esophagectomy in Complete Responders to Preoperative Chemoradiotherapy for Esophageal Squamous Cell Carcinoma (ESOPRESSO). Anticancer Res. 39. 5123-5133. 2019** | | | |
|---|---|---|---|
| **Population** | **Intervention / Comparison** | **Outcomes/Results** | **Methodical Notes** |
| **Evidence level:** 2<br>**Study type:** single-center, open-label, randomized, phase III trial<br>**Number of Patients:** 86<br>**Recruiting Phase:** November 2012 till March 2016<br>**Inclusion Criteria:** histologically confirmed, resectable cT3-T4a/anyN/M0 or anyT/N+/M0 (the 7th edition of the AJCC staging system) thoracic ESCC, age 20-75 years, Eastern Cooperative Oncology Group performance status 0-2, adequate major organs function, and no history of other cancers within 5 years. Pre-treatment staging work-up included esophago-gastroduodenoscopy with biopsy, thoracic/abdominal/pelvic computed tomography (CT), endoscopic ultrasonography, bone scan, 18F-fluorodeoxyglucose (FDG)-positron | **Intervention:** Esophagectomy in Complete Responders to Preoperative Chemoradiotherapy for Esophageal Squamous Cell Carcinoma<br>**Comparison:** | **Primary:** disease-free survival<br>**Secondary:** progression-free survival (PFS; the time between initiation of chemotherapy and progression or death), time to progression (TTP; the time between initiation of chemotherapy and progression), OS (the time between initiation of chemotherapy and death), the failure pattern, the pCR rate, treatment outcomes according to metabolic or clinical response, safety, and quality of life<br>**Results:** Among 86 patients, 38 (44.2%) achieved cCR after chemoradiotherapy; 37 were randomized to surgery (n=19) or observation (n=18). Although there were trends of better disease-free survival (DFS) toward the surgery arm in the intent-to-treat analysis (2-year | **Funding Sources:**<br>**COI:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout Rate/ITT-Analysis:**<br>**Notes:** Cochrane risk of bias tool 1 (RoB 1): (2 unclear risks of bias (#2 Selection bias: Allocation concealment, #6 Reporting bias: Selective reporting) were observed)<br>Overall risk of bias: Low<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence |

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| emission tomography (PET), and bronchoscopy when needed.<br>**Exclusion Criteria:** | | DFS, 66.7% vs. 42.7%; p=0.262) or as-treated analysis (66.7% vs. 50.2%; p=0.273), overall survival was not different between the two arms in the intent-to-treat (HR=1.48; p=0.560) or as-treated analysis (HR=1.09; p=0.903). Among the 11 patients having recurrence during observation, 8 underwent surgery (n=7) or endoscopic dissection (n=1).<br>**Author's Conclusion:** our study suggests that close observation with salvage surgery as appropriate might be a reasonable option in patients with thoracic ESCC achieving a cCR to chemoradiation. Further large-scale prospective studies are necessary to confirm our results and optimize the treatment decision in individual patients. | (Treatment benefits): 2 (Randomized trial). |

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

| **Kamarajah, S. K. et al. Postoperative and Pathological Outcomes of CROSS and FLOT as Neoadjuvant Therapy for Esophageal and Junctional Adenocarcinoma: An International Cohort Study from the Oesophagogastric Anastomosis Audit (OGAA). Ann Surg. . . 2022** | | | |
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| **Evidence level** | **Methodical Notes** | **Patient characteristics** | **Interventions** |
| **Evidence level:** 3<br>**Study type:** international, multicenter prospective cohort study | **Funding sources:**<br>**Conflict of Interests:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout rates:** | **Total no. patients:** 718<br>**Recruiting Phase:** 1st April 2018 to 31st December 2018<br>**Inclusion criteria:** adult patients undergoing elective (planned) esophagectomy for esophageal and junctional EAC (including AEG I and II) receiving either CROSS or FLOT were included. All surgical approaches (two-stage Ivor Lewis, threestage McKeown, thoracoabdominal, transhiatal using any combination of open, robotic or standard minimal access approaches) were included, as were thoracic and cervical anastomosis.<br>**Exclusion criteria:** (i) colonic interposition or small bowel jejunal interposition reconstructions<br>(ii) emergency resections<br>(iii) resections for benign disease | **Interventions:** FLOT (fluorouracil, leucovorin, oxaliplatin and the taxane docetaxel) as Neoadjuvant therapy for Esophageal and Junctional Adenocarcinoma<br><br>**Comparison:** CROSS as Neoadjuvant therapy for Esophageal and Junctional Adenocarcinoma |
| **Notes:** | Newcastle-Ottawa Scale (NOS) for Cohort studies: 8/9 stars<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 3 (Cohort study / Non-randomized controlled cohort)<br>**Author's conclusion:** This study provides real-world data CROSS was associated with higher 90-day mortality than | | |

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| | FLOT, related to cardio-pulmonary complications with CROSS. These warrant a further review into causes and mechanisms in selected patients, and at minimum suggest the need for strict radiation therapy quality assurance. Research into impact of higher pCR rates and R0 resections with CROSS compared to FLOT on long-term survival is needed. | |
| **Outcome Measures/results** | **Primary** 90-day mortality, defined as mortality within 90-days of surgery<br>**Secondary** rate of pathologic complete response (pCR), margin-negative resections, postoperative overall or major complications and anastomotic leaks | **Results:** The 90-day mortality was higher after CROSS than FLOT (5% vs 1%, p = 0.005), even on adjusted analyses (odds ratio (OR): 3.97, CI95%: 1.34 - 13.67). Postoperative mortality in CROSS were related to higher pulmonary (74% vs 60%) and cardiac complications (42% vs 20%) compared to FLOT. CROSS was associated with higher pCR rates (18% vs 10%, p = 0.004) and margin-negative resections (93% vs 76%, p < 0.001) compared with FLOT. On adjusted analyses, CROSS was associated with higher pCR rates (OR: 2.05, CI95%: 1.26 - 3.34) and margin-negative resections (OR: 4.55, CI95%: 2.70 - 7.69) compared to FLOT. |

**Steber, C. et al. Cisplatin/5-Fluorouracil (5-FU) Versus Carboplatin/Paclitaxel Chemoradiotherapy as Definitive or Pre-Operative Treatment of Esophageal Cancer. Cureus. 13. e12574. 2021**

| Evidence level | Methodical Notes | Patient characteristics | Interventions |
|---|---|---|---|
| **Evidence level:** 3<br>**Study type:** retrospective analysis of a prospectively maintained database | **Funding sources:**<br>**Conflict of Interests:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout rates:** | **Total no. patients:** 261<br>**Recruiting Phase:** June of 1999 and December of 2018<br>**Inclusion criteria:** histologically confirmed esophageal cancer at presentation, and treatment with concurrent CRT with or without surgical | **Interventions:** Cisplatin/5-Fluorouracil (5-FU) Chemoradiotherapy as Definitive or Pre-Operative Treatment of Esophageal Cancer<br><br>**Comparison:** Carboplatin/Paclitaxel Chemoradiotherapy as Definitive or Pre-Operative Treatment of Esophageal Cancer |

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| | | resection.<br>**Exclusion criteria:** | |
| **Notes:** | Newcastle-Ottawa Scale (NOS) for Cohort studies: 8/9 stars<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 3 (Cohort study / Non-randomized controlled cohort).<br>**Author's conclusion:** Carboplatin/paclitaxel was associated with decreased weight loss and improved pathologic response for trimodality patients when compared to cisplatin/5-FU. We observed no differences in OS, PFS, or post-operative death by chemotherapy regimen for both the entire cohort and trimodality patients. | | |
| **Outcome Measures/results** | **Primary** overall survival<br>**Secondary** | **Results:** We identified 261 patients treated with concurrent carboplatin/paclitaxel (n = 133) or cisplatin/5-FU (n = 128). Weight loss during CRT was lower in patients receiving carboplatin/paclitaxel (median: 7.0 pounds; 4.1% body weight) vs. cisplatin/5-FU (median: 11.0 pounds; 6.5% body weight) ($p < 0.01$). In 117 patients receiving trimodality therapy, post-operative death rates within one month of resection were similar. Pathologic complete response was better with carboplatin/paclitaxel vs. cisplatin/5-FU, 29.6% vs. 21.8% ($p = 0.03$), respectively. In the multivariable analysis, there was no association between chemotherapy regimen and overall survival (OS) or progression-free survival (PFS), though there was a trend toward improved OS with carboplatin/paclitaxel with a HR = 0.75 ($p = 0.08$). Further analysis revealed that trimodality therapy and stage were predictors for improved OS and PFS while female gender and grade predicted for improved PFS. | |

## 3.10 Schlüsselfrage 6.5: Verbessert eine präoperative Radiochemotherapie das Überleben?

**Schlüsselfrage:**

**06.5 Verbessert eine präoperative Radiochemotherapie das Überleben? Zu betrachtende Parameter: Tumorhöhenlokalisation, lokales Tumorstadium, AC versus SCC (Fragestellung 1 für Evidenzbericht: "Indikation, Nutzen und Schaden neoadjuvanter Therapieverfahren")**
P: 1)Pat. mit Plattenepithelkarzinom des Ösophagus (Stadium bis T2N1M0 (UICC6th) bzw. bis T2N1-3M0 (UICC7th) separat von Stadium T3-4NalleM0 2)Pat mit Adenokarzinom des Ösophagus oder des ösophago-gastralen Übergangs (Stadium bis T2N1M0 (UICC6th) bzw. bis T2N1-3M0 (UICC7th) separat von Stadium T3-4NalleM0
I: Neoadjuvante Radiochemotherapie (simultane RCT unabhängig von der Dosierung der Radiotherapie und der gewählten Chemotherapie)
C: a)keine neoadjuvante Therapie=chirurgische Therapie oder neoadjuvante Chemotherapie ohne Radiotherapie
O: Patientenrelevante Endpunkte: Gesamtüberlebensrate, Überlebensrate nach 5 Jahren und 3 Jahren (ggfls. „Ableitung" aus Überlebenskurven, wenn nicht im Text berichtet), medianes ÜL, Rate an R0 Resektionen, Rate an Lokal- und Fernrezidiven im Beobachtungszeitraum, Häufigkeit schwerer und lebensbedrohlicher NW durch die Radio/ Chemotherapie in der präoperativen Phase

***Inhalt:*** *6 Literaturstellen*

| Literaturstelle | Evidenzlevel | Studientyp |
|---|---|---|
| Barbour, A. P. 2020 | 3 | two single-arm, multicentre, prospective, randomised exploratory phase II trial |
| Eyck, B. M. 2021 | 3 | a multicenter randomized controlled CROSS trial |
| Kamarajah, S. K. 2022 | 3 | international, multicenter prospective cohort study |
| Park, S. R. 2019 | 2 | single-center, open-label, randomized, phase III trial |
| Steber, C. 2021 | 3 | retrospective analysis of a prospectively maintained database |

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| Yang, H. 2021 | 2 | multicenter open-label randomized phase 3 clinical trial |

***Cochrane Risk of Bias Tool 1 (RCT):*** *4 Bewertung(en)*

| **Barbour, A. P. et al. Preoperative cisplatin, fluorouracil, and docetaxel with or without radiotherapy after poor early response to cisplatin and fluorouracil for resectable oesophageal adenocarcinoma (AGITG DOCTOR): results from a multicentre, randomised controlled phase II trial. Ann Oncol. 31. 236-245. 2020** | | | |
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| **Population** | **Intervention / Comparison** | **Outcomes/Results** | **Methodical Notes** |
| **Evidence level:** 3<br>**Study type:** two single-arm, multicentre, prospective, randomised exploratory phase II trial<br>**Number of Patients:** 126<br>**Recruiting Phase:** 8 July 2009 until 29 December 2015<br>**Inclusion Criteria:** Participants had biopsy-proven, localised resectable EAC, including Siewert type I and type II disease. Eligibility criteria included T2 or T3 stage24 based on a computed tomography (CT) scan and in some instances, endoscopic ultrasound, T1b with poor differentiation or T1N1þ, and a primary tumour sufficiently FDG-avid (minimum SUVmax 3.5).<br>**Exclusion Criteria:** Patients were excluded if they had a tumour located in the cervical oesophagus or stomach | **Intervention:** Preoperative cisplatin, fluorouracil, and docetaxel with or without radiotherapy after poor early response to cisplatin and fluorouracil for resectable oesophageal adenocarcinoma<br>**Comparison:** | **Primary:** major histological response, with a response rate of at least 20%<br>**Secondary:** PFS at 3 years and overall survival (OS) at 5 years (measured from the date of randomisation), grade 3 or 4 toxicities from DCF or radiation therapy (as measured by National Cancer Institute Common Toxicity Criteria Version 3.0), and the proportion of patients with an EMR to one cycle of CF<br>**Results:** Of 124 patients recruited, major histological response was achieved in 3/45 (7%) with EMR, 6/30 (20%) DCF, and 22/35 (63%) DCFRT patients. Grade 3/4 toxicities occurred in 12/45 (27%) EMR (CF), 13/31 (42%) DCF, and 25/35 (71%) | **Funding Sources:**<br>**COI:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout Rate/ITT-Analysis:**<br>**Notes:** Cochrane risk of bias tool 1 (RoB 1): (3 unclear risks of bias (#2 selection #5 reporting #6 attrition bias) were observed) Overall risk of bias: Unclear<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 2 (Randomized trial). |

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| (i.e. Siewert type III), metastatic disease, or a history of radiation therapy to the chest, prior chemotherapy, or another malignancy within the last 5 years. | | DCFRT patients. No treatment-related deaths occurred. LR by 3 years was seen in 5/45 (11%) EMR, 10/31 (32%) DCF, and 4/35 (11%) DCFRT patients. PFS [95% confidence interval (CI)] at 36 months was 47% (31% to 61%) for EMR, 29% (15% to 45%) for DCF, and 46% (29% to 61%) for DCFRT patients. OS (95% CI) at 60 months was 53% (37% to 67%) for EMR, 31% (16% to 48%) for DCF, and 46% (29% to 61%) for DCFRT patients.<br>**Author's Conclusion:** EMR is associated with favourable OS, PFS, and low LR. For non-responders, the addition of docetaxel augmented histological response rates, but OS, PFS, and LR remained inferior compared with responders. DCFRT improved histological response and PFS/LR outcomes, matching the EMR group. Early PET/CT has the potential to tailor therapy for patients not showing an early response to chemotherapy. | Downgrade to evidence level 3 due to unclear risk of bias. |

| Eyck, B. M. et al. Ten-Year Outcome of Neoadjuvant Chemoradiotherapy Plus Surgery for Esophageal Cancer: The Randomized Controlled CROSS Trial. J Clin Oncol. 39. 1995-2004. 2021 | | | |
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| **Population** | **Intervention / Comparison** | **Outcomes/Results** | **Methodical Notes** |
| **Evidence level:** 3<br>**Study type:** a multicenter randomized controlled CROSS trial<br>**Number of Patients:** 366<br>**Recruiting Phase:** 2004 till 2008<br>**Inclusion Criteria:** patients with cT1N1M0 or cT2-3N0-1M0 (according to Union for International Cancer Control TNM Classification, sixth edition), squamous cell carcinoma or adenocarcinoma of the esophagus or esophagogastric junction<br>**Exclusion Criteria:** | **Intervention:** Neoadjuvant Chemoradiotherapy Plus Surgery for Esophageal Cancer<br>**Comparison:** | **Primary:** overall survival, calculated from date of random assignment to date of all-cause death or last day of follow-up<br>**Secondary:** cause-specific mortality, cumulative incidence and conditional cumulative incidence of death from esophageal cancer, and cumulative incidences of locoregional and distant relapse.<br>**Results:** The median follow-up was 147 months (interquartile range, 134-157). Patients receiving neoadjuvant chemoradiotherapy had better overall survival (hazard ratio [HR], 0.70; 95% CI, 0.55 to 0.89). The effect of neoadjuvant chemoradiotherapy on overall survival was not time-dependent (P value for interaction, P = .73), and landmark analyses suggested a stable effect on overall survival up to 10 years of follow-up. The absolute 10-year overall survival benefit was 13% (38% v 25%). Neoadjuvant | **Funding Sources:**<br>**COI:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout Rate/ITT-Analysis:**<br>**Notes:** Cochrane risk of bias tool 1 (RoB 1):<br>(3 unclear risks of bias (#1 Selection bias: randomization, #2 Selection bias: allocation concealment, #6 reporting bias) were observed)<br>Overall risk of bias: Unclear<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 2 (Randomized trial). Downgrade to evidence |

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| | | chemoradiotherapy reduced risk of death from esophageal cancer (HR, 0.60; 95% CI, 0.46 to 0.80). Death from other causes was similar between study arms (HR, 1.17; 95% CI, 0.68 to 1.99). Although a clear effect on isolated locoregional (HR, 0.40; 95% CI, 0.21 to 0.72) and synchronous locoregional plus distant relapse (HR, 0.43; 95% CI, 0.26 to 0.72) persisted, isolated distant relapse was comparable (HR, 0.76; 95% CI, 0.52 to 1.13).<br>**Author's Conclusion:** The overall survival benefit of patients with locally advanced resectable esophageal or junctional cancer who receive preoperative chemoradiotherapy according to CROSS persists for at least 10 years. | level 3 due to unclear risk of bias. |

**Park, S. R. et al. A Randomized Phase III Trial on the Role of Esophagectomy in Complete Responders to Preoperative Chemoradiotherapy for Esophageal Squamous Cell Carcinoma (ESOPRESSO). Anticancer Res. 39. 5123-5133. 2019**

| Population | Intervention / Comparison | Outcomes/Results | Methodical Notes |
|---|---|---|---|
| **Evidence level:** 2<br>**Study type:** single-center, open-label, randomized, phase III trial<br>**Number of Patients:** 86<br>**Recruiting Phase:** November 2012 till | **Intervention:** Esophagectomy in Complete Responders to Preoperative Chemoradiotherapy for Esophageal Squamous Cell | **Primary:** disease-free survival<br>**Secondary:** progression-free survival (PFS; the time between initiation of chemotherapy and progression or death), time to progression (TTP; the | **Funding Sources:**<br>**COI:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout Rate/ITT-** |

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| March 2016<br>**Inclusion Criteria:** histologically confirmed, resectable cT3-T4a/anyN/M0 or anyT/N+/M0 (the 7th edition of the AJCC staging system) thoracic ESCC, age 20-75 years, Eastern Cooperative Oncology Group performance status 0-2, adequate major organs function, and no history of other cancers within 5 years. Pre-treatment staging work-up included esophago-gastroduodenoscopy with biopsy, thoracic/abdominal/pelvic computed tomography (CT), endoscopic ultrasonography, bone scan, 18F-fluorodeoxyglucose (FDG)-positron emission tomography (PET), and bronchoscopy when needed.<br>**Exclusion Criteria:** | Carcinoma<br>**Comparison:** | time between initiation of chemotherapy and progression), OS (the time between initiation of chemotherapy and death), the failure pattern, the pCR rate, treatment outcomes according to metabolic or clinical response, safety, and quality of life<br>**Results:** Among 86 patients, 38 (44.2%) achieved cCR after chemoradiotherapy; 37 were randomized to surgery (n=19) or observation (n=18). Although there were trends of better disease-free survival (DFS) toward the surgery arm in the intent-to-treat analysis (2-year DFS, 66.7% vs. 42.7%; p=0.262) or as-treated analysis (66.7% vs. 50.2%; p=0.273), overall survival was not different between the two arms in the intent-to-treat (HR=1.48; p=0.560) or as-treated analysis (HR=1.09; p=0.903). Among the 11 patients having recurrence during observation, 8 underwent surgery (n=7) or endoscopic dissection (n=1).<br>**Author's Conclusion:** our study | **Analysis:**<br>**Notes:** Cochrane risk of bias tool 1 (RoB 1): (2 unclear risks of bias (#2 Selection bias: Allocation concealment, #6 Reporting bias: Selective reporting) were observed) Overall risk of bias: Low<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 2 (Randomized trial). |

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| | | suggests that close observation with salvage surgery as appropriate might be a reasonable option in patients with thoracic ESCC achieving a cCR to chemoradiation. Further large-scale prospective studies are necessary to confirm our results and optimize the treatment decision in individual patients. | |

**Yang, H. et al. Long-term Efficacy of Neoadjuvant Chemoradiotherapy Plus Surgery for the Treatment of Locally Advanced Esophageal Squamous Cell Carcinoma: The NEOCRTEC5010 Randomized Clinical Trial. JAMA Surg. 156. 721-729. 2021**

| Population | Intervention / Comparison | Outcomes/Results | Methodical Notes |
|---|---|---|---|
| **Evidence level:** 2<br>**Study type:** multicenter open-label randomized phase 3 clinical trial<br>**Number of Patients:** 451<br>**Recruiting Phase:** 1 June 2007 till 31 December 2014<br>**Inclusion Criteria:** thoracic ESCC stage T1-4N1M0/T4N0M0<br>**Exclusion Criteria:** history of other cancers (including | **Intervention:** Neoadjuvant Chemoradiotherapy Plus Surgery<br>for the Treatment of Locally Advanced Esophageal Squamous<br>**Comparison:** surgery alone | **Primary:** overall survival<br>**Secondary:** disease-free survival<br>**Results:** A total of 451 patients (mean [SD] age, 56.5 [7.0] years; 367 men [81.4%]) were randomized to the NCRT (n = 224) and surgery (n = 227) groups and were eligible for the intention-to-treat analysis. By December 31, 2019, 224 deaths had occurred. The median follow-up was 53.5 months (interquartile range, 18.2-87.4 months). Patients receiving NCRT plus surgery had prolonged overall survival compared with those receiving surgery alone (hazard ratio, 0.74; 95% CI, 0.57-0.97; P = .03), with a 5-year survival rate of 59.9% (95% | **Funding Sources:**<br>**COI:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout Rate/ITT-Analysis:**<br>**Notes:** Cochrane risk of bias tool 1 (RoB 1):<br>(2 unclear risks of bias (#2 Selection bias: Allocation concealment, #6 Reporting bias: Selective reporting) were observed) |

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| skin cancers), a history of gastrectomy<br>leading to infeasible utility of gastric conduit for reconstruction, or severe comorbidities contraindicating surgery | | CI, 52.9%-66.1%) vs 49.1% (95% CI, 42.3%-55.6%), respectively. Patients in the NCRT group compared with the surgery group also had prolonged disease-free survival (hazard ratio, 0.60; 95% CI, 0.45-0.80; P<br>**Author's Conclusion:** Treatment with NCRT according to the NEOCRTEC5010 regimen was found to significantly prolong long-term overall and disease-free survival among patients with locally advanced ESCC. Neoadjuvant chemoradiotherapy followed by surgical resection may be considered a standard of care for patients with potentially resectable locally advanced ESCC. | Overall risk of bias: Low<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 2 (Randomized trial). |

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

| **Kamarajah, S. K. et al. Postoperative and Pathological Outcomes of CROSS and FLOT as Neoadjuvant Therapy for Esophageal and Junctional Adenocarcinoma: An International Cohort Study from the Oesophagogastric Anastomosis Audit (OGAA). Ann Surg. . . 2022** | | | |
|---|---|---|---|
| **Evidence level** | **Methodical Notes** | **Patient characteristics** | **Interventions** |
| **Evidence level:** 3<br>**Study type:** international, multicenter prospective cohort study | **Funding sources:**<br>**Conflict of Interests:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout rates:** | **Total no. patients:** 718<br>**Recruiting Phase:** 1st April 2018 to 31st December 2018<br>**Inclusion criteria:** adult patients undergoing elective (planned) esophagectomy for esophageal and junctional EAC (including AEG I and II) receiving either CROSS or FLOT were included. All surgical approaches (two-stage Ivor Lewis, threestage McKeown, thoracoabdominal, transhiatal using any combination of open, robotic or standard minimal access approaches) were included, as were thoracic and cervical anastomosis.<br>**Exclusion criteria:** (i) colonic interposition or small bowel jejunal interposition reconstructions<br>(ii) emergency resections<br>(iii) resections for benign disease | **Interventions:** FLOT (fluorouracil, leucovorin, oxaliplatin and the taxane docetaxel) as Neoadjuvant therapy for Esophageal and Junctional Adenocarcinoma<br><br>**Comparison:** CROSS as Neoadjuvant therapy for Esophageal and Junctional Adenocarcinoma |
| **Notes:** | Newcastle-Ottawa Scale (NOS) for Cohort studies: 8/9 stars<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 3 (Cohort study / Non-randomized controlled cohort)<br>**Author's conclusion:** This study provides real-world data CROSS was associated with higher 90-day mortality than | | |

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| | FLOT, related to cardio-pulmonary complications with CROSS. These warrant a further review into causes and mechanisms in selected patients, and at minimum suggest the need for strict radiation therapy quality assurance. Research into impact of higher pCR rates and R0 resections with CROSS compared to FLOT on long-term survival is needed. | |
| **Outcome Measures/results** | **Primary** 90-day mortality, defined as mortality within 90-days of surgery<br>**Secondary** rate of pathologic complete response (pCR), margin-negative resections, postoperative overall or major complications and anastomotic leaks | **Results:** The 90-day mortality was higher after CROSS than FLOT (5% vs 1%, p = 0.005), even on adjusted analyses (odds ratio (OR): 3.97, CI95%: 1.34 - 13.67). Postoperative mortality in CROSS were related to higher pulmonary (74% vs 60%) and cardiac complications (42% vs 20%) compared to FLOT. CROSS was associated with higher pCR rates (18% vs 10%, p = 0.004) and margin-negative resections (93% vs 76%, p < 0.001) compared with FLOT. On adjusted analyses, CROSS was associated with higher pCR rates (OR: 2.05, CI95%: 1.26 - 3.34) and margin-negative resections (OR: 4.55, CI95%: 2.70 - 7.69) compared to FLOT. |

**Steber, C. et al. Cisplatin/5-Fluorouracil (5-FU) Versus Carboplatin/Paclitaxel Chemoradiotherapy as Definitive or Pre-Operative Treatment of Esophageal Cancer. Cureus. 13. e12574. 2021**

| Evidence level | Methodical Notes | Patient characteristics | Interventions |
|---|---|---|---|
| **Evidence level:** 3<br>**Study type:** retrospective analysis of a prospectively maintained database | **Funding sources:**<br>**Conflict of Interests:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout rates:** | **Total no. patients:** 261<br>**Recruiting Phase:** June of 1999 and December of 2018<br>**Inclusion criteria:** histologically confirmed esophageal cancer at presentation, and treatment with concurrent CRT with or without surgical | **Interventions:** Cisplatin/5-Fluorouracil (5-FU) Chemoradiotherapy as Definitive or Pre-Operative Treatment of Esophageal Cancer<br><br>**Comparison:** Carboplatin/Paclitaxel Chemoradiotherapy as Definitive or Pre-Operative Treatment of Esophageal Cancer |

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| | | resection.<br>**Exclusion criteria:** | |
| **Notes:** | Newcastle-Ottawa Scale (NOS) for Cohort studies: 8/9 stars<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 3 (Cohort study / Non-randomized controlled cohort).<br>**Author's conclusion:** Carboplatin/paclitaxel was associated with decreased weight loss and improved pathologic response for trimodality patients when compared to cisplatin/5-FU. We observed no differences in OS, PFS, or post-operative death by chemotherapy regimen for both the entire cohort and trimodality patients. | | |
| **Outcome Measures/results** | **Primary** overall survival<br>**Secondary** | **Results:** We identified 261 patients treated with concurrent carboplatin/paclitaxel (n = 133) or cisplatin/5-FU (n = 128). Weight loss during CRT was lower in patients receiving carboplatin/paclitaxel (median: 7.0 pounds; 4.1% body weight) vs. cisplatin/5-FU (median: 11.0 pounds; 6.5% body weight) ($p < 0.01$). In 117 patients receiving trimodality therapy, post-operative death rates within one month of resection were similar. Pathologic complete response was better with carboplatin/paclitaxel vs. cisplatin/5-FU, 29.6% vs. 21.8% ($p = 0.03$), respectively. In the multivariable analysis, there was no association between chemotherapy regimen and overall survival (OS) or progression-free survival (PFS), though there was a trend toward improved OS with carboplatin/paclitaxel with a HR = 0.75 ($p = 0.08$). Further analysis revealed that trimodality therapy and stage were predictors for improved OS and PFS while female gender and grade predicted for improved PFS. | |

## 3.11 Schlüsselfrage 06.6: Stellenwert der postoperativen (adjuvanten) Therapie nach präoperativer Therapie und Operation beim Ösophaguskarzinom

**Schlüsselfrage:**

**06.6 Stellenwert der postoperativen (adjuvanten) Therapie nach präoperativer Therapie und Operation beim Ösophaguskarzinom**
P: 1)Pat. mit Plattenepithelkarzinom des Ösophagus (pN0 separat von pN1 (UICC 6th) bzw. pN1-3 (7th Edition) 2)Pat mit Adenokarzinom des Ösophagus oder des ösophago-gastralen Übergangs pN0 separat von pN1 (UICC 6th) bzw. pN1-3 (7th Edition) nach präoperativer Therapie und R0 Resektion
I: Postoperative adjuvante Chemo, Radio- oder Radiochemotherapie (für RCT simultan; unabhängig von der Dosierung der Radiotherapie und der gewählten Chemotherapie
C: a)keine postoperative adjuvante Therapie
O: Patientenrelevante Endpunkte: Gesamtüberlebensrate, Überlebensrate nach 5 Jahren und 3 Jahren (ggfls. „Ableitung“ aus Überlebenskurven, wenn nicht im Text berichtet), medianes ÜL, Rate an Lokalrezidiven und Rezidiven im Beobachtungszeitraum, Häufigkeit schwerer und lebensbedrohlicher NW durch adjuvante Therapie

***Inhalt:*** *3 Literaturstellen*

| Literaturstelle | Evidenzlevel | Studientyp |
|---|---|---|
| Liu, A. 2021 | 3 | retrospective |
| Ni, W. 2021 | 2 | A Phase III Randomized Controlled Trial |
| Semenkovich, T. R. 2019 | 3 | retrospective cohort study |

***Cochrane Risk of Bias Tool 1 (RCT):*** *1 Bewertung(en)*

| **Ni, W. et al. Postoperative Adjuvant Therapy Versus Surgery Alone for Stage IIB-III Esophageal Squamous Cell Carcinoma: A Phase III Randomized Controlled Trial. Oncologist. 26. e2151-e2160. 2021** | | | |
|---|---|---|---|
| **Population** | **Intervention / Comparison** | **Outcomes/Results** | **Methodical Notes** |
| **Evidence level:** 2<br>**Study type:** A Phase III Randomized Controlled Trial<br>**Number of Patients:** 172<br>**Recruiting Phase:** October 2014 till December 2019<br>**Inclusion Criteria:** (a) age 18–68 years<br>(b) pathologically proven stage IIB–III esophageal squamous cell carcinoma (according to Union for International Cancer Control [UICC] criteria, 7th edition)<br>(c) undergoing radical resection (R0 indicates no evidence of residual tumor at circumferential margins as well as the proximal and distal margins)<br>(d) no history of other | **Intervention:** Postoperative Adjuvant Therapy for Stage IIB–III Esophageal Squamous Cell Carcinoma<br>**Comparison:** Surgery Alone for Stage IIB–III Esophageal Squamous Cell Carcinoma | **Primary:** disease-free survival<br>**Secondary:** overall survival<br>**Results:** A total of 172 patients were enrolled (SA, n = 54; PORT, n = 54; POCRT, n = 64). The 3-year DFS was significantly better in PORT/POCRT patients than in SA patients (53.8% vs. 36.7%; p = .020); the 3-year OS was also better in PORT/POCRT patients (63.9% vs. 48.0%; p = .025). The 3-year DFS for SA, PORT, and POCRT patients were 36.7%, 50.0%, 57.3%, respectively (p = .048). The 3-year OS for SA, PORT, and POCRT patients were 48.0%, 60.8%, 66.5%, respectively (p = .048).<br>**Author's Conclusion:** This study is the first randomized controlled trial to explore the effect of postoperative adjuvant therapy for patients with pathological stage IIB–III esophageal cancer. The findings suggest that postoperative treatment (PORT/POCRT) may significantly improve survival in these patients. Postoperative radiotherapy with a | **Funding Sources:**<br>**COI:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout Rate/ITT-Analysis:**<br>**Notes:** Cochrane risk of bias tool 1 (RoB 1):<br>(2 unclear risks of bias (#2 Selection bias: Allocation concealment, #6 Reporting bias: Selective reporting) were observed)<br>Overall risk of bias: Low<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 2 (Randomized trial). |

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| treatment before recruitment<br>(e) Karnofsky performance status score ≥70<br>(f) normal hematology and blood biochemistry<br>(g) fit for intensity-modulated radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT)<br>(h) willing to attend regular follow-up after treatment<br>**Exclusion Criteria:** (a) uncontrolled diabetes mellitus<br>(b) interval between the surgical procedure and adjuvant therapy >3 months<br>(c) signs of recurrence on computed tomography (CT), ultrasound, or positron emission tomography (PET)-CT<br>(d) concurrent malignancy or previous malignancy (other than basal cell skin cancer or | | reduced radiation field combined with chemotherapy appears to be an effective and safe treatment, with potential for being accepted as a standard treatment option for patients with pathological stage IIB–III esophageal squamous cell carcinoma after radical surgery. | |

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| carcinoma in situ of the cervix) within the past 5 years<br>(e) pregnancy | | | |

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

| **Liu, A. et al. Short-term response might influence the treatment-related benefit of adjuvant chemotherapy after concurrent chemoradiotherapy for esophageal squamous cell carcinoma patients. Radiat Oncol. 16. 195. 2021** | | | |
|---|---|---|---|
| **Evidence level** | **Methodical Notes** | **Patient characteristics** | **Interventions** |
| **Evidence level:** 3<br>**Study type:** retrospective | **Funding sources:**<br>**Conflict of Interests:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout rates:** | **Total no. patients:** 244<br>**Recruiting Phase:** January 2013 till December 2017<br>**Inclusion criteria:** esophageal squamous cell carcinoma patients with clinical stage II–IVa who underwent CCRT for initial therapy:<br>(1) the patients were diagnosed by endoscopy combined with pathological biopsy-proven squamous cell carcinoma<br>(2) the clinical staging for each patient was defned according to the American Joint Committee on Cancer system (8th edition) for ESCC patients and clinically diagnosed with local advanced disease (stage II–IVa)<br>(3) underwent defnitive radiotherapy (dose≥50.4 Gy, 1.8–2 Gy/fraction, three-dimensional conformal radiotherapy technology) with concurrent TP or PF doublet chemotherapy. (P indicates a type of platinum drug such as cisplatin, carboplatin or oxaliplatin, F indicates a fuoropyrimidine such as 5-fuorouracil or capecitabine, and T indicates a taxane such as paclitaxel or docetaxel) followed with or without AC<br>(4) patients who were in the 18–75 age range and | **Interventions:** adjuvant chemotherapy (AC) after concurrent chemoradiotherapy (CCRT) for esophageal squamous cell carcinoma (ESCC)<br><br>**Comparison:** |

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| | | whose Eastern Cooperative Oncology Group (ECOG) performance status score was no more than 2<br>(5) patients who did not undergo salvage surgery during the follow-up for<br>therapy response and survival evaluation.<br>**Exclusion criteria:** a prior treatment history, complications with other cancers, non-squamous cell carcinoma, clinical stage IVb, other chemotherapy regimens, non-defnite radiotherapy (dose | |
| **Notes:** | Newcastle-Ottawa Scale (NOS) for Cohort studies: 7/9 stars<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 3 (Cohort study / Non-randomized controlled cohort).<br>**Author's conclusion:** In conclusion, many oncologists consider consolidation chemotherapy for ESCC patients after CCRT to improve survival outcomes, but the efcacy of AC after CCRT is controversial. A good short-term response has been confrmed as a signifcant predictive factor for AC beneft in our study, which needs further exploration. More predictive biomarkers and models should be studied to help select the subpopulation most likely to beneft from AC. | | |
| **Outcome Measures/results** | **Primary** overall survival (OS) and progression-free survival (PFS) rates<br>**Secondary** | **Results:** From January 2013 to December 2017, 244 patients were recruited (n = 131 for CCRT + AC; n = 113 for CCRT alone) for the analysis. After propensity score matching was performed (1:1 and 99 patients for each group) with consideration of the basic clinical characteristics, no significant differences were found in OS (HR = 1.024; 95% CI 0.737-1.423; P = 0.886) or PFS (HR = 0.809; 95% CI 0.582-1.126; P = 0.197) between the two groups. The good short-term response subgroup showed a better PFS and favoured CCRT + AC treatment (HR = 0.542; 95% CI 0.336-0.876; P = 0.008), the independent predictive role of which was confirmed in additional multivariate Cox regression analysis. | |

| **Semenkovich, T. R. et al. Adjuvant Therapy for Node-Positive Esophageal Cancer After Induction and Surgery: A Multisite Study. Ann Thorac Surg. 108. 828-836. 2019** | | | |
|---|---|---|---|
| **Evidence level** | **Methodical Notes** | **Patient characteristics** | **Interventions** |
| **Evidence level:** 3<br>**Study type:** retrospective cohort study | **Funding sources:**<br>**Conflict of Interests:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout rates:** | **Total no. patients:**<br>**Recruiting Phase:** 2000–2014<br>**Inclusion criteria:** patients who received neoadjuvant treatment, underwent esophagectomy, and had positive lymph nodes on pathology<br>**Exclusion criteria:** underwent total gastrectomy, had unknown adjuvant treatment status, died prior to eligibility (â‰¤90 days) for adjuvant therapy, had pathologic M1 disease, had clinical M1 disease with missing pathologic M staging, or had a documented recurrence of cancer prior to administration of adjuvant therapy | **Interventions:** Adjuvant Therapy for Node Positive Esophageal Cancer after Induction and Surgery<br><br>**Comparison:** |
| **Notes:** | Newcastle-Ottawa Scale (NOS) for Cohort studies: 8/9 stars<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 3 (Cohort study / Non-randomized controlled cohort).<br><br>**Author's conclusion:** Adjuvant therapy was associated with improved overall survival. Therefore, consideration should be given to administration of adjuvant therapy to esophageal cancer patients who have persistent node positive disease after induction therapy and esophagectomy, and are able to tolerate additional treatment. | | |

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| **Outcome Measures/results** | **Primary** overall survival **Secondary** | **Results:** 1,082 patients were analyzed with node positive cancer following induction therapy and esophagectomy. 209 (19.3%) received adjuvant therapy and 873 (80.7%) did not. Administration of adjuvant treatment varied significantly from 3.2% to 50.0% between sites (p |

## 3.12 Schlüsselfrage 6.7: Stellenwert der präoperativen Radiotherapie im multimodalen Konzept bei AC des Ösophagus und des ösophago-gastralen Übergangs

P: Pat mit Adenokarzinom des Ösophagus oder des ösophago-gastralen Übergangs (Stadium bis T2N1M0 (UICC6th) bzw. bis T2N1-3M0 (UICC7th) separat von Stadium T3-4NalleM0
I: Neoadjuvante Radiotherapie
C: a)keine neoadjuvante Therapie=chirurgische Therapie b) neoadjuvante Chemotherapie ohne Radiotherapie c) Radiochemotherapie
O: Patientenrelevante Endpunkte: Gesamtüberlebensrate, Überlebensrate nach 5 Jahren und 3 Jahren (ggfls. „Ableitung“ aus Überlebenskurven, wenn nicht im Text berichtet), medianes ÜL, Rate an R0 Resektionen, Rate an Lokal- und Fernrezidiven im Beobachtungszeitraum, Häufigkeit schwerer und lebensbedrohlicher NW durch die Radiotherapie in der präoperativen Phase

***Inhalt:*** *2 Literaturstellen*

| Literaturstelle | Evidenzlevel | Studientyp |
|---|---|---|
| Deng, W. 2020 | 2 | Prospective, Phase III, Randomized Controlled Study |
| Park, S. R. 2019 | 2 | single-center, open-label, randomized, phase III trial |

***Cochrane Risk of Bias Tool 1 (RCT):*** *2 Bewertung(en)*

| **Deng, W. et al. Postoperative Radiotherapy in Pathological T2-3N0M0 Thoracic Esophageal Squamous Cell Carcinoma: Interim Report of a Prospective, Phase III, Randomized Controlled Study. Oncologist. 25. e701-e708. 2020** | | | |
|---|---|---|---|
| **Population** | **Intervention / Comparison** | **Outcomes/Results** | **Methodical Notes** |
| **Evidence level:** 2<br>**Study type:** Prospective, Phase III, Randomized Controlled Study<br>**Number of Patients:** 167<br>**Recruiting Phase:** October 2012 to February 2018<br>**Inclusion Criteria:** Patients who received R0 esophagectomy and at least twofield lymphadenectomy (resection of mediastinal and abdominal lymph nodes) as their first treatment and who were pathologically confirmed as having T2-3N0 thoracic esophageal squamous cell carcinoma, according to the Union for International Cancer Control (UICC) 7th tumor-node-metastasis (TNM) classification<br>**Exclusion Criteria:** Patients with residual diseases, recurrences, or | **Intervention:** Postoperative Radiotherapy in Pathological T2-3N0M0 Thoracic Esophageal Squamous Cell Carcinoma<br>**Comparison:** | **Primary:** disease-free survival<br>**Secondary:** ocal-regional recurrence rate, overall survival, and radiation-related toxicities<br>**Results:** From October 2012 to February 2018, 167 patients were enrolled in this study. We analyzed 157 patients whose follow-up time was more than 1 year or who had died. The median follow-up time was 45.6 months. The 3-year disease-free survival rates were 75.1% (95% confidence interval [CI] 65.9-85.5) in the postoperative radiotherapy group and 58.7% (95% CI 48.2-71.5) in the surgery group (hazard ratio 0.53, 95% CI 0.30-0.94, p = .030). Local-regional recurrence rate decreased significantly in the radiotherapy group (10.0% vs. 32.5% in the surgery group, p = .001). The overall survival and distant metastasis rates were not significantly different | **Funding Sources:**<br>**COI:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout Rate/ITT-Analysis:**<br>**Notes:** Cochrane risk of bias tool 1 (RoB 1):<br>(1 high risk of bias (#2 Selection bias), 1 unclear risks of bias (#6 Reporting bias) were observed)<br>Overall risk of bias: Low<br><br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 2 (Randomized trial). |

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| distant metastases before randomization; severe postoperative complications or comorbidities that ruled them out for receiving radiotherapy; or a history of other secondary malignancies | | between two groups. Grade 3 toxicity rate related to radiotherapy was 12.5%. **Author's Conclusion:** This study suggested that postoperative radiotherapy in pathological T2-3N0M0 thoracic esophageal squamous cell carcinoma could potentially increase DFS and reduce local-regional recurrence with low-grade toxicities. However, further enrollment and long-term follow-up are needed to validate the efficacy and safety of this treatment strategy | |

**Park, S. R. et al. A Randomized Phase III Trial on the Role of Esophagectomy in Complete Responders to Preoperative Chemoradiotherapy for Esophageal Squamous Cell Carcinoma (ESOPRESSO). Anticancer Res. 39. 5123-5133. 2019**

| Population | Intervention / Comparison | Outcomes/Results | Methodical Notes |
|---|---|---|---|
| **Evidence level:** 2<br>**Study type:** single-center, open-label, randomized, phase III trial<br>**Number of Patients:** 86<br>**Recruiting Phase:** November 2012 till March 2016<br>**Inclusion Criteria:** histologically confirmed, resectable cT3-T4a/anyN/M0 or anyT/N+/M0 (the 7th edition of the AJCC staging system) | **Intervention:** Esophagectomy in Complete Responders to Preoperative Chemoradiotherapy for Esophageal Squamous Cell Carcinoma<br>**Comparison:** | **Primary:** disease-free survival<br>**Secondary:** progression-free survival (PFS; the time between initiation of chemotherapy and progression or death), time to progression (TTP; the time between initiation of chemotherapy and progression), OS (the time between initiation of chemotherapy and death), the failure pattern, the pCR rate, treatment | **Funding Sources:**<br>**COI:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout Rate/ITT-Analysis:**<br>**Notes:** Cochrane risk of bias tool 1 (RoB 1): (2 unclear risks of bias (#2 Selection bias: |

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| thoracic ESCC, age 20-75 years, Eastern Cooperative Oncology Group performance status 0-2, adequate major organs function, and no history of other cancers within 5 years. Pre-treatment staging work-up included esophago-gastroduodenoscopy with biopsy, thoracic/abdominal/pelvic computed tomography (CT), endoscopic ultrasonography, bone scan, 18F-fluorodeoxyglucose (FDG)-positron emission tomography (PET), and bronchoscopy when needed.<br>**Exclusion Criteria:** | | outcomes according to metabolic or clinical response, safety, and quality of life<br>**Results:** Among 86 patients, 38 (44.2%) achieved cCR after chemoradiotherapy; 37 were randomized to surgery (n=19) or observation (n=18). Although there were trends of better disease-free survival (DFS) toward the surgery arm in the intent-to-treat analysis (2-year DFS, 66.7% vs. 42.7%; p=0.262) or as-treated analysis (66.7% vs. 50.2%; p=0.273), overall survival was not different between the two arms in the intent-to-treat (HR=1.48; p=0.560) or as-treated analysis (HR=1.09; p=0.903). Among the 11 patients having recurrence during observation, 8 underwent surgery (n=7) or endoscopic dissection (n=1).<br>**Author's Conclusion:** our study suggests that close observation with salvage surgery as appropriate might be a reasonable option in patients with thoracic ESCC achieving a cCR to chemoradiation. Further large-scale | Allocation concealment, #6<br>Reporting bias: Selective reporting) were observed)<br>Overall risk of bias: Low<br><br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 2 (Randomized trial). |

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| | | prospective studies are necessary to confirm our results and optimize the treatment decision in individual patients. | |

## 3.13 Schlüsselfrage 7: Stellenwert und Indikation der definitiven Radio(chemo)therapie

**Schlüsselfrage:**

**07 Stellenwert und Indikation der definitiven Radio(chemo)therapie Zu betrachtende Parameter: Tumorhöhenlokalisation, lokales Tumorstadium, AC versus SCC (Fragestellung 1 für Evidenzbericht: „Indikation, Nutzen und Schaden neoadjuvanter Therapieverfahren“)**
P: 1)Pat. mit nicht fernmetastasiertem Plattenepithelkarzinom Ösophagus (Stadium Talle Nalle M0), 2) AEG (Stadium Talle Nalle M0)
I: definitive simultane Radiochemotherapie (mindestens 30 Gy (unabhängig von der Fraktionierung und der gewählten Chemotherapie)
C: OP alleine oder multimodale Verfahren unter Einschluss der OP
O: Patientenrelevante Endpunkte: Gesamtüberlebensrate, Überlebensrate nach 5 Jahren und 3 Jahren (ggfls. „Ableitung“ aus Überlebenskurven, wenn nicht im Text berichtet), medianes ÜL, Rate an Lokal- und Fernrezidiven im Beobachtungszeitraum, Häufigkeit schwerer und lebensbedrohlicher NW bzw. Letalität durch die Radio/ Chemotherapie im Vergleich zu anderen Therapieverfahren

***Inhalt:*** *12 Literaturstellen*

| Literaturstelle | Evidenzlevel | Studientyp |
|---|---|---|
| Chapman, B. C. 2019 | 3 | a retrospective cohort study |
| Chen, P. 2020 | 4 | cohort study |
| de Vos-Geelen, J. 2020 | 3 | retrospective observational cohort study |
| Del Calvo, H. 2021 | 3 | retrospective cohort study |
| Jestin Hannan, C. 2020 | 3 | population-based cohort study |
| Jiang, W. 2020 | 3 | study of a large, contemporary national database |

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|---|---|---|
| Jung, H. K. 2020 | 3 | retrospective cohort study |
| Kamarajah, S. K. 2020 | 3 | National Population-based Cohort Study |
| Mishra, S. 2021 | 4 | retrospective study |
| Pang, Q. 2020 | 4 | retrospective |
| Raman, V. 2019 | 3 | retrospective cohort study |
| Wujanto, C. 2021 | 3 | retrospective |

***NEWCASTLE - OTTAWA Checklist: Cohort:*** *12 Bewertung(en)*

| **Chapman, B. C. et al. Analysis of the National Cancer Database Esophageal Squamous Cell Carcinoma in the United States. Ann Thorac Surg. 108. 1535-1542. 2019** | | | |
|---|---|---|---|
| **Evidence level** | **Methodical Notes** | **Patient characteristics** | **Interventions** |
| **Evidence level:** 3<br>**Study type:** a retrospective cohort study | **Funding sources:**<br>**Conflict of Interests:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout rates:** | **Total no. patients:** 11229<br>**Recruiting Phase:** 2004 to 2013<br>**Inclusion criteria:** patients with stage I to III ESCC<br>**Exclusion criteria:** Patients with stage IV cancer and unknown stage, no treatment recorded, or missing vital status or follow-up time | **Interventions:** (1) definitive chemoradiation therapy (CR)<br>(2) neoadjuvant therapy followed by esophageal resection (ER)<br>(3) ER alone<br>(4) ER followed by adjuvant therapy<br><br>**Comparison:** |
| **Notes:** | Newcastle-Ottawa Scale (NOS) for Cohort studies: 8/9 stars<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 3 (Cohort study / Non-randomized controlled cohort).<br>**Author's conclusion:** The use of neoadjuvant therapy followed by esophagectomy in patients with ESCC is associated with improved long-term survival after adjusting for patient, facility, and tumor-related characteristics. Patients treated at high-volume facilities were more likely to receive neoadjuvant therapy, and a substantial inverse relationship was found between annual surgical volume and long-term survival. These findings suggest that regionalizing treatment of patients with ESCC to high-volume facilities may improve survival outcomes. | | |
| **Outcome Measures/results** | **Primary** overall survival<br>**Secondary** | **Results:** We identified 11,229 patients with ESCC undergoing definitive CR (78.6%); neoadjuvant therapy followed by ER (8.5%), ER alone (10.1%), and ER followed by adjuvant therapy (2.6%). Compared with neoadjuvant therapy, both ER alone and definitive CR were | |

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| | | associated with substantially increased mortality. Patients treated at high-volume centers (>20), regardless of whether they underwent ER, had improved survival compared with facilities that performed 10 to 19, 5 to 9, and less than 5 ERs per year. |

**Chen, P. et al. Characterization of 500 Chinese patients with cervical esophageal cancer by clinicopathological and treatment outcomes. Cancer Biol Med. 17. 219-226. 2020**

| Evidence level | Methodical Notes | Patient characteristics | Interventions |
|---|---|---|---|
| **Evidence level:** 4<br>**Study type:** cohort study | **Funding sources:**<br>**Conflict of Interests:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout rates:** | **Total no. patients:** 500<br>**Recruiting Phase:** 1973–2018<br>**Inclusion criteria:** patients with accurate tumor location records and treatments for esophageal cancer<br>**Exclusion criteria:** | **Interventions:** patients treated with surgery<br><br>**Comparison:** patients receiving non-surgical treatments (radiotherapy, radiochemotherapy, and chemotherapy) |
| **Notes:** | Newcastle-Ottawa Scale (NOS) for Cohort studies: 6/9 stars<br>Downgrade due to 0 stars in comparability domain.<br>No description of adjustment for confounding.<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 3 (Cohort study / Non-randomized controlled cohort).<br>Downgrade to evidence level 4 due to high risk of bias.<br>**Author's conclusion:** The present study determined the clinicopathological characteristics of CEC patients in terms of gender, alcohol consumption, cigarette smoking, family history, LNM, anastomotic leakage, and incisal edge residues. In CEC patients, the survival outcomes with curative esophagectomy (with or without total laryngectomy) and radiotherapy were similar. Considering the low quality of life following total laryngectomy and anastomotic leakage, radiotherapy should be the initial choice for treatment of CEC in Chinese patients. | | |

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| **Outcome Measures/results** | **Primary** to determine the relationship between pathological characteristics, treatment protocols, and survival outcomes<br>**Secondary** | **Results:** Among the 500 CEC patients, 278 (55.6%) were male, and the median age was 60.9 Â± 9.4 years. A total of 496 patients (99.2%) were diagnosed with squamous cell carcinoma. In 171 (34.2%) patients who received surgery, 22 (12.9%) had undergone laryngectomy. In 322 (64.4%) patients who received non-surgical treatments, 245 (76.1%) received radiotherapy. Stratified survival analysis showed that only T stage was related with survival outcomes for CEC patients in the surgical group, and the outcomes between laryngectomy and non-laryngectomy patients were similar. It was noteworthy that the 5-year survival rate was similar in CEC patients among the different groups treated with surgery, radiotherapy, chemotherapy, or radiochemotherapy (P = 0.244). |

**de Vos-Geelen, J. et al. A national study to assess outcomes of definitive chemoradiation regimens in proximal esophageal cancer. Acta Oncol. 59. 895-903. 2020**

| Evidence level | Methodical Notes | Patient characteristics | Interventions |
|---|---|---|---|
| **Evidence level:** 3<br>**Study type:** retrospective observational cohort study | **Funding sources:**<br>**Conflict of Interests:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout rates:** | **Total no. patients:** 200<br>**Recruiting Phase:** 2004 till 2014<br>**Inclusion criteria:** patients with locally advanced squamous cell cancer of the proximal esophagus, stage cT1N Ã¾ M0 or cT2-4N0-3M0<br>**Exclusion criteria:** | **Interventions:** cisplatin (Cis) or carboplatin-paclitaxel (CP) combined with low (â‰¤50.4â€‰Gy) or high (>50.4â€‰Gy) dose radiotherapy (RT) in proximal esophageal cancer<br><br>**Comparison:** |
| **Notes:** | Newcastle-Ottawa Scale (NOS) for Cohort studies: 8/9 stars<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 3 (Cohort study / Non-randomized controlled cohort).<br>**Author's conclusion:** In conclusion, the small sample size of this study restricts a definitive conclusion regarding OS | | |

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| | differences between the CRT regimens. Based on the superior safety profile, in addition to a more feasible outpatient implementation, we suggest a CRT regimen with carboplatin and paclitaxel in the curative setting for patients with proximal EC. | |
| **Outcome Measures/results** | **Primary** overall survival<br>**Secondary** safety of four contemporary CRT regimens | **Results:** Two hundred patients were included. Fifty-four, 39, 95, and 12 patients were treated with Cis-low-dose RT, Cis-high-dose RT, CP-low-dose RT, and CP-high-dose RT, respectively. Median follow-up was 62.6â€‰months (95% CI: 47.9–77.2â€‰months). Median OS (21.9â€‰months; 95% CI: 16.9–27.0â€‰months) was comparable between treatment groups (logrank pâ€‰=â€‰.88), confirmed in the fully adjusted and PS weighted model (pâ€‰>â€‰.05). Grades 3–5 acute adverse events were less frequent in patients treated with CP-low-dose RT versus Cis-high-dose RT (OR 3.78; 95% CI: 1.31–10.87; pâ€‰=â€‰.01). The occurrence of grades 3–5 late toxicities was not different between treatment groups. |

| **Del Calvo, H. et al. Surgery provides improved overall survival in surgically fit octogenarians with esophageal cancer after chemoradiation therapy. J Thorac Dis. 13. 5875-5886. 2021** | | | |
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| **Evidence level** | **Methodical Notes** | **Patient characteristics** | **Interventions** |
| **Evidence level:** 3<br>**Study type:** retrospective cohort study | **Funding sources:**<br>**Conflict of Interests:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout rates:** | **Total no. patients:** 21710<br>**Recruiting Phase:** 2004 to 2015<br>**Inclusion criteria:** patients diagnosed with esophageal cancer<br>**Exclusion criteria:** under the age of 80, patients without a TNM stage of II or III, patients with unknown treatment, and patients with missing vital data | **Interventions:** patients receiving chemoradiation therapy followed by surgery<br><br>**Comparison:** patients who underwent chemoradiation only |

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| **Notes:** | Newcastle-Ottawa Scale (NOS) for Cohort studies: 7/9 stars<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 3 (Cohort study / Non-randomized controlled cohort).<br><br>**Author's conclusion:** Most octogenarians with locally advanced esophageal cancer underwent definitive chemoradiation therapy. Very few patients underwent chemoradiation followed by surgery; however, the multimodality treatment provided increased overall survival. Surgically fit octogenarians should be considered for chemoradiation therapy followed by surgery. | |
| **Outcome Measures/results** | **Primary** overall survival<br>**Secondary** | **Results:** There were 21,710 octogenarians (15%) with esophageal cancer in the NCDB database. Among octogenarians, there were 6,960 patients (32%) who had clinical stage II-III esophageal cancer. Among 6,922 patients whose treatment data were available, the most common therapy was chemoradiation (n=3,360, 49%). Two of the most common therapies that included surgical resection were surgery only (n=314, 5%) and chemoradiation therapy followed by surgery (n=172, 2%). Among different treatments, the best 5-year overall survival was achieved in patients receiving chemoradiation therapy followed by surgery (P |

**Jestin Hannan, C. et al. Geographical differences in cancer treatment and survival for patients with oesophageal and gastro-oesophageal junctional cancers. Br J Surg. 107. 1500-1509. 2020**

| Evidence level | Methodical Notes | Patient characteristics | Interventions |
|---|---|---|---|
| **Evidence level:** 3<br>**Study type:** population-based cohort study | **Funding sources:**<br>**Conflict of Interests:**<br>**Randomization:** | **Total no. patients:** 5959<br>**Recruiting Phase:** 2006 till 2015<br>**Inclusion criteria:** Treatment with curative intent includes dCRT and surgery with or without neoadjuvant or perioperative oncological treatment. Patients who underwent endoscopic surgery were | **Interventions:** treatment with curative intent and surgical resection of oesophageal and gastro-oesophageal junctional cancers |

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| | **Blinding:**<br>**Dropout rates:** | also included in the surgery group.<br><br>**Exclusion criteria:** | **Comparison:** |
| **Notes:** | Newcastle-Ottawa Scale (NOS) for Cohort studies: 9/9 stars<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 3 (Cohort study / Non-randomized controlled cohort).<br><br>**Author's conclusion:** Patients diagnosed in counties with higher rates of treatment with curative intent and higher rates of surgery had better survival | | |
| **Outcome Measures/results** | **Primary** Overall survival<br>**Secondary** | **Results:** Some 5959 patients were included, of whom 1503 (25Â·2 per cent) underwent surgery. Median overall survival after diagnosis was 7Â·7, 8Â·8 and 11Â·1 months respectively in counties with low, intermediate and high rates of treatment with curative intent. Corresponding survival times for the surgical resection groups were 7Â·4, 9Â·3 and 11Â·0 months. In the multivariable analysis, a higher rate of treatment with curative intent (time ratio 1Â·17, 95 per cent c.i. 1Â·05 to 1Â·30; P < 0Â·001) and a higher resection rate (time ratio 1Â·24, 1Â·12 to 1Â·37; P < 0Â·001) were associated with improved survival after adjustment for relevant confounders. | |

**Jiang, W. et al. Post-treatment mortality after definitive chemoradiotherapy versus resection for esophageal cancer. Dis Esophagus. 33. . 2020**

| Evidence level | Methodical Notes | Patient characteristics | Interventions |
|---|---|---|---|
| **Evidence level:** 3<br>**Study type:** study of a large, contemporary | **Funding sources:**<br>**Conflict of Interests:**<br>**Randomization:** | **Total no. patients:** 15585<br>**Recruiting Phase:** 2004 - 2014<br>**Inclusion criteria:** Patients with newly-diagnosed, histologically-confirmed cT1–3 N0–1 M0 squamous cell or adenocarcinoma of | **Interventions:** surgical-based therapy of esophageal cancer |

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| national database | **Blinding:**<br>**Dropout rates:** | the esophagus. All patients were required to have received either of the two recognized paradigms for EC1: dCRT, defined as concurrent CT and RT to a dose ≥50 Gy; or surgicalbased therapy, defined as esophagectomy alone or preceded by CT and/or RT (dose ≥ 41.4 Gy)<br>**Exclusion criteria:** prior history of cancer, palliative care treatment(s), and missing follow-up/survival information | **Comparison:** dCRT of esophageal cancer |
| **Notes:** | Newcastle-Ottawa Scale (NOS) for Cohort studies: 8/9 stars<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 3 (Cohort study / Non-randomized controlled cohort).<br><br>**Author's conclusion:** This novel study of a large, contemporary national database describes short-term mortality, and predictors thereof, in locally advanced EC patients treated with surgical-based versus organ-sparing approaches. Following propensity matching in all patients, surgical-based therapy was associated with a higher rate of 30-day mortality, which became statistically insignificant by 90 days. In the unadjusted cohort, differences in 30- and 90-day mortality were most pronounced in patients > 70 years of age. Because management of locally advanced EC is highly multidisciplinary, these findings may be utilized by multidisciplinary providers as well as patients, so as to better inform shared decision-making. | | |
| **Outcome Measures/results** | **Primary** 30- and 90-day mortality<br>**Secondary** | **Results:** Of 15,585 patients, 9,278 (59.5%) received surgical-based therapy and 6,307 (40.5%) underwent dCRT. In the unadjusted population, despite nonsignificant differences at 30 days (3.3% dCRT, 3.6% surgical-based), the dCRT cohort experienced higher 90-day mortality (11.0% vs. 7.5%, P < 0.001). Following PSM, however, dCRT patients experienced significantly lower 30-day mortality (P < 0.001), with nonsignificant differences at 90 days (P = 0.092). Surgical-based management yielded similar (or better) mortality as dCRT in â‰¤70-year-old patients; however, dCRT was associated with reduced mortality in subjects > 70 years old. In addition to the intervention group, factors predictive for 30- and 90-day mortality included age, gender, | |

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| | | insurance status, facility type, comorbidity index, tumor location, histology, and T/N classification. |

**Jung, H. K. et al. Treatment pattern and overall survival in esophageal cancer during a 13-year period: A nationwide cohort study of 6,354 Korean patients. PLoS One. 15. e0231456. 2020**

| Evidence level | Methodical Notes | Patient characteristics | Interventions |
|---|---|---|---|
| **Evidence level:** 3<br>**Study type:** retrospective cohort study | **Funding sources:**<br>**Conflict of Interests:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout rates:** | **Total no. patients:** 6354<br>**Recruiting Phase:** January 1, 2005 - December 31, 2017<br>**Inclusion criteria:** The inclusion criteria were pathologically confirmed esophageal cancer cases that were extracted based on the relevant ICD-10 diagnostic codes (C150–C159). To enhance the specificity of the diagnosis, patients were only included if they visited the hospital at least three times during the first 3 months after the initial diagnosis of esophageal cancer.<br>**Exclusion criteria:** However, we excluded cases based on the following criteria: 1) patients who were treated at or transferred to another hospital within 1 month (n = 130), 2) patients who had metastatic cancer or direct invasion of the esophagus (e.g., lung, thyroid, breast, or head and neck cancer) (n = 6), 3) patients with missing data regarding cancer stage (n = 795), treatment modality (n = 146), and histology (n = 32), 4) patients with dysplasia (n = 48), 5) patients with a previous diagnosis of esophageal cancer (n = 79), and 6) patients | **Interventions:** changes in the diagnosis, treatment, and prognosis of esophageal cancer based on a real-world cancer cohort<br><br>**Comparison:** changes in the diagnosis, treatment, and prognosis of esophageal cancer from randomized controlled trials |

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| | | with other histological forms (non-SCC and non-AC; n = 65). | |
| **Notes:** | Newcastle-Ottawa Scale (NOS) for Cohort studies: 8/9 stars<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 3 (Cohort study / Non-randomized controlled cohort).<br>**Author's conclusion:** In conclusion, early esophageal cancer accounts for an increasing proportion of all esophageal cancer in Korea, while endoscopic resection provided similar long-term survival compared to surgery in early cancer. Surgery with multi-modality therapy are increasingly selected for patients with locally advanced esophageal cancer (>50% of patients), and provide a better survival that is comparable to that of definitive CCRT. | | |
| **Outcome Measures/results** | **Primary** Treatment pattern and overall survival<br>**Secondary** | **Results:** We identified 6,354 patients with newly diagnosed esophageal cancer (mean age: 64.9 Â± 9.0 years, 96.9% squamous cell carcinoma). The proportion of early esophageal cancer increased from 24.7% in 2005 to 37.2% in 2015 (p | |

**Kamarajah, S. K. et al. Definitive Chemoradiotherapy Compared to Neoadjuvant Chemoradiotherapy With Esophagectomy for Locoregional Esophageal Cancer: National Population-Based Cohort Study. Ann Surg. . . 2020**

| Evidence level | Methodical Notes | Patient characteristics | Interventions |
|---|---|---|---|
| **Evidence level:** 3<br>**Study type:** National Population-based Cohort Study | **Funding sources:**<br>**Conflict of Interests:**<br>**Randomization:** | **Total no. patients:** 19532<br>**Recruiting Phase:** 2004 to 2015<br>**Inclusion criteria:** Any patients diagnosed with a nonmetastatic esophageal cancer (adenocarcinoma or SCC) according to the International Classification of Disease for Oncology, Third Edition (ICD-O-3) who received DCR or | **Interventions:** Definitive Chemoradiotherapy with Esophagectomy for Locoregional Esophageal Cancer<br><br>**Comparison:** Neoadjuvant |

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| | **Blinding:**<br>**Dropout rates:** | NCRS between 2004 and 2015 in the de-identified NCDB were included.<br>**Exclusion criteria:** The exclusion criteria were: other histology subtypes such as mucinous tumors, neuroendocrine tumors, and other histologies; patients who underwent endoscopic resection; other concurrent cancer diagnoses; those who did not receive neoadjuvant chemoradiotherapy; and patients with metastatic esophageal cancer. | Chemoradiotherapy with Esophagectomy for Locoregional Esophageal Cancer |
| **Notes:** | Newcastle-Ottawa Scale (NOS) for Cohort studies: 7/9 stars<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 3 (Cohort study / Non-randomized controlled cohort).<br><br>**Author's conclusion:** In summary, this study demonstrated that NCRS is associated with improved survival in patients with esophageal adenocarcinoma and SCC compared to DCR. However, in selected patients with persistent or recurrent disease after DCR, SALV offers similar survival to NCRS. These results highlight a need for a renewed appraisal of the role of surgery and ensuring the quality of surgery following neoadjuvant CRT in the treatment of patients esophageal cancers. As adjuvant and neoadjuvant treatment paradigms for esophageal cancers continue to evolve, prospective evaluation of radiotherapy in combination with modern systemic chemotherapy regimens should be conducted with consideration of subgroupspecific effects. | |
| **Outcome Measures/results** | **Primary** overall survival<br>**Secondary** | **Results:** Comparison of baseline demographics of the unmatched cohort revealed that patients receiving NCRS were younger, had a lower burden of medical comorbidities, lower proportion of squamous cell carcinoma (SCC), and more positive lymph nodes. Following matching, NCRS was associated with significantly improved survival compared with DCR [hazard ratio (HR): 0.60, 95% confidence Interval (CI): 0.57-0.63, P < 0.001], which persisted in subset analyses of patients with adenocarcinoma (HR: 0.60, 95% CI: 0.56-0.63, P < 0.001) and SCC (HR: 0.58, 95% CI: 0.53-0.63, P < | |

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| | | 0.001). Of 829 receiving SALV after DCR, 823 patients were matched to 1643 NCRS. There was no difference in overall survival between SALV and NCRS (HR: 1.00, 95% CI: 0.90-1.11, P = 1.0). |

**Mishra, S. et al. Assessing failure patterns of radical intent radiation strategies in patients with locally advanced carcinoma of the esophagus. Cancer Rep (Hoboken). 4. e1332. 2021**

| Evidence level | Methodical Notes | Patient characteristics | Interventions |
|---|---|---|---|
| **Evidence level:** 4<br>**Study type:** retrospective study | **Funding sources:**<br>**Conflict of Interests:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout rates:** | **Total no. patients:** 123<br>**Recruiting Phase:** January 2011 - December 2014<br>**Inclusion criteria:** or NACRTâ€□assigned patients, those who proceeded with surgery were selected to understand the failure patterns for this group. Pretreatment workup included complete history, physical examination, routine blood and biochemical test, barium swallow test, pulmonary function test, contrastâ€□enhanced computed tomography (CT) of neck/chest/abdomen, and endoscopy with biopsies. The PET/CT staging was not routinely done.<br>**Exclusion criteria:** | **Interventions:** Definitive CRT (dCRT): patients deemed unsuitable for surgery in view of medical reasons (comorbidity/performance/unresectable) or personal choice received dCRT. These patients received 60â€□66â€‰Gy/30â€□33# with concurrent weekly Cisplatin 35â€‰mg/m2<br><br>**Comparison:** Neoadjuvant CRT (NACRT) followed by Surgery: operable and fit patients, T2â€□4â€‰Â±â€‰nodeâ€□positive with performance ≥80, were selected for this approach. These patients received a dose of 45â€‰Gy in 25 fractions with concurrent weekly Cisplatin 35â€‰mg/m2. They were reassessed both clinically and radiologically with CECT scan after NACRT in a multidisciplinary clinic for surgery. The majority underwent a transthoracic resection with twoâ€□field lymph node dissection. |

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| **Notes:** | Newcastle-Ottawa Scale (NOS) for Cohort studies: 6/9 stars<br>Downgrade due 0 stars in comparability domain.<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 3 (Cohort study / Non-randomized controlled cohort).<br>Downgrade to evidence level 4 due to high risk of bias.<br>**Author's conclusion:** In conclusion, LRF are a frequent occurrence both in dCRT and NACRT with RLNF being common in NACRT as opposed to LF in dCRT. Among regional nodes, mediastinal nodal failure was the most common in both the groups. With respect to field design, regional failures in dCRT were out of field, but most of them had concurrent distant metastasis. Conversely, regional failures in the NACRT group were infield (high mediastinum), and without concurrent distant metastasis. Concurrent chemotherapy enhances locoregional control and decreases distant metastasis in patients undergoing dCRT while young age predicts for increased LRF and DM. Modification of RT fields would unlikely be helpful. Optimization of systemic therapy for dCRT and field of dissection for NACRT might be warranted. | |
| **Outcome Measures/results** | **Primary** overall survival<br>**Secondary** | **Results:** Cumulative LRF: 64% in Group 1 vs 35% in Group 2 (P = .050). Cumulative LF: 59% in Group 1 vs 12% in Group 2 (P = .000). Cumulative RLNF: 30% in Group 1 vs 24% in Group 2 (P = .592). Most common RLNF: mediastinum for both groups (6% vs 12.5%, respectively). Distant metastasis: 40.4% Group 1 vs 17% Group 2 (P = .129), predominantly lung (Group 1, 5%), and nonregional nodes (Group 2, 8.3%). Univariate analysis identified age â‰¤50, absence of concurrent chemotherapy, dose â‰¤50â€‰Gy, and incomplete radiotherapy to predict higher odds of LRF and DM for Group 1; absence of comorbidities predicted for lower odds of LRF for Group 2. Age â‰¤50 predicted for higher odds of RNLR for Group 1, while absence of comorbidities predicted for lower odds of RNLR in Group 2. Multivariate analysis identified age â‰¤50, incomplete radiotherapy, and absence of concurrent chemotherapy to predict higher odds of LRF for Group 1. Age â‰¤50, absence of concurrent chemotherapy predicted higher odds of DM for Group 1. Absence of comorbidity predicted lower odds of LRF in Group 2. |

| Pang, Q. et al. Annual report of the esophageal cancer radiation group of the Department of Radiotherapy, Tianjin Medical University Cancer Institute & Hospital. Ann Transl Med. 8. 1156. 2020 | | | |
|---|---|---|---|
| **Evidence level** | **Methodical Notes** | **Patient characteristics** | **Interventions** |
| **Evidence level:** 4<br>**Study type:** retrospective | **Funding sources:**<br>**Conflict of Interests:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout rates:** | **Total no. patients:** 1464<br>**Recruiting Phase:** 2015 - 2019<br>**Inclusion criteria:** patients with esophageal cancer who received radiotherapy (RT)<br>**Exclusion criteria:** | **Interventions:** RT procedures, RT methods, treatment types, treatment outcomes and complications<br><br>**Comparison:** |
| **Notes:** | Newcastle-Ottawa Scale (NOS) for Cohort studies: 6/9 stars<br>Downgrade due 0 stars in comparability domain.<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 3 (Cohort study / Non-randomized controlled cohort).<br>Downgrade to evidence level 4 due to high risk of bias.<br><br>**Author's conclusion:** Standardized treatment procedures, multidisciplinary cooperation, and the integration of clinical treatments and clinical trials are of great importance in esophageal cancer treatment and are the foundation for good treatment outcomes. We hope the outcomes of ongoing clinical trials with more patients enrolled in the near future could further improve treatment outcomes. | | |
| **Outcome Measures/results** | **Primary** overall survival<br>**Secondary** | **Results:** In 2015–2019, 1,464 patients with esophageal cancer received RT at the Department of Radiotherapy, TJMUCH. Of these, 1,176 patients received definitive chemoradiotherapy (CRT), 100 received preoperative neoadjuvant CRT, 120 received postoperative adjuvant RT, 49 received post-relapse RT, and 19 received palliative RT for advanced esophageal cancer. Among the patients who received definitive CRT, the incidences of grade 2 and higher radiation | |

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| | | esophagitis, radiation pneumonitis, and leukopenia were 19.4%, 3.6%, and 19.7%, respectively; the incidences of grade 3–4 radiation esophagitis, radiation pneumonitis, and leukopenia were 9.4%, 1.2%, and 5.4%, respectively; no grade 5 acute adverse events were observed. Esophageal fistula was the major side effect during the advanced stage of RT. In 2015–2018, 44 patients (5%, 44/846) developed esophageal fistula; of these, 34 cases occurred after RT, and 10 cases occurred during RT. The overall survival was based on the data of 544 patients with esophageal cancer who underwent definitive RT at TJMUCH between March 2010 and September 2016. The median follow-up time was 21.6 months. The median survival was 19.6 months; and the 1-, 3-, and 5-year overall survival rates were 69.4%, 37.2%, and 32.3%, respectively. In 2015-2019, approximately 201 patients participated in different prospective clinical trials. |

**Raman, V. et al. Surgery Is Associated With Survival Benefit in T4a Esophageal Adenocarcinoma: A National Analysis. Ann Thorac Surg. 108. 1633-1639. 2019**

| Evidence level | Methodical Notes | Patient characteristics | Interventions |
|---|---|---|---|
| **Evidence level:** 3<br>**Study type:** retrospective cohort study | **Funding sources:**<br>**Conflict of Interests:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout rates:** | **Total no. patients:** 182<br>**Recruiting Phase:** 2010–2015<br>**Inclusion criteria:** patients with clinical T4aN0–3M0 esophageal adenocarcinoma treated with either surgical resection with or without perioperative therapy or definitive chemotherapy and radiation<br>**Exclusion criteria:** Patients who did not receive complete definitive therapy by NCCN recommendations, namely those who received definitive chemotherapy alone or radiation alone, who did not receive concurrent chemoradiation, and who | **Interventions:** esophagectomy<br><br>**Comparison:** definitive chemoradiation |

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| | | received <= 40 Gy of radiation, along with patients with missing survival data were excluded. | |
| **Notes:** | Newcastle-Ottawa Scale (NOS) for Cohort studies: 9/9 stars<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 3 (Cohort study / Non-randomized controlled cohort).<br><br>**Author's conclusion:** In this national analysis, surgery for cT4a esophageal adenocarcinoma was associated with improved outcomes when compared to definitive chemoradiation. Surgery should be considered for medically fit patients with cT4aN0–3M0 esophageal adenocarcinoma. | | |
| **Outcome Measures/results** | **Primary** overall survival<br>**Secondary** | **Results:** Of 182 patients in the study, 85 (47%) underwent esophagectomy and 97 (53%) underwent chemoradiation. In the surgery cohort, 79 patients (93%) received perioperative chemotherapy. Unadjusted and multivariable analyses demonstrated a significant survival benefit associated with surgery compared to definitive chemoradiotherapy (adjusted hazard ratio [HR] 0.32; 95%CI 0.21, 0.50). A 1:1 propensity score-matched analysis of 63 patient pairs also revealed a significant OS benefit with surgery compared to chemoradiotherapy alone (HR 0.26; 95%CI 0.16, 0.43). | |

**Wujanto, C. et al. Outcomes of oesophageal cancer treated with neoadjuvant compared with definitive chemoradiotherapy. Ann Acad Med Singap. 50. 536-547. 2021**

| Evidence level | Methodical Notes | Patient characteristics | Interventions |
|---|---|---|---|
| **Evidence level:** 3<br>**Study type:** retrospective | **Funding sources:**<br>**Conflict of Interests:**<br>**Randomization:** | **Total no. patients:** 96<br>**Recruiting Phase:** 2005 - 2017<br>**Inclusion criteria:** patients with histologically confirmed oesophageal | **Interventions:** oesophageal cancer treated with neoadjuvant chemoradiotherapy followed by surgery |

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| | **Blinding:**<br>**Dropout rates:** | carcinoma who underwent curative intent chemoRT +/- surgery<br>**Exclusion criteria:** Patients who received prior definitive, neoadjuvant or palliative intent RT<br>were excluded. | **Comparison:** oesophageal cancer treated with neoadjuvant chemoradiotherapy followed by definitive chemoradiotherapy |
| **Notes:** | Newcastle-Ottawa Scale (NOS) for Cohort studies: 8/9 stars<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 3 (Cohort study / Non-randomized controlled cohort).<br><br>**Author's conclusion:** In this study, we report outcomes comparable to internationally published data. Our results suggest that NACRT plus surgery reduced local recurrences and improved OS; however, careful selection of patient is warranted to minimise perioperative risks. With the predominant histology of our cohort being SCC, results from our study may be more relevant for SCCs within the Asian population. | | |
| **Outcome Measures/results** | **Primary** overall survival and disease-free survival<br>**Secondary** | **Results:** We identified 96 patients with median age of 64 years and squamous cell carcinoma in 82.3%. Twenty-nine patients (30.2%) received NACRT plus surgery, 67 patients (69.8%) received definitive chemoRT. Median follow-up was 13.5 months. The 3/5-year OS were 26.4%/13.4%, and 59.6%/51.6% in the definitive chemoRT and NACRT plus surgery groups, respectively. The 3/5-year DFS were 19.3%/12.3%, and 55.7%/37.2% in the definitive chemoRT and NACRT plus surgery groups, respectively. NACRT plus surgery significantly improved OS (hazard ratio [HR] 0.40, 95% confidence interval [CI] 0.22-0.72, P | |

## 3.14 Schlüsselfrage- 8.1: Rolle des PET-CTs, endoskopischen Ultraschalls bzw. Kontrastmittel-Spiral-CT und Endoskopie zur Therapieprädiktion Remissionsvorhersage

P: 1)Pat. (die Therapie bekommen) mit gesichertem PlattenepithelKarzinom o. mit Adenokarzinom des Ösophagus oder AEG 1-3 unter präoperativer Chemotherapie separat von präoperativer Radiochemotherapie
I: a)frühe Verlaufskontrolle (innerhalb von 2 Wochen nach Therapiebeginn) b)späte Verlaufskontrolle (zum Abschluss der Therapie bzw. vor der geplanten Operation)
C: 1)Kein PETCT 2)bzw. kein endoskopischer Ultraschall 3)bzw. kein KontrastmittelSpiral-CT 4) bzw. keine Endoskopie
O: Endpunkte: Vorhersagewahrscheinlichkeit für klinisch komplette Remission, histologisches Ansprechen nach Therapie, progressionsfreies Überleben und Gesamtüberleben durch die frühe bzw. späte Untersuchung (PET-CT bzw. EUS bzw. CT bzw. Endoskopie

***Inhalt:*** *7 Literaturstellen*

| Literaturstelle | Evidenzlevel | Studientyp |
|---|---|---|
| Borggreve, A. S. 2020 | 3 | prospective multicenter study |
| Goodman, K. A. 2021 | 2 | Randomized Phase II Study |
| Kitajima, K. 2020 | 3 | retrospective multicenter study |
| Münch, S. 2020 | 4 | retrospective |
| Nakajo, M. 2020 | 3 | multicentre retrospective study |
| Tustumi, F. 2021 | 3 | retrospective cohort study |

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| Zhang, C. 2021 | 3 | retrospective study |

***Cochrane Risk of Bias Tool 1 (RCT):*** *1 Bewertung(en)*

| **Goodman, K. A. et al. Randomized Phase II Study of PET Response-Adapted Combined Modality Therapy for Esophageal Cancer: Mature Results of the CALGB 80803 (Alliance) Trial. J Clin Oncol. 39. 2803-2815. 2021** | | | |
|---|---|---|---|
| **Population** | **Intervention / Comparison** | **Outcomes/Results** | **Methodical Notes** |
| **Evidence level:** 2<br>**Study type:** Randomized Phase II Study<br>**Number of Patients:** 241<br>**Recruiting Phase:** November 9, 2011 till May 7, 2015<br>**Inclusion Criteria:** surgically resectable, histologically confirmed esophageal adenocarcinoma, including Siewert EGJ adenocarcinomas types 1 and 2, with stage cT1N1-3M0 or T2-4NanyM0 according to the 2010 (7th edition) staging criteria of the American Joint Commission on Cancer. Patients were also required to have Eastern Cooperative Oncology Group performance status 0-1 and adequate renal, hepatic, and cardiac functions. Staging included computed tomography (CT) scan of the chest and abdomen, and | **Intervention:** oxaliplatin, leucovorin, and fluorouracil<br>**Comparison:** carboplatin-paclitaxel | **Primary:** pathologic complete response (pCR) rate in nonresponders after switching chemotherapy<br>**Secondary:**<br>**Results:** Two hundred forty-one eligible patients received Protocol treatment, of whom 225 had an evaluable repeat PET. The pCR rates for PET nonresponders after induction FOLFOX who crossed over to CP (n = 39) or after induction CP who changed to FOLFOX (n = 50) was 18.0% (95% CI, 7.5 to 33.5) and 20% (95% CI, 10 to 33.7), respectively. The pCR rate in responders who received induction FOLFOX was 40.3% (95% CI, 28.9 to 52.5) and 14.1% (95% CI, 6.6 to 25.0) in responders to CP. With a median follow-up of 5.2 years, median overall survival was 48.8 months (95% CI, 33.2 months to not estimable) for | **Funding Sources:**<br>**COI:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout Rate/ITT-Analysis:**<br>**Notes:** Cochrane risk of bias tool 1 (RoB 1):<br>(1 high risk of bias (#2 Performance bias: Blinding of participants and personnel);<br>2 unclear risks of bias (#2 Selection bias: Allocation concealment, #6 Reporting bias: Selective reporting) were observed)<br>Overall risk of bias: Low |

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| locoregional staging was determined by endoscopic ultrasound if technically feasible. All disease (tumor and nodes) was required to be both surgically resectable and capable of inclusion in a radiotherapy field. Patients were required to have an FDG-avid tumor with a maximum standardized uptake value (SUVmax) of > 5.0 in the primary tumor on baseline combined PET-CT scan. **Exclusion Criteria:** patients with involved cervical or supraclavicular lymph nodes were not eligible and any T4 tumors with clear evidence of invasion of the vertebral column, heart, great vessels, or tracheobronchial tree were excluded | | PET responders and 27.4 months (95% CI, 19.4 months to not estimable) for nonresponders. For induction FOLFOX patients who were PET responders, median survival was not reached. **Author's Conclusion:** Early response assessment using PET imaging as a biomarker to individualize therapy for patients with esophageal and esophagogastric junction adenocarcinoma was effective, improving pCR rates in PET nonresponders. PET responders to induction FOLFOX who continued on FOLFOX during chemoradiation achieved a promising 5-year overall survival of 53%. | Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 2 (Randomized trial). |

***OXFORD (2011) Appraisal Sheet: Prognostic Studies:*** *6 Bewertung(en)*

| **Borggreve, A. S. et al. Preoperative Prediction of Pathologic Response to Neoadjuvant Chemoradiotherapy in Patients With Esophageal Cancer Using (18)F-FDG PET/CT and DW-MRI: A Prospective MulticenterÂ Study. Int J Radiat Oncol Biol Phys. 106. 998-1009. 2020** | | | |
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| **Population** | **Intervention** | **Outcomes/Results** | |
| **Evidence level:** 3<br><br>**Study type:** prospective multicenter study<br><br>**Number of Patient:** 82 patients included, 69 patients eligible for analysis<br><br>**Recruitung Phase:** Between October 2013 and July 2017<br><br>**Inclusion Criteria:** newly diagnosed biopsy-proven esophageal cancer who were scheduled to receive nCRT followed by surgery<br><br>**Exclusion Criteria:** age of <18 years, previous treatment with thoracic surgery or thoracic | **Intervention:** Patients scheduled to receive nCRT followed by esophagectomy for esophageal cancer underwent 18F-FDG PET/CT and DW-MRI scanning prior to start of nCRT, during nCRT, and before esophagectomy. Response to nCRT was based on histopathological evaluation of the resection specimen. Relative changes in 18F-FDG PET/CT and DW-MRI parameters were compared between patients with pCR and non-pCR groups.<br>At Institution 1 and Institution 2, the neoadjuvant treatment regimen consisted of carboplatin/paclitaxel with concurrent radiotherapy (41.4 Gy in 23 fractions of 1.8 Gy).At Institution 3, the regimen consisted of 5-fluorouracil with either platinum or taxane-based chemotherapy and concurrent radiotherapy (50.4 Gy in 28 fractions of 1.8 Gy). All patients were treated with an intensity-modulated radiation therapy (IMRT) technique. At a median of 8 weeks (interquartile range [IQR]: 7-10 weeks) after completion of nCRT, patients underwent a transhiatal or transthoracic | **Primary:**<br><br>**Secondary:**<br><br>**Results:** pCR was found in 26.1% of 69 patients. Relative changes in 18F-FDG PET/CT parameters after nCRT (Î”SUVmean,post p=0.016, and Î”TLGpost p=0.024), as well as changes in DW-MRI parameters during nCRT (Î”ADCduring p=0.008) were significantly different between pCR and non-pCR. A c-statistic of 0.84 was obtained for a model with Î”ADCduring, Î”SUVmean,post and histology in classifying patients as pCR (versus 0.82 for Î”ADCduring and 0.79 for Î”SUVmean,post alone).<br><br>**Author's Conclusion:** Changes on 18F-FDG PET/CT after nCRT and early changes on DW-MRI during nCRT can help identify pCR to nCRT in esophageal cancer. Moreover, 18F-FDG PET/CT and DW-MRI might be of complementary value in the assessment of pCR. | |

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| radiotherapy, and contraindications for 18F-FDG PET/CT or MRI. | esophagectomy with two-field lymphadenectomy and gastric conduit reconstruction with either cervical or intrathoracic anastomosis, depending on patient characteristics and local preference<br><br>**Comparison:** | | |
| **Methodical Notes** | | | |
| **Funding Sources:** partially funded by Elekta Inc. and by National Institutes of Health/National Cancer Institute Cancer Center Support Grant P30CA016672 disclosed in online article<br><br>**COI:** R.v.H. and J.P.R. are proctoring surgeons for Intuitive Surgical Inc. and train other surgeons in robot-assisted minimally invasive esophagectomy. J.J.W. receives research funding from Elekta Inc. S.H.L. receives research funding from Elekta Inc., Genentech, Hitachi Chemicals, New River Labs, Beyond Spring Pharmaceuticals, and is a member of the Advisory Board of AstraZeneca. All of the above are not in conflict with the research in question. All other authors have nothing to disclose.(from online article)<br><br>**Randomization:**<br><br>**Blinding:**<br><br>**Dropout Rate/ITT-Analysis:**<br><br>**Notes:** Oxford Checklist for prognostic studies<br>1 unclear domain identified (1.4 If subgroups with different prognoses are identified, did adjustment for important prognostic factors take place?) | | | |

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| Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Prognosis): 3 (Cohort study or control arm of randomized trial). | | |
| **Kitajima, K. et al. Assessment of tumor response to definitive chemoradiotherapy and prognosis prediction in patients with esophageal cancer judged by PET response criteria in solid tumors: multicenter study in Japan. Nucl Med Commun. 41. 443-451. 2020** | | |
| **Population** | **Intervention** | **Outcomes/Results** |
| **Evidence level:** 3<br><br>**Study type:** retrospective multicenter study<br><br>**Number of Patient:** 181<br><br>**Recruitung Phase:** January 2009 till December 2016<br><br>**Inclusion Criteria:** Patients who underwent the initial FDGPET/CT scan as a pretreatment staging examination for biopsy-proven esophageal cancer followed by a second FDG-PET/CT examination within 3 months after completion of chemoradiotherapy<br><br>**Exclusion Criteria:** | **Intervention:** FDG-PET/CT<br><br>**Comparison:** | **Primary:** progression-free survival (PFS) and overall survival (OS)<br><br>**Secondary:**<br><br>**Results:** Complete metabolic response (CMR), partial metabolic response (PMR), stable metabolic disease (SMD), and progressive metabolic disease (PMD) shown by PERCIST were seen in 42 (23.2%), 113 (62.4%), 14 (7.7%), and 12 (6.6%) patients, respectively. Progression developed in 137 (75.7%) patients and 101 (56.1%) patients died (median follow-up 16.9, range 3.2-124.9 months). Those who achieved CMR showed significantly longer PFS and OS as compared with patients who did not (PMR, SMD, and PMD) (both $P < 0.0001$). In univariate analysis, initial clinical T status ($P = 0.0048$), N status ($P = 0.011$), and TNM stage ($P = 0.0006$), PERCIST ($P < 0.0001$), and reduction rate of peak lean body mass standardized uptake value ($P < 0.0001$), of metabolic tumor volume ($P < 0.0001$), and of total lesion glycolysis (TLG) ($P < 0.0001$) were associated with significantly increased OS. Multivariate analysis confirmed |

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| | | PERCIST [hazard ratio (HR): 13.15, 95% confidence interval (CI), 4.54-55.8; P < 0.0001], and TLG reduction rate (HR: 2.21, 95% CI, 1.04-4.68; P = 0.040) as independent OS predictors.<br><br>**Author's Conclusion:** In conclusion, PERCIST response criteria used for two separate FDG-PET/CT scans of patients with esophageal cancer were shown useful for evaluating therapeutic response to definitive chemoradiotherapy, as well as prediction of progression and death. We consider that they can contribute to appropriate patient management. | |
| **Methodical Notes** | | | |
| **Funding Sources:**<br><br>**COI:**<br><br>**Randomization:**<br><br>**Blinding:**<br><br>**Dropout Rate/ITT-Analysis:**<br><br>**Notes:** Oxford Checklist for prognostic studies<br>1 unclear domain identified (1.4 If subgroups with different prognoses are identified, did adjustment for important prognostic factors take place?) | | | |

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| Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Prognosis): 3 (Cohort study or control arm of randomized trial). | | | |
| **Münch, S. et al. Impact of (18)F-FDG-PET/CT on the identification of regional lymph node metastases and delineation of the primary tumor in esophageal squamous cell carcinoma patients. Strahlenther Onkol. 196. 787-794. 2020** | | | |
| **Population** | **Intervention** | **Outcomes/Results** | |
| **Evidence level:** 4<br><br>**Study type:** retrospective<br><br>**Number of Patient:** 76<br><br>**Recruitung Phase:** 2011 - 2016<br><br>**Inclusion Criteria:** ESCC patients who underwent PET/CT<br><br>**Exclusion Criteria:** patients without sufficient FDG uptake, early tumor stages (Tis or T1), without LNM or LNM which were only seen by endoscopic ultrasound | **Intervention:** Impact of 18F-FDG-PET/CT on the identification of regional lymph node metastases and delineation of the primary tumor in esophageal squamous cell carcinoma<br><br>**Comparison:** | **Primary:** patterns of lymph node metastases and their correlation with the primary tumor<br><br>**Secondary:**<br><br>**Results:** Significantly more LNM were identified with 18F-FDG-PET/CT (177 LNM) compared to CT alone (131 LNM, $p < 0.001$). The most common sites of LNM were paraesophageal (63% of patients, 37% of LNM) and paratracheal (33% of patients, 20% of LNM), while less than 5% of patients had supraclavicular, subaortic, diaphragmatic, or hilar LNM. With regard to the primary tumor, 51% of LNM were at the same height, while 25% and 24% of lymph node metastases were above and below the primary tumor, respectively. For thirty-three LNM (19%), the distance to the primary tumor was larger than 4 cm. No significant difference was seen between LCT/EUS (median 6 cm) and LPET (median 6 cm, $p = 0.846$)<br><br>**Author's Conclusion:** In conclusion, 18F-FDG-PET can help | |

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| | | to identify subclinical lymph node metastases which are located outside of recommended radiation fields. PET-based involved-field irradiation might be the ideal compromise between small treatment volumes and decreasing the risk of undertreatment of subclinical metastatic lymph nodes and should be further evaluated. | |
| **Methodical Notes** | | | |
| **Funding Sources:**<br><br>**COI:**<br><br>**Randomization:**<br><br>**Blinding:**<br><br>**Dropout Rate/ITT-Analysis:**<br><br>**Notes:** Oxford Checklist for prognostic studies<br>4 unclear domains identified (1.1 - 1.4)<br><br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Prognosis): 3 (Cohort study or control arm of randomized trial).<br><br>Downgrade to evidence level 4 due to high risk of bias. | | | |

| Nakajo, M. et al. The clinical value of PERCIST to predict tumour response and prognosis of patients with oesophageal cancer treated by neoadjuvant chemoradiotherapy. Clin Radiol. 75. 79.e9-79.e18. 2020 | | | |
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| **Population** | **Intervention** | **Outcomes/Results** | |
| **Evidence level:** 3<br><br>**Study type:** multicentre retrospective study<br><br>**Number of Patient:** 60<br><br>**Recruitung Phase:** January 2007 - June 2016<br><br>**Inclusion Criteria:** patients with oesophageal cancer who underwent 2-[18F]-fluoro-2-deoxy-D-glucose positron-emission tomography/computed tomography (18F-FDG-PET/CT) before and after NACRT prior to surgery<br><br>**Exclusion Criteria:** | **Intervention:** Positron Emission Tomography Response Criteria in Solid Tumours (PERCIST)<br><br>**Comparison:** | **Primary:** tumour response and prognosis of patients<br><br>**Secondary:**<br><br>**Results:** There were 30 responders and 30 non-responders pathologically. The complete metabolic response (CMR), partial metabolic response (PMR), stable metabolic disease (SMD), and progressive metabolic disease (PMD) were seen in 22, 29, seven, and two patients, respectively. There was a significant correlation between pathological response and PERCIST ($p<0.001$). Forty patients showed eventual progression, and 20 patients were alive without progression between the start of NACRT and last clinical follow-up (median follow-up period; 27 months [range, 3-107]). Pathological stage and PERCIST were significant for progression-free survival (PFS; $p=0.044$ and 0.006, respectively) and also significant for overall survival (OS; $p=0.009$ and 0.001, respectively) at univariate analysis. Pathological lymph node staging was also significant for OS at univariate analysis ($p=0.018$). At multivariate analysis, PERCIST remained significant and independent for PFS (hazard | |

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| | | ratio [HR]: 1.59, p=0.046) and OS (HR: 1.82, p=0.008).<br><br>**Author's Conclusion:** In conclusion, the present results indicate that PERCIST may be useful for predicting tumour response and prognosis of patients with oesophageal cancer who received NACRT before surgery. | |
| **Methodical Notes** | | | |
| **Funding Sources:**<br><br>**COI:**<br><br>**Randomization:**<br><br>**Blinding:**<br><br>**Dropout Rate/ITT-Analysis:**<br><br>**Notes:** Oxford Checklist for prognostic studies<br>1 unclear domain identified (1.4 If subgroups with different prognoses are identified, did adjustment for important prognostic factors take place?)<br><br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Prognosis): 3 (Cohort study or control arm of randomized trial). | | | |

| **Tustumi, F. et al. Prognostic value of 18F-fluorodeoxyglucose PET/computed tomography metabolic parameters measured in the primary tumor and suspicious lymph nodes before neoadjuvant therapy in patients with esophageal carcinoma. Nucl Med Commun. 42. 437-443. 2021** | | | |
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| **Population** | **Intervention** | **Outcomes/Results** | |
| **Evidence level:** 3<br><br>**Study type:** retrospective cohort study<br><br>**Number of Patient:** 117<br><br>**Recruitung Phase:** 2009 to 2019<br><br>**Inclusion Criteria:** patients with esophageal cancer who received trimodal therapy: completed neoadjuvant chemoradiotherapy using platinum- and taxane-based regimens, followed by curative intent esophagectomy. A transthoracic approach with two-field lymph node dissection was performed for tumors extending proximally to the tracheal bifurcation. For tumors involving the esophagogastric junction, a transhiatal resection was preferred. Gastric tube reconstruction with cervical anastomosis was the preferred technique. | **Intervention:** association of SUVmax and volumetric parameters (MTV and TLG) measured on 18F-FDG PET/CT studies performed prior and post neoadjuvant therapy, as well as the variations in these values pre-to-post neoadjuvant therapy<br><br>**Comparison:** | **Primary:** overall survival<br><br>**Secondary:**<br><br>**Results:** Before neoadjuvant therapy, 106 patients underwent PET/CT, and 39 patients underwent post-neoadjuvant therapy PET/CT exams. Before neoadjuvanttherapy, PET/CT showed that all the variables of the evaluated lymph nodes were statistically significant in predicting OS. Postneoadjuvanttherapy, none of the PET/CT variables of lymph nodes were related to prognosis. On the other hand, all primary tumor volumetric variables were related to overall survival. The MTV (HR: 4.66; 95% CI: 1.54-14.08) and TLG (HR: 4.86; 95% CI: 1.66-14.26) of the primary tumor post neoadjuvanttherapy and the variations in MTV (HR: 2.95; 95% CI: 1.01-3.52) and TLG (HR: 3.49; 95% CI: 1.01-3.52) of the primary tumor pre-to-post-neoadjuvanttherapy were prognostic variables. | |

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| **Exclusion Criteria:** | | **Author's Conclusion:** PET/CT is a noninvasive imaging method that functionally evaluates metabolic activity, and the absolute values of and changes in SUVmax and volumetric variables provide important information on patient prognosis and may improve patient selection for surgical treatment. Measuring metabolic parameters offers an easy approach towards determining patient prognosis, as the majority of patients receive PET/CT during staging. Clinicians can predict which patients will respond favorably to neoadjuvant therapy and esophagectomy and customize the follow-up of each patient. Personalized medicine is a goal of modern cancer therapy and aims for individually optimized treatments that are dependent on the tumor characteristics of each individual patient. | |
| **Methodical Notes** | | | |
| **Funding Sources:**<br><br>**COI:**<br><br>**Randomization:**<br><br>**Blinding:** | | | |

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| **Dropout Rate/ITT-Analysis:**<br><br>**Notes:** Oxford Checklist for prognostic studies<br>2 unclear domain identified (1.1 Was the defined representative sample of patients assembled at a common (usually early) point in the course of their disease?<br>1.4 If subgroups with different prognoses are identified, did adjustment for important prognostic factors take place?)<br><br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Prognosis): 3 (Cohort study or control arm of randomized trial). | | | |
| **Zhang, C. et al. Prediction of lymph node metastases using pre-treatment PET radiomics of the primary tumour in esophageal adenocarcinoma: an external validation study. Br J Radiol. 94. 20201042. 2021** | | | |
| **Population** | **Intervention** | **Outcomes/Results** | |
| **Evidence level:** 3<br><br>**Study type:** retrospective study<br><br>**Number of Patient:** 190<br><br>**Recruitung Phase:** 2010 - 2016<br><br>**Inclusion Criteria:** patients with fluorodeoxyglucose (FDG) avid tumours treated with neoadjuvant therapy | **Intervention:** predictive value of PET radiomic features for LNMs by comparing three models: (1) a model based on clinical variables alone<br>(2) a model based on PET radiomics alone and<br>(3) a combined model developed by clinical variables and PET radiomic features<br><br>**Comparison:** | **Primary:** predictive value of PET radiomic features for LNMs<br><br>**Secondary:**<br><br>**Results:** The incidence of lymph node metastases was 58% in both cohorts. The areas under the curve of the clinical, radiomics and combined models were 0.79, 0.69 and 0.82 in the developmental cohort, and 0.65, 0.63 and 0.69 in the external validation cohort, with good calibration demonstrated. The area under the curve of current cN-stage in development and validation cohorts was 0.60 and 0.66, respectively. For overall survival, the combined clinical and radiomics model achieved the best discrimination performance in the external validation cohort (X2 = 6.08, df = 1, p = 0.01). | |

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| **Exclusion Criteria:** Patients with oesophageal stents in situ | | **Author's Conclusion:** Accurate diagnosis of LNMs is crucial for predicting prognosis and guiding treatment decisions in oesophageal adenocarcinoma, but radiological cN-staging is currently suboptimal. Despite obtaining signal for improved prediction in a development cohort, this study showed that models using clinical variables and PET radiomics derived from the primary tumour were not fully replicated in an external validation cohort from an international centre. We plan to further validate and confirm these findings in larger external cohorts. New techniques for improving the diagnostic accuracy of LNMs are required. | |
| **Methodical Notes** | | | |
| **Funding Sources:**<br><br>**COI:**<br><br>**Randomization:**<br><br>**Blinding:**<br><br>**Dropout Rate/ITT-Analysis:**<br><br>**Notes:** Oxford Checklist for prognostic studies:<br>1 unclear domain identified (1.4 If subgroups with different prognoses are identified, did adjustment for important prognostic factors take place?) | | | |

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| Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Prognosis): 3 (Cohort study or control arm of randomized trial). | |

## 3.15 Schlüsselfrage 8.2: Stellenwert des PET-CT zur Bestrahlungsplanung

**Schlüsselfrage:**

**08.2 Stellenwert des PET-CT zur Bestrahlungsplanung**
P: 1)Pat. zur geplanten Radio(chemo)therapie mit gesichertem PlattenepithelKarzinom o. mit Adenokarzinom des Ösophagus oder AEG 1-3, alle Stadien aber M0
I: PET-CT
C: kein PET-CT, b) CT, c) MRT
O: Patientenrelevante Endpunkte: Gesamtüberlebensrate, Überlebensrate nach 5 Jahren und 3 Jahren (ggfls. „Ableitung“ aus Überlebenskurven, wenn nicht im Text berichtet), medianes ÜL, Rate an R0 Resektionen, Rate an Lokal- und Fernrezidiven im Beobachtungszeitraum, Häufigkeit schwerer und lebensbedrohlicher NW durch die Radio(chemo)therapie

***Inhalt:*** *4 Literaturstellen*

| Literaturstelle | Evidenzlevel | Studientyp |
|---|---|---|
| Bhatnagar, S. 2019 | n/a | Comparison of two radiologic assessments(CT and PET/CT) |
| Goodman, K. A. 2021 | 2 | Randomized Phase II Study |
| Kitajima, K. 2020 | 3 | retrospective multicenter study |
| Münch, S. 2020 | 4 | retrospective |

***Cochrane Risk of Bias Tool 1 (RCT):*** *1 Bewertung(en)*

| **Goodman, K. A. et al. Randomized Phase II Study of PET Response-Adapted Combined Modality Therapy for Esophageal Cancer: Mature Results of the CALGB 80803 (Alliance) Trial. J Clin Oncol. 39. 2803-2815. 2021** | | | |
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| **Population** | **Intervention / Comparison** | **Outcomes/Results** | **Methodical Notes** |
| **Evidence level:** 2<br>**Study type:** Randomized Phase II Study<br>**Number of Patients:** 241<br>**Recruiting Phase:** November 9, 2011 till May 7, 2015<br>**Inclusion Criteria:** surgically resectable, histologically confirmed esophageal adenocarcinoma, including Siewert EGJ adenocarcinomas types 1 and 2, with stage cT1N1-3M0 or T2-4NanyM0 according to the 2010 (7th edition) staging criteria of the American Joint Commission on Cancer. Patients were also required to have Eastern Cooperative Oncology Group performance status 0-1 and adequate renal, hepatic, and cardiac functions. Staging included computed tomography (CT) scan of the chest and abdomen, and locoregional staging was determined by endoscopic ultrasound if technically | **Intervention:** oxaliplatin, leucovorin, and fluorouracil<br>**Comparison:** carboplatin-paclitaxel | **Primary:** pathologic complete response (pCR) rate in nonresponders after switching chemotherapy<br>**Secondary:**<br>**Results:** Two hundred forty-one eligible patients received Protocol treatment, of whom 225 had an evaluable repeat PET. The pCR rates for PET nonresponders after induction FOLFOX who crossed over to CP (n = 39) or after induction CP who changed to FOLFOX (n = 50) was 18.0% (95% CI, 7.5 to 33.5) and 20% (95% CI, 10 to 33.7), respectively. The pCR rate in responders who received induction FOLFOX was 40.3% (95% CI, 28.9 to 52.5) and 14.1% (95% CI, 6.6 to 25.0) in responders to CP. With a median follow-up of 5.2 years, median overall survival was 48.8 months (95% CI, 33.2 months to not estimable) for PET responders and 27.4 months (95% CI, 19.4 months to not estimable) for | **Funding Sources:**<br>**COI:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout Rate/ITT-Analysis:**<br>**Notes:** Cochrane risk of bias tool 1 (RoB 1):<br>(1 high risk of bias (#2 Performance bias: Blinding of participants and personnel);<br>2 unclear risks of bias (#2 Selection bias: Allocation concealment, #6 Reporting bias: Selective reporting) were observed)<br>Overall risk of bias: Low<br>Oxford Centre for Evidence-Based |

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| feasible. All disease (tumor and nodes) was required to be both surgically resectable and capable of inclusion in a radiotherapy field. Patients were required to have an FDG-avid tumor with a maximum standardized uptake value (SUVmax) of > 5.0 in the primary tumor on baseline combined PET-CT scan. **Exclusion Criteria:** patients with involved cervical or supraclavicular lymph nodes were not eligible and any T4 tumors with clear evidence of invasion of the vertebral column, heart, great vessels, or tracheobronchial tree were excluded | | nonresponders. For induction FOLFOX patients who were PET responders, median survival was not reached. **Author's Conclusion:** Early response assessment using PET imaging as a biomarker to individualize therapy for patients with esophageal and esophagogastric junction adenocarcinoma was effective, improving pCR rates in PET nonresponders. PET responders to induction FOLFOX who continued on FOLFOX during chemoradiation achieved a promising 5-year overall survival of 53%. | Medicine 2011 Levels of Evidence (Treatment benefits): 2 (Randomized trial). |

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

| **Kitajima, K. et al. Assessment of tumor response to definitive chemoradiotherapy and prognosis prediction in patients with esophageal cancer judged by PET response criteria in solid tumors: multicenter study in Japan. Nucl Med Commun. 41. 443-451. 2020** | | | |
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| **Population** | **Intervention** | **Outcomes/Results** | |
| **Evidence level:** 3<br>**Study type:** retrospective multicenter study<br>**Number of Patient:** 181<br>**Recruitung Phase:** January 2009 till December 2016<br>**Inclusion Criteria:** Patients who underwent the | **Intervention:** FDG-PET/CT<br>**Comparison:** | **Primary:** progression-free survival (PFS) and overall survival (OS)<br>**Secondary:**<br>**Results:** Complete metabolic response (CMR), partial metabolic response (PMR), stable metabolic disease (SMD), and | |

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| initial FDGPET/CT scan as a pretreatment staging examination for biopsy-proven esophageal cancer followed by a second FDG-PET/CT examination within 3 months after completion of chemoradiotherapy<br>**Exclusion Criteria:** | | progressive metabolic disease (PMD) shown by PERCIST were seen in 42 (23.2%), 113 (62.4%), 14 (7.7%), and 12 (6.6%) patients, respectively. Progression developed in 137 (75.7%) patients and 101 (56.1%) patients died (median follow-up 16.9, range 3.2-124.9 months). Those who achieved CMR showed significantly longer PFS and OS as compared with patients who did not (PMR, SMD, and PMD) (both P < 0.0001). In univariate analysis, initial clinical T status (P = 0.0048), N status (P = 0.011), and TNM stage (P = 0.0006), PERCIST (P < 0.0001), and reduction rate of peak lean body mass standardized uptake value (P < 0.0001), of metabolic tumor volume (P < 0.0001), and of total lesion glycolysis (TLG) (P < 0.0001) were associated with significantly increased OS. Multivariate analysis confirmed PERCIST [hazard ratio (HR): 13.15, 95% confidence interval (CI), 4.54-55.8; P < 0.0001], and TLG reduction rate (HR: 2.21, 95% CI, 1.04-4.68; P = 0.040) as independent OS predictors.<br>**Author's Conclusion:** In conclusion, PERCIST response criteria used for two separate FDG-PET/CT scans of patients with esophageal cancer were shown useful for evaluating therapeutic response to definitive chemoradiotherapy, as well as prediction of progression and death. We consider that they can contribute to appropriate patient management. | |
| **Methodical Notes** | | | |
| **Funding Sources:**<br>**COI:** | | | |

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| **Randomization:**<br>**Blinding:**<br>**Dropout Rate/ITT-Analysis:**<br>**Notes:** Oxford Checklist for prognostic studies<br>1 unclear domain identified (1.4 If subgroups with different prognoses are identified, did adjustment for important prognostic factors take place?)<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Prognosis): 3 (Cohort study or control arm of randomized trial). | | | |
| **Münch, S. et al. Impact of (18)F-FDG-PET/CT on the identification of regional lymph node metastases and delineation of the primary tumor in esophageal squamous cell carcinoma patients. Strahlenther Onkol. 196. 787-794. 2020** | | | |
| **Population** | **Intervention** | **Outcomes/Results** | |
| **Evidence level:** 4<br>**Study type:** retrospective<br>**Number of Patient:** 76<br>**Recruitung Phase:** 2011 - 2016<br>**Inclusion Criteria:** ESCC patients who underwent PET/CT<br>**Exclusion Criteria:** patients without sufficient FDG uptake, early tumor stages (Tis or T1), without LNM or LNM which were only seen by endoscopic ultrasound | **Intervention:** Impact of 18F-FDG-PET/CT on the identification of regional lymph node metastases and delineation of the primary tumor in esophageal squamous cell carcinoma<br>**Comparison:** | **Primary:** patterns of lymph node metastases and their correlation with the primary tumor<br>**Secondary:**<br>**Results:** Significantly more LNM were identified with 18F-FDG-PET/CT (177 LNM) compared to CT alone (131 LNM, pâ€¯ | |
| | | **Author's Conclusion:** In conclusion, 18F-FDG-PET can help to identify subclinical lymph node metastases which are located outside of recommended radiation fields. PET-based involved-field irradiation might be the ideal compromise between small treatment volumes and decreasing the risk of undertreatment of subclinical metastatic lymph nodes and should be further evaluated. | |
| **Methodical Notes** | | | |

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| **Funding Sources:**<br>**COI:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout Rate/ITT-Analysis:**<br>**Notes:** Oxford Checklist for prognostic studies<br>4 unclear domains identified (1.1 - 1.4)<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Prognosis): 3 (Cohort study or control arm of randomized trial).<br>Downgrade to evidence level 4 due to high risk of bias. | |

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

| **Bhatnagar, S. et al. The Impact of Positron Emission Tomography/Computed Tomography Addition to Contrast-Enhanced Computed Tomography Findings during Radiation Treatment Planning of Locally Advanced Carcinoma Esophagus. J Med Phys. 44. 276-282. 2019** | | | |
|---|---|---|---|
| **Evidence level** | **Methodical Notes** | **Patient characteristics** | **Interventions** |
| **Evidence level:** n/a<br>**Study type:** Comparison of two radiologic assessments(CT and PET/CT) | **Funding sources:** No funding<br>**Conflict of Interests:** no conflicts of interest<br>**Randomization:**<br>**Blinding:**<br>**Dropout rates:** | **Total no. patients:** 50 patients<br>**Recruiting Phase:** between January 2011 and 2013<br>**Inclusion criteria:** Previously untreated, histologically confirmed esophageal neoplasms with no tracheoesophageal/tracheobronchial fistula in patients between 20 and 80 years of age with a Karnofskyâ€™s Performance Scale â‰§60% and minimum<br>weight â‰§30 kg; males and nonpregnant, nonnursing females with no contraindication to injection of contrast or to radiotherapy (RT) to be taken up for any form of radiation first, be it definitive concurrent chemoradiation therapy, palliative external beam RT, radical RT, or neoadjuvant RT with concurrent chemotherapy<br>**Exclusion criteria:** | **Interventions:** CT<br><br>**Comparison:** PET-CT |
| **Notes:** | **Author's conclusion:** PET-CT tremendously changes treatment plans by expanding the gross tumor volume and including regions which might otherwise have been missed on purely CT-based plans. Of the 50 patients, it changed the contouring and treatment planning of 35 patients and did not impact the remaining 15. | | |
| **Outcome Measures/results** | **Primary**<br>**Secondary** | **Results:** Of 50 patients, the length of the primary lesion increased by ≥10 mm in 18 (36%) patients and by 5 mm in 8 (16%) and by<br>NNS or a new involved structure was picked up by PET scan in 22 (44%) patients. PET brought | |

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| | | about a change in dose to OARs in 27 (54%) patients [Table 4]. It increased the dose to OARs (such as thyroid, spinal cord, heart, lung, kidney, and liver) by more than or 5% in 1 (2%) patient.<br>Overall PET brought about technical changes in treatment plan such as beam number, geometry, orientation, and weightage in 13 (26%) of patients and no technical change in the remaining 37 (15 + 22) or 74% of patients. |

## 3.16 Schlüsselfrage 9: Stellenwert der Operation nach Ansprechen auf eine Chemo(radio)therapie (Patienten mit klinisch kompletter Remission) beim Ösophaguskarzinom/ inklusive AEG

P: 1)Pat. mit nicht fernmetastasiertem Plattenepithelkarzinom Ösophagus (Stadium Talle Nalle M0), 2) AEG (Stadium Talle Nalle M0)
I: Resektion
C: a) keine Resektion, b) definitive Radiochemotherapie, c) watch and wait
O: Patientenrelevante Endpunkte: Gesamtüberlebensrate, Überlebensrate nach 5 Jahren und 3 Jahren (ggfls. „Ableitung“ aus Überlebenskurven, wenn nicht im Text berichtet), medianes ÜL, Rate an R0 Resektionen, Rate an Lokal- und Fernrezidiven im Beobachtungszeitraum, Häufigkeit schwerer und lebensbedrohlicher NW durch die Radio- oder Chemotherapie in der präoperativen Phase

***Inhalt:*** *3 Literaturstellen*

| Literaturstelle | Evidenzlevel | Studientyp |
|---|---|---|
| Kamarajah, S. K. 2022 | 3 | population-based cohort study |
| Mitchell, K. G. 2020 | 4 | retrospective data analysis |
| Park, S. R. 2019 | 2 | single-center, open-label, randomized, phase III trial |

***Cochrane Risk of Bias Tool 1 (RCT):*** *1 Bewertung(en)*

| **Park, S. R. et al. A Randomized Phase III Trial on the Role of Esophagectomy in Complete Responders to Preoperative Chemoradiotherapy for Esophageal Squamous Cell Carcinoma (ESOPRESSO). Anticancer Res. 39. 5123-5133. 2019** | | | |
|---|---|---|---|
| **Population** | **Intervention / Comparison** | **Outcomes/Results** | **Methodical Notes** |
| **Evidence level:** 2<br>**Study type:** single-center, open-label, randomized, phase III trial<br>**Number of Patients:** 86 patients (17.7% of the target number)<br>**Recruiting Phase:** Between November 2012 and March 2016. The accrual was slower than expected, causing early study closure<br>**Inclusion Criteria:** histologically confirmed, resectable cT3-T4a/anyN/M0 or anyT/N+/M0 (the 7th edition of the AJCC staging system) thoracic ESCC, age 20-75 years, Eastern Cooperative Oncology | **Intervention:** Surgery for Patients with cCR after two cycles of induction chemotherapy and then chemoradiotherapy (50.4 Gy/28 fractions)<br>**Comparison:** Observation for Patients with cCR after two cycles of induction chemotherapy and then chemoradiotherapy (50.4 Gy/28 fractions) | **Primary:** disease-free survival (DFS), which was defined as the time between randomization and progression or death from any cause<br>**Secondary:** d progression-free survival (PFS; the time between initiation of chemotherapy and progression or death), time to progression (TTP; the time between initiation of chemotherapy and progression), OS (the time between initiation of chemotherapy and death), the failure pattern, the pCR rate, treatment outcomes according to metabolic or clinical response, safety, and quality of life<br>**Results:** Among 86 patients, 38 (44.2%) achieved cCR after chemoradiotherapy; 37 were randomized to surgery (n=19) or observation (n=18). Although there were trends of better disease-free survival (DFS) toward the surgery arm in the | **Funding Sources:** No information provided<br>**COI:** The Authors declare no conflict of interest relevant to this article<br>**Randomization:** 1:1<br>**Blinding:** No, open label<br>**Dropout Rate/ITT-Analysis:**<br>**Notes:** Cochrane risk of bias tool 1 (RoB 1):<br>(2 unclear risks of bias (#2 Selection bias: Allocation concealment, #6 Reporting bias: Selective reporting) were observed)<br>Overall risk of bias: Low<br><br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment |

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| Group performance status 0-2,<br>adequate major organs function, and no history of other cancers<br>within 5 years.<br>**Exclusion Criteria:** | | intent-to-treat analysis (2-year DFS, 66.7% vs. 42.7%; p=0.262) or as-treated analysis (66.7% vs. 50.2%; p=0.273), overall survival was not different between the two arms in the intent-to-treat (HR=1.48; p=0.560) or astreated analysis (HR=1.09; p=0.903). Among the 11 patients having recurrence during observation, 8 underwent surgery (n=7) or endoscopic dissection (n=1).<br>**Author's Conclusion:** Close observation with salvage surgery might be a reasonable option in resectable ESCC patients achieving cCR after chemoradiation | benefits): 2 (Randomized trial). |

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

| **Kamarajah, S. K. et al. Definitive Chemoradiotherapy Compared to Neoadjuvant Chemoradiotherapy With Esophagectomy for Locoregional Esophageal Cancer: National Population-based Cohort Study. Ann Surg. 275. 526-533. 2022** | | | |
|---|---|---|---|
| **Evidence level** | **Methodical Notes** | **Patient characteristics** | **Interventions** |
| **Evidence level:** 3<br><br>**Study type:** population-based cohort study | **Funding sources:** not mentioned<br><br>**Conflict of Interests:** not mentioned<br><br>**Randomization:**<br><br>**Blinding:**<br><br>**Dropout rates:** | **Total no. patients:** definitive chemoradiotherapy (DCR)(n = 5977) neoadjuvant chemoradiotherapy with planned esophagectomy (NCRS) (n = 13555)<br><br>**Recruiting Phase:** Data from the National Cancer Database (NCDB) from 2004 to 2015<br><br>**Inclusion criteria:** Any patients diagnosed with a nonmetastatic esophageal cancer (adenocarcinoma or SCC according to the International Classification of Disease for Oncology, Third Edition (ICD-O-3) who received DCR or NCRS between 2004 and 2015 in the de-identified NCDB were included.<br><br>**Exclusion criteria:** other histology subtypes such as mucinous tumors, neuroendocrine tumors, and other histologies; patients who underwent endoscopic resection; other concurrent cancer diagnoses; those who did not receive neoadjuvant chemoradiotherapy; and patients with metastatic esophageal cancer. | **Interventions:** DCR<br><br>**Comparison:** DCR |
| **Notes:** | Newcastle-Ottawa Scale (NOS) for Cohort studies: 8/9 stars | | |

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| | Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 3 (Cohort study / Non-randomized controlled cohort).<br><br>**Author's conclusion:** Surgery remains an integral component of the management of patients with esophageal cancer. Neoadjuvant therapy followed by planned esophagectomy appears to remain the optimum curative treatment regime in patients with locoregional esophageal cancer. | |
| **Outcome Measures/results** | **Primary**<br><br>**Secondary** | **Results:** Comparison of baseline demographics of the unmatched cohort revealed that patients receiving NCRS were younger, had a lower burden of medical comorbidities, lower proportion of squamous cell carcinoma (SCC), and more positive lymph nodes. Following matching, NCRS was associated with significantly improved survival compared with DCR [hazard ratio (HR): 0.60, 95% confidence Interval (CI): 0.57-0.63, P < 0.001], which persisted in subset analyses of patients with adenocarcinoma (HR: 0.60, 95% CI: 0.56-0.63, P < 0.001) and SCC (HR: 0.58, 95% CI: 0.53-0.63, P < 0.001). Of 829 receiving SALVafter DCR, 823 patients were matched to 1643 NCRS. There was no difference in overall survival between SALV and NCRS (HR: 1.00, 95% CI: 0.90-1.11, P Â¼ 1.0). |

**Mitchell, K. G. et al. Morbidity following salvage esophagectomy for squamous cell carcinoma: the MD Anderson experience. Dis Esophagus. 33. . 2020**

| Evidence level | Methodical Notes | Patient characteristics | Interventions |
|---|---|---|---|
| **Evidence level:** 4 | **Funding sources:** no data provided | **Total no. patients:** 76 patients | **Interventions:** salvage esophagectomy (for failure of |

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| **Study type:** retrospective data analysis | **Conflict of Interests:** no data provided<br><br>**Randomization:**<br><br>**Blinding:**<br><br>**Dropout rates:** | **Recruiting Phase:** Data of ESCC patients collected between 2004 and 2016 at the University of Texas MD Anderson Cancer Center (MDACC) Anderson Cancer Center (MDACC)<br><br>**Inclusion criteria:** patients with ESCC of the thoracic esophagus and GEJ who underwent esophagectomy following chemoradiotherapy<br><br>**Exclusion criteria:** | definitive bimodality therapy) and planned esophagectomy (as a component of trimodality therapy)<br><br>**Comparison:** |
| **Notes:** | Newcastle-Ottawa Scale (NOS) for Cohort studies: 6/9 stars<br>Downgrade due to 0 stars in comparability domain.<br><br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 3 (Cohort study / Non-randomized controlled cohort).<br><br>Downgrade to evidence level 4 due to high risk of bias.<br><br>**Author's conclusion:** esophagectomy following chemoradiotherapy for ESCC at our institution has been associated with frequent postoperative morbidity and considerable rates of mortality in both planned and salvage settings. Although a selective approach to surgery may permit organ preservation in many patients with ESCC, these results highlight that salvage esophagectomy for<br>failure of definitive-intent treatment of ESCC may also constitute a difficult clinical undertaking in some cases. | | |

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| **Outcome Measures/results** | **Primary** composite outcome of major postoperative morbidity or mortality was defined as a major pulmonary complication (acute respiratory distress syndrome, pneumonia, respiratory failure requiring reintubation, or tracheostomy), a major cardiovascular complication (arrhythmia requiring pharmacologic intervention, myocardial infarction, pulmonary embolism, or cardiac arrest), anastomotic leak (requiring endoscopic intervention [grade II] or greater severity), chylothorax requiring operative intervention, and any death within 90 days postoperatively.<br>Overall survival (OS) was defined as the time from completion of chemoradiotherapy to death from any cause<br><br>**Secondary** | **Results:** Of 76 patients who met inclusion criteria, 46.1% (35) underwent salvage esophagectomy. Major postoperative complications (major cardiovascular and pulmonary events, anastomotic leak [grade â‰¥ 2], and 90-day mortality)<br>were frequent and occurred in 52.6% of the cohort (planned resection: 36.6% [15/41]; salvage esophagectomy: 71.4% [25/35]). Observed rates of 30- and 90-day mortality for the entire cohort were 7.9% (planned: 7.3% [3/41]; salvage: 8.6% [3/35]) and 13.2% (planned: 9.8% [4/41]; salvage: 17.1% 6/35]), respectively. |

## 3.17 Schlüsselfrage 11.1 Stellenwert der palliativen Chemotherapie (Fragestellungen 2 und 3 für Evidenzbericht: Definition einer multidisziplinären Therapie in der Palliation und Indikation, Nutzen und Schaden der palliativen Chemotherapie

P: Patienten im Stadium IV und mit lokoregionär fortgeschrittenen, primär inoperablen Plattenepithel- und Adenokarzinomen des Ösophagus und Adenokarzinomen des gastroösophagealen Übergangs 1-3
I: 1) palliative Chemotherapie, 2) Zweitlinienchemo therapie palliativ , 3) Radiotherapie palliativ, 4) Brachytherapie palliativ, 5) Radiochemotherapie palliativ, 6) Stentimplantation palliativ, 7) palliative OP 8) Immuntherapie (Pembrolizumab, Nivolumab, Tislelizumab, Cambrelizumab..)
C: Die jeweils anderen Verfahren
O: Patientenrelevante Endpunkte: Lebensqualität (QoL), Nutzen, Schaden (Therapienebenwirkungen/Toxizität), Perforation, Blutung, Todesfall), Remissionsrate, Progressionsfreies Überleben, symptomfreies Überleben (symptomfree survival) (time without signs and symptoms), Gesamtüberlebensrate/ Überlebenszeit, Speziell für 6) Stentimplantation zusätzlich: Dysphagiefreies Überleben ohne Stentverschluss, Dysphagieminderung

***Inhalt:*** *7 Literaturstellen*

| Literaturstelle | Evidenzlevel | Studientyp |
|---|---|---|
| Chao, J. 2021 | 3 | post hoc analysis of the phase 2 KEYNOTE-059 (third-line treatment or higher) single-arm trial and the phase 3 KEYNOTE-061 (second-line treatment) and KEYNOTE-062 (first-line treatment) randomized trials i |
| Doki, Y. 2022 | 3 | randomized, open label, phase 3 trial |
| Janjigian, Y. Y. 2021 | 2 | Randomized, Multicenter, Open-Label, Phase 3 Study |

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| Luo, H. 2021 | 2 | randomized, double-blind, placebo-controlled, multicenter, phase 3 trial |
| Moehler, M. 2021 | 3 | open-label,randomized phase III trial |
| Shitara, K. 2020 | 2 | randomized, controlled, partially blinded Phase 3 trial |
| Van Cutsem, E. 2021 | 3 | health-related quality of life (HRQOL) analysis of the Keynote-062 (randomised phase III trial) data |

***Cochrane Risk of Bias Tool 1 (RCT):*** *7 Bewertung(en)*

| **Chao, J. et al. Assessment of Pembrolizumab Therapy for the Treatment of Microsatellite Instability-High Gastric or Gastroesophageal Junction Cancer among Patients in the KEYNOTE-059, KEYNOTE-061, and KEYNOTE-062 Clinical Trials. JAMA oncology. 7. 895?902. 2021** | | | |
|---|---|---|---|
| **Population** | **Intervention / Comparison** | **Outcomes/Results** | **Methodical Notes** |
| **Evidence level:** 3<br>**Study type:** post hoc analysis of the phase 2 KEYNOTE-059 (third-line treatment or higher) single-arm trial and the phase 3 KEYNOTE-061 (second-line treatment) and KEYNOTE-062 (first-line treatment) randomized trials i<br>**Number of Patients:** Patients who had tumors that were evaluable for microsatellite instability-high status were included:<br>174 of 259 patients enrolled in KEYNOTE-059, 514 of 592 patients enrolled in KEYNOTE-061 | **Intervention:** KEYNOTE-059: pembrolizumab monotherapy<br>KEYNOTE-061: pembrolizumab monotherapy<br>KEYNOTE-062: pembrolizumab monotherapy or , pembrolizumab plus chemotherapy (cisplatin and 5-fluorouracil or capecitabine)<br>**Comparison:** KEYNOTE-059: no comparator<br>KEYNOTE-061: paclitaxel<br>KEYNOTE-062: chemotherapy alone | **Primary:** Overall survival<br>**Secondary:** progression free survival, objective response rate, duration of response<br>**Results:** 7 of 174 patients (4.0%) in KEYNOTE-059, 27 of 514 patients (5.3%) in KEYNOTE-061, and 50 of 682 patients (7.3%) in KEYNOTE-062 with evaluable tumors had MSI-H gastric or gastroesophageal junction cancer.<br><br>Among patients with MSI-H tumors, the median OS for pembrolizumab monotherapy was not reached (ie, >50% of patients were still alive at data cutoff) in KEYNOTE-059 (95% CI, 1.1 months to not reached) or KEYNOTE-061 (95% CI, 5.6 months to not reached) compared with a median OS of 8.1 months (95% CI, 2.0-16.7 months) for chemotherapy alone in | **Funding Sources:** This study and assistance with medical writing were funded by Merck Sharp & Dohme, a subsidiary of Merck, and supported by grant 5K12CA001727-23 from the National Institutes of Health (Dr Chao).<br>Role of the Funder/Sponsor: Employees of Merck Sharp & Dohme were involved in the design and conduct of the study and in the collection,management, analysis, and interpretation of the data. Drs Chen, Adelberg, Shih, Shah, and Bhagia,employees of Merck, were involved in the review and approval of the manuscript and the decision to submit the manuscript for publication.<br>**COI:** Dr Chao reported receiving manuscript-writing assistance from |

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| 682 of 763 patients enrolled in KEYNOTE-062.<br><br>**Recruiting Phase:** Patients were enrolled from: March 2, 2015, to March 26, 2016, in KEYNOTE-059; June 4, 2015, to July 26, 2016, in KEYNOTE-061; September 18, 2015, to May 26, 2017, in KEYNOTE-062,<br>with data cutoff dates of August 8, 2018; October 26, 2017; and March 26, 2019; respectively<br><br>**Inclusion Criteria:** patients with advanced G/GEJ cancer<br>**Exclusion Criteria:** | | KEYNOTE-061. In KEYNOTE-062, the median OS was not reached for both pembrolizumab monotherapy (95% CI, 10.7 months to not reached) and pembrolizumab plus chemotherapy (95% CI, 3.6 months to not reached) compared with a median OS of 8.5 months (95% CI, 5.3-20.8 months) for chemotherapy alone The estimated 12-month OS rates for pembrolizumab monotherapy among patients with MSI-H tumors were 71% (95% CI, not available) for KEYNOTE-059 and 73% (95% CI, 44%-89%) for KEYNOTE-061 (compared with 25% [95% CI, 6%-50%] for chemotherapy alone in KEYNOTE-061). In KEYNOTE-062, the estimated 12-month OS rates were 79% (95% CI, 47%-92%) for pembrolizumabmonotherapy, 71% (95% CI, 43%-87%) for pembrolizumab plus chemotherapy, and 47% (95% CI, 24%-67%) for chemotherapy alone.<br>In KEYNOTE059 and KEYNOTE-061, the estimated 24-month OS rates for pembrolizumab monotherapy were 57% (95% CI, not available) and 59% (95% CI, 31%-79%), respectively (24-month OS rate not available for chemotherapy alone in | Merck Sharp & Dohme during the conduct of the study and receiving grants from Brooklyn ImmunoTherapeutics and Merck and personal fees from Amgen, AstraZeneca, Boston Biomedical, Daiichi Sankyo, Foundation Medicine, MacroGenics, Merck, Ono Pharmaceutical, and Taiho Pharmaceutical outside the submitted work.<br>Dr Fuchs reported receiving personal fees from Agios Pharmaceuticals, Amylin Pharmaceuticals, Bain Capital, CytomX Therapeutics, Daiichi Sankyo, Eli Lilly, Entrinsic Health, EvolveImmune Therapeutics, Genentech, Merck, Taiho Pharmaceutical, and Unum Therapeutics; owning stock in CytomX Therapeutics and Entrinsic Health; cofounding EvolveImmune Therapeutics; serving as the director of CytomX Therapeutics and EvolveImmune Therapeutics; and providing expert testimony for Amylin Pharmaceuticals and Eli Lilly outside |

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| | | KEYNOTE-061). In KEYNOTE-062, the estimated 24-month OS rates were 71% (95% CI, 41%-88%) for pembrolizumab monotherapy, 65% (95% CI, 38%-82%) for pembrolizumab plus chemotherapy, and 26% (95% CI, 10%-57%) for chemotherapy alone.<br>The median progression-free survival (PFS) for pembrolizumab was NR (95% CI, 1.1 months to NR) in KEYNOTE-059 and 17.8 months (95% CI, 2.7 months to NR) in KEYNOTE-061 (vs 3.5 months [95% CI, 2.0-9.8 months] for chemotherapy). In KEYNOTE-062, the median PFS was 11.2 months (95% CI, 1.5 months to NR) for pembrolizumab, NR (95% CI, 3.6 months to NR) for pembrolizumab plus chemotherapy, and 6.6 months (95% CI, 4.4-8.3 months) for chemotherapy.<br>The objective response rate (ORR) for pembrolizumab was 57.1% in KEYNOTE-059 and 46.7% (vs 16.7% for chemotherapy) in KEYNOTE-061. In KEYNOTE-062, the ORR was 57.1% for pembrolizumab , 64.7% for pembrolizumab plus chemotherapy, and 36.8% for chemotherapy.<br>The median duration of response was not | the submitted work.<br>Dr Shitara reported receiving grants from Astellas Pharma, Chugai Pharmaceutical, Daiichi Sankyo, Eli Lilly, Merck, Medi Science, Ono Pharmaceutical, Sumitomo Dainippon Pharma, and Taiho Pharmaceutical and personal fees from AbbVie, Astellas Pharma, Bristol Myers Squibb, Eli Lilly, GlaxoSmithKline, Novartis, Pfizer, Takeda Pharmaceutical, and Yakult Honsha outside the submitted work.<br>Dr Tabernero reported receiving personal fees from Array BioPharma, AstraZeneca, Bayer, BeiGene, Biocartis, Boehringer Ingelheim, Chugai Pharmaceutical, Eli Lilly, F. Hoffmann-La Roche, Foundation Medicine, Genentech, Genmab, HalioDx, Halozyme Therapeutics, Imugene, Inflection Biosciences, Ipsen Biopharmaceuticals, Kura Oncology, Menarini, Merck Serono, Merck Sharp & Dohme, Merrimack Pharmaceuticals, Merus, Molecular Partners, Novartis, Peptomyc, Pfizer, |

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| | | reached for pembrolizumab monotherapy in both KEYNOTE059 (range, 20.0-26.8 months) and KEYNOTE-061 (range, 5.5- 26.0 months) and not reached for chemotherapy alone (range, 2.2-12.2 months) in KEYNOTE-061. In KEYNOTE-062, the median duration of response was 21.2 months (range, 1.4+ to 33.6 months, with + indicating no progressive disease at last assessment) for pembrolizumab monotherapy, not reached (range, 1.6+ to 34.5+ months) for pembrolizumab plus chemotherapy, and 7.0 months (range, 2.0-30.4+ months) for chemotherapy alone.<br><br>**Author's Conclusion:** The findings of this analysis support MSI-H status as a biomarker for pembrolizumab therapy among patients with advanced gastric or gastroesophageal junction cancer and warrant its prospective validation in ongoing first-line studies. | Pharmacyclics, ProteoDesign, Rafael Pharmaceuticals, Roche Diagnostics, Sanofi, SeaGen (formerly Seattle Genetics), Servier Laboratories, Symphogen, Taiho Pharmaceutical, and VCN Biosciences outside the submitted work.<br>Dr Muro reported receiving grants from Merck Sharp & Dohme during the conduct of the study and receiving grants from Amgen, Astellas Pharma, Daiichi Sankyo, Merck Sharp & Dohme, Merck Serono, Ono Pharmaceutical, Parexel, Pfizer, Sanofi, Solasia Pharma, and Taiho Pharmaceutical and personal fees from Amgen, AstraZeneca, Bayer, Bristol Myers Squibb, Chugai Pharmaceutical, Eli Lilly, Ono Pharmaceutical, Sanofi, Takeda Pharmaceutical, and Taiho Pharmaceutical outside the submitted work.<br>Dr Van Cutsem reported receiving grants from Amgen, Bayer, Bristol Myers Squibb, Boehringer Ingelheim, Celgene, Eli Lilly, Ipsen |

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| | | | Biopharmaceuticals, Merck KGaA, Merck Sharp & Dohme, Novartis, Roche, and Servier Laboratories and serving on the advisory boards of Array BioPharma, AstraZeneca, Bayer, Biocartis, Bristol Myers Squibb, Celgene, Daiichi Sankyo, Eli Lilly, GlaxoSmithKline, Halozyme Therapeutics, Incyte, Ipsen Biopharmaceuticals, Merck KGaA, Merck Sharp & Dohme, Novartis, Pierre Fabre, Roche, Servier Laboratories, Sirtex Medical, and Taiho Pharmaceutical outside the submitted work.<br>Dr Bang reported receiving grants from Astellas Pharma, AstraZeneca, Bayer, BeiGene, Boehringer Ingelheim, Boston Biomedical, Bristol Myers Squibb, CKD Pharmaceuticals, Curis, Daiichi Sankyo, Eli Lilly, Five Prime Therapeutics, Genentech, Genexine, GlaxoSmithKline, GC Pharma, MacroGenics, Merck Serono, Merck Sharp & Dohme, Novartis, Ono Pharmaceutical, Pfizer, Taiho Pharmaceutical, and Takeda |

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| | | | Pharmaceutical and serving as a consultant or advisor for Astellas Pharma, AstraZeneca, Bayer, BeiGene, Bristol Myers Squibb, Daiichi Sankyo, Eli Lilly, Genentech, Genexine, GC Pharma, Hanmi Pharmaceutical, Merck Serono, Merck Sharp & Dohme, Novartis, Samyang Biopharm, and Taiho Pharmaceutical outside the submitted work.<br>Dr De Vita reported serving as a consultant or advisor for Celgene and Eli Lilly outside the submitted work.<br>Dr Chau reported receiving grants from Merck Sharp & Dohme during the conduct of the study and receiving grants from Eli Lilly, Janssen-Cilag, and Sanofi Oncology and personal fees from AstraZeneca, Bayer, Bristol Myers Squibb, Eli Lilly, Five Prime Therapeutics, Merck Serono, Merck Sharp & Dohme, Oncologie, Pierre Fabre, and Roche outside the submitted work.<br>Dr Elme reported receiving grants from Merck Sharp & Dohme during the conduct of the study and receiving |

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| | | | grants from Roche and personal fees from Amgen, Astra Zeneca, Ipsen Biopharmaceuticals, Merck Sharp & Dohme, and Roche outside the submitted work.<br>Dr ÖzgüroÄŸlu reported receiving grants from Merck Sharp & Dohme during the conduct of the study and receiving personal fees from Astellas Pharma, AstraZeneca, Bristol Myers Squibb, Janssen Pharmaceuticals, Novartis, Roche, and Sanofi outside the submitted work.<br>Dr Catenacci reported receiving grants from Merck Sharp & Dohme and personal fees from Astellas Pharma, Bristol Myers Squibb, Daiichi Sankyo, Eli Lilly, Five Prime Therapeutics, Foundation Medicine, Genentech, Gritstone Oncology, Guardant Health, Merck, Pieris Pharmaceuticals, Taiho Pharmaceutical, and Tempus Labs during the conduct of the study.<br>Dr Yoon reported receiving grants from Merck and personal fees from BeiGene, Bristol Myers Squibb, and MacroGenics outside the submitted |

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| | | | work.<br>Dr Wainberg reported receiving grants from Bristol Myers Squibb, Five Prime Therapeutics, Merck Serono, Novartis, and Ipsen Biopharmaceuticals and personal fees from AstraZeneca, Bayer, Daiichi Sankyo, Eli Lilly, MacroGenics, and Merck outside the submitted work. No other disclosures were reported.<br><br>**Randomization:**<br>**Blinding:**<br>**Dropout Rate/ITT-Analysis:**<br>**Notes:** Cochrane risk of bias tool 1 (RoB 1):<br>(6 unclear risks of bias (#1 - #6) were observed)<br>Overall risk of bias: Unclear<br><br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 2 (Randomized trial).<br><br>Downgrade to evidence level 3 due to high risk of bias. |

## 3.18 Schlüsselfrage 11.2: Stellenwert der Immuntherapie – Erstlinie

**Schlüsselfrage:**

**11.2 Stellenwert der Immuntherapie - Erstlinie (PICO s.o.)**
P: Patienten im Stadium IV und mit lokoregionär fortgeschrittenen, primär inoperablen Plattenepithel- und Adenokarzinomen des Ösophagus und Adenokarzinomen des gastroösophagealen Übergangs 1-3
I: 1) palliative Chemotherapie, 2) Zweitlinienchemo therapie palliativ , 3) Radiotherapie palliativ, 4) Brachytherapie palliativ, 5) Radiochemotherapie palliativ, 6) Stentimplantation palliativ, 7) palliative OP 8) Immuntherapie (Pembrolizumab, Nivolumab, Tislelizumab, Cambrelizumab..)
C: Die jeweils anderen Verfahren
O: Patientenrelevante Endpunkte: Lebensqualität (QoL), Nutzen, Schaden (Therapienebenwirkungen/Toxizität), Perforation, Blutung, Todesfall), Remissionsrate, Progressionsfreies Überleben, symptomfreies Überleben (symptomfree survival) (time without signs and symptoms), Gesamtüberlebensrate/ Überlebenszeit, Speziell für 6) Stentimplantation zusätzlich: Dysphagiefreies Überleben ohne Stentverschluss, Dysphagieminderung

***Inhalt:*** *7 Literaturstellen*

| Literaturstelle | Evidenzlevel | Studientyp |
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| Chao, J. 2021 | 3 | post hoc analysis of the phase 2 KEYNOTE-059 (third-line treatment or higher) single-arm trial and the phase 3 KEYNOTE-061 (second-line treatment) and KEYNOTE-062 (first-line treatment) randomized trials i |
| Doki, Y. 2022 | 3 | randomized, open label, phase 3 trial |
| Janjigian, Y. Y. 2021 | 2 | Randomized, Multicenter, Open-Label, Phase 3 Study |

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| Luo, H. 2021 | 2 | randomized, double-blind, placebo-controlled, multicenter, phase 3 trial |
| Moehler, M. 2021 | 3 | open-label,randomized phase III trial |
| Shitara, K. 2020 | 2 | randomized, controlled, partially blinded Phase 3 trial |
| Van Cutsem, E. 2021 | 3 | health-related quality of life (HRQOL) analysis of the Keynote-062 (randomised phase III trial) data |

***Cochrane Risk of Bias Tool 1 (RCT):*** *7 Bewertung(en)*

| **Chao, J. et al. Assessment of Pembrolizumab Therapy for the Treatment of Microsatellite Instability-High Gastric or Gastroesophageal Junction Cancer among Patients in the KEYNOTE-059, KEYNOTE-061, and KEYNOTE-062 Clinical Trials. JAMA oncology. 7. 895?902. 2021** | | | |
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| **Population** | **Intervention / Comparison** | **Outcomes/Results** | **Methodical Notes** |
| **Evidence level:** 3<br>**Study type:** post hoc analysis of the phase 2 KEYNOTE-059 (third-line treatment or higher) single-arm trial and the phase 3 KEYNOTE-061 (second-line treatment) and KEYNOTE-062 (first-line treatment) randomized trials i<br>**Number of Patients:** Patients who had tumors that were evaluable for microsatellite instability–high status were included:<br>174 of 259 patients enrolled in KEYNOTE-059, 514 of 592 patients enrolled in KEYNOTE-061 | **Intervention:** KEYNOTE-059: pembrolizumab monotherapy<br>KEYNOTE-061: pembrolizumab monotherapy<br>KEYNOTE-062: pembrolizumab monotherapy or , pembrolizumab plus chemotherapy (cisplatin and 5-fluorouracil or capecitabine)<br>**Comparison:** KEYNOTE-059: no comparator<br>KEYNOTE-061: paclitaxel<br>KEYNOTE-062: chemotherapy alone | **Primary:** Overall survival<br>**Secondary:** progression free survival, objective response rate, duration of response<br>**Results:** 7 of 174 patients (4.0%) in KEYNOTE-059, 27 of 514 patients (5.3%) in KEYNOTE-061, and 50 of 682 patients (7.3%) in KEYNOTE-062 with evaluable tumors had MSI-H gastric or gastroesophageal junction cancer. Among patients with MSI-H tumors, the median OS for pembrolizumab monotherapy was not reached (ie, >50% of patients were still alive at data cutoff) in KEYNOTE-059 (95% CI, 1.1 months to not reached) or KEYNOTE-061 (95% CI, 5.6 months to not reached) compared with a median OS of 8.1 months (95% CI, 2.0-16.7 months) for chemotherapy alone in KEYNOTE-061. In KEYNOTE-062, the median | **Funding Sources:** This study and assistance with medical writing were funded by Merck Sharp & Dohme, a subsidiary of Merck, and supported by grant 5K12CA001727-23 from the National Institutes of Health (Dr Chao).<br>Role of the Funder/Sponsor: Employees of Merck Sharp & Dohme were involved in the design and conduct of the study and in the collection,management, analysis, and interpretation of the data. Drs Chen, Adelberg, Shih, Shah, and Bhagia,employees of Merck, were involved in the review and approval of the manuscript and the decision to submit the manuscript for publication.<br>**COI:** Dr Chao reported receiving manuscript-writing assistance from |

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| 682 of 763 patients enrolled in KEYNOTE-062.<br>**Recruiting Phase:** Patients were enrolled from: March 2, 2015, to March 26, 2016, in KEYNOTE-059; June 4, 2015, to July 26, 2016, in KEYNOTE-061; September 18, 2015, to May 26, 2017, in KEYNOTE-062,<br>with data cutoff dates of August 8, 2018; October 26, 2017; and March 26, 2019; respectively<br>**Inclusion Criteria:** patients with advanced G/GEJ cancer<br>**Exclusion Criteria:** | | OS was not reached for both pembrolizumab monotherapy (95% CI, 10.7 months to not reached) and pembrolizumab plus chemotherapy (95% CI, 3.6 months to not reached) compared with a median OS of 8.5 months (95% CI, 5.3-20.8 months) for chemotherapy alone The estimated 12-month OS rates for pembrolizumab monotherapy among patients with MSI-H tumors were 71% (95% CI, not available) for KEYNOTE-059 and 73% (95% CI, 44%-89%) for KEYNOTE-061 (compared with 25% [95% CI, 6%-50%] for chemotherapy alone in KEYNOTE-061). In KEYNOTE-062, the estimated 12-month OS rates were 79% (95% CI, 47%-92%) for pembrolizumabmonotherapy, 71% (95% CI, 43%-87%) for pembrolizumab plus chemotherapy, and 47% (95% CI, 24%-67%) for chemotherapy alone.<br>In KEYNOTE059 and KEYNOTE-061, the estimated 24-month OS rates for pembrolizumab monotherapy were 57% (95% CI, not available) and 59% (95% CI, 31%-79%), respectively (24-month OS rate not available for chemotherapy alone in KEYNOTE-061). In KEYNOTE-062, the | Merck Sharp & Dohme during the conduct of the study and receiving grants from Brooklyn ImmunoTherapeutics and Merck and personal fees from Amgen, AstraZeneca, Boston Biomedical, Daiichi Sankyo, Foundation Medicine, MacroGenics, Merck, Ono Pharmaceutical, and Taiho Pharmaceutical outside the submitted work.<br>Dr Fuchs reported receiving personal fees from Agios Pharmaceuticals, Amylin Pharmaceuticals, Bain Capital, CytomX Therapeutics, Daiichi Sankyo, Eli Lilly, Entrinsic Health, EvolveImmune Therapeutics, Genentech, Merck, Taiho Pharmaceutical, and Unum Therapeutics; owning stock in CytomX Therapeutics and Entrinsic Health; cofounding EvolveImmune Therapeutics; serving as the director of CytomX Therapeutics and EvolveImmune Therapeutics; and providing expert testimony for Amylin Pharmaceuticals and Eli Lilly outside |

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| | | estimated 24-month OS rates were 71% (95% CI, 41%-88%) for pembrolizumab monotherapy, 65% (95% CI, 38%-82%) for pembrolizumab plus chemotherapy, and 26% (95% CI, 10%-57%) for chemotherapy alone.<br>The median progression-free survival (PFS) for pembrolizumab was NR (95% CI, 1.1 months to NR) in KEYNOTE-059 and 17.8 months (95% CI, 2.7 months to NR) in KEYNOTE-061 (vs 3.5 months [95% CI, 2.0-9.8 months] for chemotherapy). In KEYNOTE-062, the median PFS was 11.2 months (95% CI, 1.5 months to NR) for pembrolizumab, NR (95% CI, 3.6 months to NR) for pembrolizumab plus chemotherapy, and 6.6 months (95% CI, 4.4-8.3 months) for chemotherapy.<br>The objective response rate (ORR) for pembrolizumab was 57.1% in KEYNOTE-059 and 46.7% (vs 16.7% for chemotherapy) in KEYNOTE-061. In KEYNOTE-062, the ORR was 57.1% for pembrolizumab , 64.7% for pembrolizumab plus chemotherapy, and 36.8% for chemotherapy.<br>The median duration of response was not reached for pembrolizumab monotherapy | the submitted work.<br>Dr Shitara reported receiving grants from Astellas Pharma, Chugai Pharmaceutical, Daiichi Sankyo, Eli Lilly, Merck, Medi Science, Ono Pharmaceutical, Sumitomo Dainippon Pharma, and Taiho Pharmaceutical and personal fees from AbbVie, Astellas Pharma, Bristol Myers Squibb, Eli Lilly, GlaxoSmithKline, Novartis, Pfizer, Takeda Pharmaceutical, and Yakult Honsha outside the submitted work.<br>Dr Tabernero reported receiving personal fees from Array BioPharma, AstraZeneca, Bayer, BeiGene, Biocartis, Boehringer Ingelheim, Chugai Pharmaceutical, Eli Lilly, F. Hoffmann-La Roche, Foundation Medicine, Genentech, Genmab, HalioDx, Halozyme Therapeutics, Imugene, Inflection Biosciences, Ipsen Biopharmaceuticals, Kura Oncology, Menarini, Merck Serono, Merck Sharp & Dohme, Merrimack Pharmaceuticals, Merus, Molecular Partners, Novartis, Peptomyc, Pfizer, |

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| | | in both KEYNOTE059 (range, 20.0-26.8 months) and KEYNOTE-061 (range, 5.5- 26.0 months) and not reached for chemotherapy alone (range, 2.2-12.2 months) in KEYNOTE-061. In KEYNOTE-062, the median duration of response was 21.2 months (range, 1.4+ to 33.6 months, with + indicating no progressive disease at last assessment) for pembrolizumab monotherapy, not reached (range, 1.6+ to 34.5+ months) for pembrolizumab plus chemotherapy, and 7.0 months (range, 2.0-30.4+ months) for chemotherapy alone.<br><br>**Author's Conclusion:** The findings of this analysis support MSI-H status as a biomarker for pembrolizumab therapy among patients with advanced gastric or gastroesophageal junction cancer and warrant its prospective validation in ongoing first-line studies. | Pharmacyclics, ProteoDesign, Rafael Pharmaceuticals, Roche Diagnostics, Sanofi, SeaGen (formerly Seattle Genetics), Servier Laboratories, Symphogen, Taiho Pharmaceutical, and VCN Biosciences outside the submitted work.<br>Dr Muro reported receiving grants from Merck Sharp & Dohme during the conduct of the study and receiving grants from Amgen, Astellas Pharma, Daiichi Sankyo, Merck Sharp & Dohme, Merck Serono, Ono Pharmaceutical, Parexel, Pfizer, Sanofi, Solasia Pharma, and Taiho Pharmaceutical and personal fees from Amgen, AstraZeneca, Bayer, Bristol Myers Squibb, Chugai Pharmaceutical, Eli Lilly, Ono Pharmaceutical, Sanofi, Takeda Pharmaceutical, and Taiho Pharmaceutical outside the submitted work.<br>Dr Van Cutsem reported receiving grants from Amgen, Bayer, Bristol Myers Squibb, Boehringer Ingelheim, Celgene, Eli Lilly, Ipsen |

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| | | | Biopharmaceuticals, Merck KGaA, Merck Sharp & Dohme, Novartis, Roche, and Servier Laboratories and serving on the advisory boards of Array BioPharma, AstraZeneca, Bayer, Biocartis, Bristol Myers Squibb, Celgene, Daiichi Sankyo, Eli Lilly, GlaxoSmithKline, Halozyme Therapeutics, Incyte, Ipsen Biopharmaceuticals, Merck KGaA, Merck Sharp & Dohme, Novartis, Pierre Fabre, Roche, Servier Laboratories, Sirtex Medical, and Taiho Pharmaceutical outside the submitted work.<br>Dr Bang reported receiving grants from Astellas Pharma, AstraZeneca, Bayer, BeiGene, Boehringer Ingelheim, Boston Biomedical, Bristol Myers Squibb, CKD Pharmaceuticals, Curis, Daiichi Sankyo, Eli Lilly, Five Prime Therapeutics, Genentech, Genexine, GlaxoSmithKline, GC Pharma, MacroGenics, Merck Serono, Merck Sharp & Dohme, Novartis, Ono Pharmaceutical, Pfizer, Taiho Pharmaceutical, and Takeda |

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| | | | Pharmaceutical and serving as a consultant or advisor for Astellas Pharma, AstraZeneca, Bayer, BeiGene, Bristol Myers Squibb, Daiichi Sankyo, Eli Lilly, Genentech, Genexine, GC Pharma, Hanmi Pharmaceutical, Merck Serono, Merck Sharp & Dohme, Novartis, Samyang Biopharm, and Taiho Pharmaceutical outside the submitted work.<br>Dr De Vita reported serving as a consultant or advisor for Celgene and Eli Lilly outside the submitted work.<br>Dr Chau reported receiving grants from Merck Sharp & Dohme during the conduct of the study and receiving grants from Eli Lilly, Janssen-Cilag, and Sanofi Oncology and personal fees from AstraZeneca, Bayer, Bristol Myers Squibb, Eli Lilly, Five Prime Therapeutics, Merck Serono, Merck Sharp & Dohme, Oncologie, Pierre Fabre, and Roche outside the submitted work.<br>Dr Elme reported receiving grants from Merck Sharp & Dohme during the conduct of the study and receiving |

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| | | | grants from Roche and personal fees from Amgen, Astra Zeneca, Ipsen Biopharmaceuticals, Merck Sharp & Dohme, and Roche outside the submitted work.<br>Dr ÖzgüroÄŸlu reported receiving grants from Merck Sharp & Dohme during the conduct of the study and receiving personal fees from Astellas Pharma, AstraZeneca, Bristol Myers Squibb, Janssen Pharmaceuticals, Novartis, Roche, and Sanofi outside the submitted work.<br>Dr Catenacci reported receiving grants from Merck Sharp & Dohme and personal fees from Astellas Pharma, Bristol Myers Squibb, Daiichi Sankyo, Eli Lilly, Five Prime Therapeutics, Foundation Medicine, Genentech, Gritstone Oncology, Guardant Health, Merck, Pieris Pharmaceuticals, Taiho Pharmaceutical, and Tempus Labs during the conduct of the study.<br>Dr Yoon reported receiving grants from Merck and personal fees from BeiGene, Bristol Myers Squibb, and MacroGenics outside the submitted |

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| | | | work.<br>Dr Wainberg reported receiving grants from Bristol Myers Squibb, Five Prime Therapeutics, Merck Serono, Novartis, and Ipsen Biopharmaceuticals and personal fees from AstraZeneca, Bayer, Daiichi Sankyo, Eli Lilly, MacroGenics, and Merck outside the submitted work. No other disclosures were reported.<br>**Randomization:**<br>**Blinding:**<br>**Dropout Rate/ITT-Analysis:**<br>**Notes:** Cochrane risk of bias tool 1 (RoB 1):<br>(6 unclear risks of bias (#1 - #6) were observed)<br>Overall risk of bias: Unclear<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 2 (Randomized trial).<br>Downgrade to evidence level 3 due to high risk of bias. |
| **Doki, Y. et al. Nivolumab Combination Therapy in Advanced Esophageal Squamous-Cell Carcinoma. New England journal of medicine. 386. 449?462. 2022** | | | |

| Population | Intervention / Comparison | Outcomes/Results | Methodical Notes |
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| **Evidence level:** 3<br>**Study type:** randomized, open label, phase 3 trial<br>**Number of Patients:** 970 patients randomized<br>**Recruiting Phase:** June 2017 through November 2019<br>**Inclusion Criteria:** at least 18 years of age;<br>unresectable advanced, recurrent, or metastatic esophageal squamous-cell carcinoma, regardless of PD-L1 expression status;<br>disease not amenable to curative treatments;<br>no previous systemic therapy for advanced disease<br>histologically confirmed esophageal squamous-cell or adenosquamous-cell carcinoma | **Intervention:** Nivolumab + Ipilimumab<br>Nivolumab + Cisplatin + Fluorouacil<br>**Comparison:** Cisplatin + Fluorouracil | **Primary:** Overall Survival (OS) and Progression-free Survival (PFS) in Participants With Tumor Cell PD-L1 as assessed by BICR per RECIST1.1<br>**Secondary:** Overall Survival (OS) in All Randomized Participants<br>Progression-free Survival (PFS) in All Randomized Participants as Assessed by BICR per RECIST1.1<br>Objective Response Rate (ORR) as Assessed by BICR per RECIST1.1<br>**Results:** Patients were randomly assigned to receive nivolumab plus chemotherapy (321 patients), nivolumab plus ipilimumab (325 patients), or chemotherapy alone (324 patients).<br>At a 13-month minimum follow-up, overall survival was significantly longer with nivolumab plus chemotherapy than with chemotherapy alone, both among patients with tumor-cell PD-L1 expression of 1% or greater (median, 15.4 vs. 9.1 months; hazard ratio, 0.54; 99.5% confidence interval [CI], 0.37 to 0.80; P | **Funding Sources:** Supported by Bristol Myers Squibb and Ono Pharmaceutical<br>**COI:** Disclosure forms provided by the authors are available with the full text of this article at NEJM.org<br>**Randomization:** Patients were randomly assigned to receive nivolumab plus chemotherapy (321 patients), nivolumab plus ipilimumab (325 patients), or chemotherapy alone (324 patients)<br>**Blinding:** None (Open Label)<br>**Dropout Rate/ITT-Analysis:**<br>**Notes:** Cochrane risk of bias tool 1 (RoB 1):<br>(4 unclear risks of bias (#1 Selection bias: Random sequence generation, #2 2. Selection bias: Allocation concealment, #5. Attrition bias: Incomplete outcome data, #6. Reporting bias: Selective reporting) were observed)<br>Overall risk of bias: Unclear<br>Oxford Centre for Evidence-Based |

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| measurable disease, according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1.<br>**Exclusion Criteria:** Presence of tumor cells in the brain or spinal cord which are symptomatic or require treatment<br>Active known or suspected autoimmune disease<br>Any serious or uncontrolled medical disorder or active infection<br>Known history of positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)<br>Any positive test result for hepatitis B or C indicating acute or chronic infection and/or detectable virus | | Overall survival was also significantly longer with nivolumab plus ipilimumab than with chemotherapy among patients with tumor-cell PD-L1 expression of 1% or greater (median, 13.7 vs. 9.1 months; hazard ratio, 0.64; 98.6% CI, 0.46 to 0.90; P=0.001) and in the overall population (median, 12.7 vs. 10.7 months; hazard ratio, 0.78; 98.2% CI, 0.62 to 0.98; P=0.01). Among patients with tumor-cell PD-L1 expression of 1% or greater, a significant progression-free survival benefit was also seen with nivolumab plus chemotherapy over chemotherapy alone (hazard ratio for disease progression or death, 0.65; 98.5% CI, 0.46 to 0.92; P=0.002) but not with nivolumab plus ipilimumab as compared with chemotherapy.<br>The incidence of treatment-related adverse events of grade 3 or 4 was 47% with nivolumab plus chemotherapy, 32% with nivolumab plus ipilimumab, and 36% with chemotherapy alone.<br><br>**Author's Conclusion:** Both first-line treatment with nivolumab plus chemotherapy and first-line treatment | Medicine 2011 Levels of Evidence (Treatment benefits): 2 (Randomized trial).<br>Downgrade to evidence level 3 due to high risk of bias. |

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| | | with nivolumab plus ipilimumab resulted in significantly longer overall survival than chemotherapy alone in patients with advanced esophageal squamous-cell carcinoma, with no new safety signals identified. | |

**Janjigian, Y. Y. et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. Lancet. 398. 27-40. 2021**

| Population | Intervention / Comparison | Outcomes/Results | Methodical Notes |
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| **Evidence level:** 2<br>**Study type:** Randomized, Multicenter, Open-Label, Phase 3 Study<br>**Number of Patients:** 1581 patients<br>**Recruiting Phase:** March 2017 through April 2019<br>**Inclusion Criteria:** 18 years of age or older<br>previously untreated, unresectable advanced or metastatic gastric, GEJ, or oesophageal adenocarcinoma, | **Intervention:** Nivolumab + Ipilimumab<br>Nivolumab + XELOX or Nivolumab + FOLFOX<br>**Comparison:** XELOX (Oxaliplatin + Capecitabine)<br>FOLFOX (Oxaliplatin + Leucovorin + Fluorouracil) | **Primary:** OS (time from randomisation to death) or progression-free survival (PFS; time from randomisation to the date of first documented tumour progression or death) by BICR per RECIST version 1.1, evaluated in patients with PD-L1 CPS ≥5<br>**Secondary:** OS in patients with PD-L1 CPS ≥1 and all randomised patients<br>BICR-assessed PFS and objective response rate at different PD-L1 CPS cutoffs and in all randomised patients<br>**Results:** The median follow-up for OS was: nivolumab-plus-chemotherapy, 13Â·1 months (IQR, 6Â·7–19Â·1) and chemotherapy, 11Â·1 months (5Â·8–16Â·1). | **Funding Sources:** The study was sponsored and conducted by Bristol Myers Squibb, in collaboration with Ono Pharmaceutical Co., Ltd<br>**COI:** Extensive list of disclosures for each author, see article.<br>**Randomization:** nivolumab plus chemotherapy (XELOX [capecitabine and oxaliplatin] or FOLFOX [fluorouracil, leucovorin, and oxaliplatin])<br>or nivolumab plus ipilimumab versus chemotherapy alone at a 1:1:1 ratio<br>**Blinding:** None (Open Label) |

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| regardless of PD-L1 expression.<br>Measurable lesions (at least one lesion) or evaluable disease per Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1<br>Eastern Cooperative Oncology Group performance status of 0 or 1<br>adequate organ function<br>availability to provide a fresh or archival tumour sample to evaluate PD-L1<br>**Exclusion Criteria:** known HER2-positive status<br>;untreated central nervous system metastases<br>peripheral neuropathy (> grade 1)<br>active, known, or suspected autoimmune disease<br>positive test result for hepatitis B or hepatitis C virus | | Nivolumab plus chemotherapy demonstrated superior OS, with a 29% reduction in the risk of death compared with chemotherapy (HR 0Â·71 [98Â·4% CI 0Â·59–0Â·86]; p< 0Â·0001) and a 3Â·3-month improvement in median OS (14Â·4 months [95% CI 13Â·1–16Â·2] vs 11Â·1 months [10Â·0–12Â·1], respectively) in patients with PD-L1 CPS ≥5.<br>Nivolumab plus chemotherapy also provided superior PFS in patients with PD-L1 CPS ≥5, with a 32% reduction in the risk of progression or death versus chemotherapy (HR 0Â·68 [98% CI 0Â·56–0Â·81]; p<br>Nivolumab plus chemotherapy demonstrated a significant improvement in OS in patients with PD-L1 CPS ≥1 and all randomised patients versus chemotherapy (HR 0Â·77 [99Â·3% CI 0Â·64–0Â·92]; p<br>HRs of 0Â·74 (95% CI 0Â·65–0Â·85) and 0Â·77 (0Â·68–0Â·87) indicated that PFS benefit was also observed with nivolumab plus chemotherapy versus chemotherapy in patients with PD-L1 CPS ≥1 and all randomised patients, respectively.<br>In the primary population, 226 (60% [95% CI 55–65]) of 378 patients in the nivolumab plus chemotherapy group and 177 (45% [40–50]) | **Dropout Rate/ITT-Analysis:**<br>**Notes:** Cochrane risk of bias tool 1 (RoB 1):<br>(1 unclear risks of bias (#6 Reporting bias: Selective reporting) were observed)<br>Overall risk of bias: Low<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 2 (Randomized trial). |

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| known history of positive test for human immunodeficiency virus or known acquired immunodeficiency syndrome | | of 391 patients in the chemotherapy group achieved an objective response (per BICR assessment). The proportion of patients with a complete response was 12% and 7%, respectively, and median duration of response was 9Â·5 months (95% CI 8Â·0–11Â·4) versus 7Â·0 months (5Â·7–7Â·9), respectively.<br>The proportion of patients with PD-L1 CPS<br>Results for nivolumab plus ipilimumab versus chemotherapy remain blinded and will be reported later.<br><br>**Author's Conclusion:** Nivolumab is the first PD-1 inhibitor to demonstrate superior OS, along<br>with PFS benefit, and an acceptable safety profile, in combination with chemotherapy versus chemotherapy alone in previously untreated patients with advanced gastric/GEJ/oesophageal adenocarcinoma. Nivolumab-plus-chemotherapy represents a potential standard first-line treatment for these patients. | |
| **Luo, H. et al. Effect of Camrelizumab vs Placebo Added to Chemotherapy on Survival and Progression-Free Survival in Patients With Advanced or Metastatic Esophageal Squamous Cell Carcinoma: the ESCORT-1st Randomized Clinical Trial. JAMA. 326. 916?925. 2021** | | | |

| Population | Intervention / Comparison | Outcomes/Results | Methodical Notes |
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| **Evidence level:** 2<br>**Study type:** randomized, double-blind, placebo-controlled,<br>multicenter, phase 3 trial<br>**Number of Patients:** 596 patients randomized<br>**Recruiting**<br>**Phase:** December 3, 2018 to May 12, 2020 (final follow-up, October 30, 2020)<br>**Inclusion Criteria:** eaged 18 through 75 years<br>histologically or cytologically confirmed ESCC<br>unresectable, locally advanced, or recurrent disease that precluded esophagectomy or definitive chemoradiation, or distant metastatic disease<br>received no previous | **Intervention:** camrelizumab plus paclitaxel + cisplatin<br>**Comparison:** placebo plus paclitaxel + cisplatin | **Primary:** overall survival (significance threshold, 1-sided P < .02) progression-free survival (significance threshold, 1-sided P < .005)assessed band<br>**Secondary:** progression-free survival assessed by<br>investigator, objective response rate (proportion of patients<br>whose best overall response was complete or partial<br>response), disease control rate (proportion of patients whose<br>best overall response was complete response, partial<br>response, or stable disease), duration of response (the time<br>from the first response to disease progression or death from<br>any cause, whichever occurred first), probability of overall<br>survival, adverse events, and health–related quality of life<br>**Results:** Of the 596 patients randomized (median age, 62 years [interquartile range, 56-67 years]; 523 men [87.8%]), 1 patient in the | **Funding Sources:** Jiangsu Hengrui Pharmaceuticals Co, Ltd.<br>**COI:** Dr Wu reported receiving personal fees from AstraZeneca, Roche, Bristol Myers Squibb, MSD, Pfizer, Lilly, Boehringer Ingelheim, Merck, Innovent, and Jiangsu Hengrui Pharmaceuticals Co Ltd.<br>Drs Shen, Yang, and Zou reported being employees of Jiangsu Hengrui Pharmaceuticals Co, Ltd.<br>Dr Xu reported serving as a consultant or an advisor to Bristol Myers Squibb, Merck Serono, Roche, Astellas, and AstraZeneca.<br>**Randomization:** 1:1 ratio to either the camrelizumab-chemotherapy group or the placebo-chemotherapy group<br>**Blinding:** double-blind<br>**Dropout Rate/ITT-Analysis:** |

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| systemic therapy (patients who had progressed ≥6 months after [neo]adjuvant therapy or definitive chemoradiation were eligible)<br>Eastern Cooperative Oncology Group performance status score of 0 or 1<br>at least 1 measurable lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1<br>life expectancy of at least 12 weeks<br>adequate organ function required to provide fresh or archival tumor samples for PD-L1 expression assessment.<br>**Exclusion Criteria:** presence of other malignancies<br>active or a history of autoimmune disease | | placebo-chemotherapy group did not receive planned treatment.<br>A total of 490 patients (82.2%) had discontinued the study treatment.<br>The median follow-up was 10.8 months.<br>The overall survival for the camrelizumabchemotherapy group was a median of 15.3 months (95% CI, 12.8-17.3; 135 deaths) vs a median of 12.0 months (95% CI, 11.0-13.3; 174 deaths) for the placebo-chemotherapy group (hazard ratio [HR] for death, 0.70 [95% CI, 0.56-0.88]; 1-sided P = .001).<br>Progression-free survival for camrelizumab plus chemotherapy was a median of 6.9 months (95% CI, 5.8-7.4; 199 progression or deaths) vs 5.6 months (95% CI, 5.5-5.7; 229 progression or deaths) for the placebo-chemotherapy group (HR for progression or death, 0.56 [95% CI, 0.46-0.68]; 1-sided P < .001).<br>Treatment-related adverse events of grade 3 or higher occurred in 189 patients (63.4%) in the camrelizumab-chemotherapy group and 201 (67.7%) in the placebo-chemotherapy group, including treatment-related deaths among 9 patients (3.0%) and 11 patients | **Notes:** Cochrane risk of bias tool 1 (RoB 1):<br>(1 unclear risks of bias (#6. Reporting bias: Selective reporting) were observed)<br>Overall risk of bias: Low<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 2 (Randomized trial). |

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| central nervous system metastases<br>use of antitumor therapies or live vaccine within the 4 weeks preceding study enrollment | | (3.7%), respectively.<br>**Author's Conclusion:** Among patients with advanced or metastatic esophageal squamous cell carcinoma, the addition of camrelizumab to chemotherapy, compared with placebo and chemotherapy, significantly improved overall survival and progression-free survival. | |

| **Moehler, M. et al. Phase III Trial of Avelumab Maintenance After First-Line Induction Chemotherapy Versus Continuation of Chemotherapy in Patients With Gastric Cancers: results From JAVELIN Gastric 100. Journal of clinical oncology. 39. 966?977. 2021** | | | |
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| **Population** | **Intervention / Comparison** | **Outcomes/Results** | **Methodical Notes** |
| **Evidence level:** 3<br>**Study type:** open-label,randomized phase III trial<br>**Number of Patients:** 805 patients enrolled, subsequently, 499 patients with disease control were randomized<br>**Recruiting**<br>**Phase:** December 31, 2015 to November 29, 2017<br>**Inclusion**<br>**Criteria:** untreated, unresectable, human | **Intervention:** Avelumab Maintenance after 12 weeks of First-Line Induction Chemotherapy with oxaliplatin plus a fluoropyrimidine (5-FU/LV or Capecitabine) and no progress<br>**Comparison:** Continuation of Chemotherapy fter 12 weeks of First-Line Induction Chemotherapy with oxaliplatin plus a fluoropyrimidine (5-FU/LV or Capecitabine) and no progress | **Primary:** overall survival (OS) in all randomly assigned patients or the PD-L1–positive randomly assigned population ($ 1% of tumor cells; 73-10 assay)<br>**Secondary:** PFS (time from random assignment to first documentation of PD per RECIST [version 1.1]<br>best overall response (best response among all tumor assessments from baseline [at random assignment, after induction chemotherapy] per RECIST [version 1.1])<br>duration of response (time from first documentation of objective response in | **Funding Sources:** Merck KGaA, Darmstadt<br>**COI:** Extensive list of funding and disclosures of the authors in online article<br>**Randomization:**<br>**Blinding:** No, open-label<br>**Dropout Rate/ITT-Analysis:**<br>**Notes:** Cochrane risk of bias tool 1 (RoB 1):<br>(4 unclear risks of bias (1# Selection bias: Random sequence generation, #2. Selection bias: Allocation concealment, #5. Attrition |

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| epidermal growth factor receptor 2–negative, locally advanced or metastatic GC or GEJC<br>age ≥ 18 years<br>Eastern Cooperative Oncology Group performance status of 0 or 1<br>recently obtained (â‰¤ 6 months) tumor specimen<br>**Exclusion Criteria:** HER2-positive tumor<br>prior immune checkpoint inhibitor therapy<br>untreated or symptomatic brain metastasis | | the maintenance phase until PD per RECIST [version 1.1] or death)<br>**Results:** A total of 805 patients received induction; 499 were randomly assigned to avelumab (n = 249) or continued chemotherapy (n = 250). Median OS was 10.4 months (95% CI, 9.1 to 12.0 months) versus 10.9 months (95% CI, 9.6 to 12.4 months) and 24-month OS rate was 22.1% versus 15.5% with avelumab versus chemotherapy, respectively (hazard ratio [HR], 0.91; 95% CI, 0.74 to 1.11; P = .1779). In the PD-L1–positive population (n = 54), the HR for OS was 1.13 (95% CI, 0.57 to 2.23; P = .6352). In an exploratory analysis of the PD-L1–positive population, defined as combined positive score ≥ 1 (22C3 assay; n = 137), median OS was 14.9 months (95% CI, 8.7 to 17.3 months) with avelumab versus 11.6 months (95% CI, 8.4 to 12.6 months) with chemotherapy (unstratified HR, 0.72; 95% CI, 0.49 to 1.05). With avelumab and chemotherapy, treatment-related adverse events (TRAEs) occurred in 149 | bias: ncomplete outcome data, 6. Reporting bias: Selective reporting) were observed)<br>Overall risk of bias: Unclear<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 2 (Randomized trial).<br>Downgrade to evidence level 3 due to high risk of bias. |

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| | | (61.3%) and 184 (77.3%) patients, including grade ≥ 3 TRAEs in 31 (12.8%) and 78 (32.8%) patients, respectively. **Author's Conclusion:** AVELIN Gastric 100 did not demonstrate superior OS with avelumab maintenance versus continued chemotherapy in patients with advanced GC or GEJC overall or in a prespecified PD-L1–positive population. | |

| **Shitara, K. et al. Efficacy and Safety of Pembrolizumab or Pembrolizumab Plus Chemotherapy vs Chemotherapy Alone for Patients With First-line, Advanced Gastric Cancer: the KEYNOTE-062 Phase 3 Randomized Clinical Trial. JAMA oncology. 6. 1571?1580. 2020** | | | |
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| **Population** | **Intervention / Comparison** | **Outcomes/Results** | **Methodical Notes** |
| **Evidence level:** 2 **Study type:** randomized, controlled, partially blinded Phase 3 trial **Number of Patients:** 763 patients **Recruiting Phase:** between September 18, 2015, and May 26, 2017. **Inclusion Criteria:** untreated, locally advanced/unresectable or | **Intervention:** pembrolizumab 200 mg or pembrolizumab plus chemotherapy (cisplatin 80 mg/m2/d on day 1 plus fluorouracil 800 mg/m2/d on days 1 to 5 or capecitabine 1000 mg/m2 twice daily) **Comparison:** chemotherapy plus placebo, | **Primary:** overall survival (OS) and progression-free survival (PFS) in patients with PD-L1 CPS of 1 or greater or 10 or greater progression-free survival (PFS) per RECIST 1.1 by BICR in PD-L1 CPS of 1 or greater **Secondary:** ORR, duration of response (DOR) per RECIST 1.1 by BICR in PD-L1 CPS of 1 or greater, safety and tolerability, and health-related quality of life. | **Funding Sources:** Merck Sharp & Dohme Corp, a subsidiary of Merck & Co, Inc, Kenilworth, New Jersey **COI:** Extensive list of funding and disclosures for the authors **Randomization:** 1:1:1 pembrolizumab (200 mg every 3 weeks), pembrolizumab plus chemotherapy (cisplatin 80 mg/m2 /d on day 1 plus fluorouracil 800 mg/m2 /d on days 1-5 or capecitabine 1000 mg/m2 twice |

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| metastatic G/GEJ cancer with PD-L1 CPS of 1 or greater<br>**Exclusion Criteria:** | | **Results:** 763 patients were randomized to pembrolizumab (n = 256), pembrolizumab plus chemotherapy (n = 257), or chemotherapy (n = 250).<br>At final analysis, after a median (range) follow-up of 29.4 (22.0-41.3) months, pembrolizumab was noninferior to chemotherapy for OS in patients with CPS of 1 or greater (median, 10.6 vs 11.1 months; hazard ratio [HR], 0.91; 99.2% CI, 0.69-1.18). Pembrolizumab monotherapy was not superior to chemotherapy in patients with CPS of 1 or greater.<br>Pembrolizumab prolonged OS vs chemotherapy in patients with CPS of 10 or greater (median, 17.4 vs 10.8 months; HR, 0.69; 95% CI, 0.49-0.97), but this difference was not statistically tested.<br>Pembrolizumab plus chemotherapy was not superior to chemotherapy for OS in patients with CPS of 1 or greater (12.5 vs 11.1 months; HR, 0.85; 95% CI, 0.70-1.03; P = .05) or | daily on days 1-14 every 3 weeks), or placebo plus chemotherapy.<br>**Blinding:** partially blinded: Patients and site and sponsor personnel were blinded to pembrolizumab or placebo in the combination and chemotherapy groups<br>**Dropout Rate/ITT-Analysis:**<br>**Notes:** Cochrane risk of bias tool 1 (RoB 1):<br>(1 unclear risks of bias (#6 Reporting bias: Selective reporting) were observed)<br>Overall risk of bias: Low<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 2 (Randomized trial). |

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| | | CPS of 10 or greater (12.3 vs 10.8 months; HR, 0.85; 95% CI, 0.62-1.17; P = .16) or for PFS in patients with CPS of 1 or greater (6.9 vs 6.4 months; HR, 0.84; 95% CI, 0.70-1.02; P = .04).<br>Grade 3 to 5 treatment-related adverse event rates for pembrolizumab, pembrolizumab plus chemotherapy, and chemotherapy were 17%, 73%, and 69%, respectively<br>**Author's Conclusion:** This phase 3 randomized clinical trial found that among patients with untreated, advanced G/GEJ cancer, pembrolizumab was noninferior to chemotherapy, with fewer adverse events observed. Pembrolizumab or pembrolizumab plus chemotherapy was not superior to chemotherapy for the OS and PFS end points tested. | |
| **Van Cutsem, E. et al. Quality of life with first-line pembrolizumab for PD-L1-positive advanced gastric/gastroesophageal junction adenocarcinoma: results from the randomised phase III KEYNOTE-062 study. ESMO open. 6. 100189. 2021** | | | |

| Population | Intervention / Comparison | Outcomes/Results | Methodical Notes |
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| **Evidence level:** 3<br>**Study type:** health-related quality of life (HRQOL) analysis of the Keynote-062 (randomised phase III trial) data<br>**Number of Patients:** HRQOL population 495 patients<br>**Recruiting Phase:** between September 18, 2015, and May 26, 2017.<br>**Inclusion Criteria:** Keynote-062 participants who received ≥ 1 dose of study treatment and completed ≥ 1 HRQOL questionnaire [European Organisation for the Research and Treatment of Cancer (EORTC) 30-question quality-of-life (QLQ-C30), EORTC 22-question quality-of-life gastric-cancer-specific module (QLQ-STO22)]<br>**Exclusion Criteria:** | **Intervention:** pembrolizumab 200 mg or<br>pembrolizumab plus chemotherapy (cisplatin 80 mg/m2/d on day 1 plus fluorouracil 800 mg/m2/d on days 1 to 5 or capecitabine 1000 mg/m2 twice daily)<br>**Comparison:** chemotherapy plus placebo, | **Primary:** Least squares mean (LSM) change (baseline to week 18) in global health status/quality of life (GHS/QOL; EORTC QLQ-C30)<br>time to deterioration (TTD) in GHS/QOL, nausea/vomiting and appetite loss scores (EORTC QLQ-C30) and abdominal pain/discomfort scores (EORTC QLQ-STO22)<br>**Secondary:**<br>**Results:** The HRQOL population comprised 495 patients with CPS ≥ 1 (pembrolizumab, 252; chemotherapy, 243). Compliance rates at week 18 were similar for pembrolizumab and chemotherapy (EORTC QLQ-C30, 87.9% and 81.9%; EORTC QLQ-STO22, 87.9% and 81.3%, respectively). There was no between-arm difference in LSM score change in GHS/QOL [0.16; 95% confidence interval (CI) 5.01 to 4.69; P=0.948]. The LSM score change for most subscales showed | **Funding Sources:** Merck Sharp & Dohme Corp. (no grant number), a subsidiary of Merck & Co., Inc. (no grant number), Kenilworth, NJ, USA<br>**COI:** Extensive list of funding and disclosures for the authors<br>**Randomization:** 1:1:1<br>**Blinding:**<br>**Dropout Rate/ITT-Analysis:**<br>**Notes:** Cochrane risk of bias tool 1 (RoB 1):<br>(1 high risk of bias was observed #4. Detection bias: Blinding of outcome assessment)<br>3 unclear risks of bias (#1. Selection bias: Random sequence generation, #2. Selection bias: Allocation concealment, #6. Reporting bias: Selective reporting were observed)<br>Overall risk of bias: Unclear |

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| | | comparable worsening in both arms. TTD for GHS/QOL [hazard ratio (HR), 0.96; 95% CI, 0.67-1.38; P= 0.826], appetite loss (HR, 0.83; 95% CI, 0.58-1.20; P Â¼ 0.314) and pain (HR, 1.22; 95% CI, 0.78-1.91; P= 0.381) were similar between arms. Longer TTD was observed for pembrolizumab versus chemotherapy for nausea/vomiting (HR, 0.61; 95% CI, 0.44-0.85; P= 0.003).<br>**Author's Conclusion:** HRQOL was maintained with first-line treatment with pembrolizumab in patients with PD-L1epositive advanced gastric/GEJ cancer and was similar between pembrolizumab and chemotherapy in this population | Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits/ harms): 2 (Randomized trial). Downgrade to evidence level 3 due to high risk of bias. |

## 3.19 Schlüsselfrage 12.1: Stellenwert der Zweitlinienchemotherapie

**Schlüsselfrage:**

**12.1 Stellenwert der Zweitlinienchemotherapie (PICO s.o.)**
P: Patienten im Stadium IV und mit lokoregionär fortgeschrittenen, primär inoperablen Plattenepithel- und Adenokarzinomen des Ösophagus und Adenokarzinomen des gastroösophagealen Übergangs 1-3
I: 1) palliative Chemotherapie, 2) Zweitlinienchemo therapie palliativ , 3) Radiotherapie palliativ, 4) Brachytherapie palliativ, 5) Radiochemotherapie palliativ, 6) Stentimplantation palliativ, 7) palliative OP 8) Immuntherapie (Pembrolizumab, Nivolumab, Tislelizumab, Cambrelizumab..)
C: Die jeweils anderen Verfahren
O: Patientenrelevante Endpunkte: Lebensqualität (QoL), Nutzen, Schaden (Therapienebenwirkungen/Toxizität), Perforation, Blutung, Todesfall), Remissionsrate, Progressionsfreies Überleben, symptomfreies Überleben (symptomfree survival) (time without signs and symptoms), Gesamtüberlebensrate/ Überlebenszeit, Speziell für 6) Stentimplantation zusätzlich: Dysphagiefreies Überleben ohne Stentverschluss, Dysphagieminderung

***Inhalt:*** *5 Literaturstellen*

| Literaturstelle | Evidenzlevel | Studientyp |
|---|---|---|
| Cao, Y. 2022 | 3 | randomized, open-label, phase III trial |
| Chao, J. 2021 | 3 | post hoc analysis of the phase 2 KEYNOTE-059 (third-line treatment or higher) single-arm trial and the phase 3 KEYNOTE-061 (second-line treatment) and KEYNOTE-062 (first-line treatment) randomized trials i |
| Fuchs, C. S. 2021 | 2 | randomized phase 3 trial, re-evaluation of data after 2 additional years of follow up (cutof: 10/07/2019) |

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| Kato, K. 2019 | 2 | randomised, open-label, phase 3 trial |
| Shitara, K. 2021 | 2 | randomized, open-label, phase III trial |

***Cochrane Risk of Bias Tool 1 (RCT):*** *5 Bewertung(en)*

| **Cao, Y. et al. Pembrolizumab versus chemotherapy for patients with esophageal squamous cell carcinoma enrolled in the randomized KEYNOTE-181 trial in Asia. ESMO Open. 7. . 2022** | | | |
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| **Population** | **Intervention / Comparison** | **Outcomes/Results** | **Methodical Notes** |
| **Evidence level:** 3<br>**Study type:** randomized, open-label, phase III trial<br>**Number of Patients:** 340 Asian patients<br>**Recruiting Phase:**<br>**Inclusion Criteria:** histologically confirmed SCC or adenocarcinoma of the esophagus, including human epidermal growth factor receptor 2/neu-negative Siewert type I adenocarcinoma of the esophagogastric junction documented radiographic or clinical progression on one previous line of standard therapy<br>**Exclusion Criteria:** | **Intervention:** pembrolizumab 200 mg every 3 weeks<br>**Comparison:** investigatorâ€™s choice of standard-of-care chemotherapy [paclitaxel (80-100 mg/m2 on days 1, 8, and 15 of each 28-day cycle), docetaxel (75 mg/m2 on day 1 of each 21-day cycle), or irinotecan (180 mg/m2 on day 1 of each 14-day cycle)] | **Primary:** overall survival (OS) in patients with programmed death-ligand 1 (PD-L1) combined positive score (CPS) 10, in patients with esophageal SCC (ESCC), and in all patients.<br>**Secondary:**<br>**Results:** In Asian patients with ESCC, median OS was 10.0 months with pembrolizumab and 6.5 months with chemotherapy [hazard ratio (HR), 0.63; 95% CI 0.50-0.80; nominal P < 0.0001]. Median progression-free survival was 2.3 months with pembrolizumab and 3.1 months with chemotherapy (HR, 0.79; 95% CI 0.63-0.99; nominal P = 0.020). Objective response rate was 17.1% with pembrolizumab and 7.1% with chemotherapy; median duration of response was 10.5 months and 7.7 months, respectively.<br>In patients with PD-L1 CPS 1 [CPS ≥1, | **Funding Sources:** Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA<br>**COI:** Extensive list of fundings and disclosures for the authors.<br>**Randomization:** 1:1<br>**Blinding:** No, open label<br>**Dropout Rate/ITT-Analysis:**<br>**Notes:** Cochrane risk of bias tool 1 (RoB 1):<br>(3 unclear risks of bias (#1. Selection bias: Random sequence generation, 2. Selection bias: Allocation concealment, #6. Reporting bias: Selective reporting) were observed) |

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| | | 0.57 (0.44-0.75); CPS ≥5, 0.56 (0.41-0.76); CPS ≥10, 0.53 (0.37-0.75)]. Treatment-related adverse events were reported in 71.8% of patients in the pembrolizumab group and 89.8% in the chemotherapy group; grade 3-5 events were reported in 20.0% and 44.6%, respectively. **Author's Conclusion:** Pembrolizumab monotherapy demonstrated promising efficacy in Asian patients with ESCC, with fewer treatment-related adverse events than chemotherapy. PD-L1 CPS ≥1 is an appropriate cut-off and a predictive marker of pembrolizumab efficacy in Asian patients with ESCC. | Overall risk of bias: Unclear<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 2 (Randomized trial). Downgrade to evidence level 3 due to high risk of bias. |

**Chao, J. et al. Assessment of Pembrolizumab Therapy for the Treatment of Microsatellite Instability-High Gastric or Gastroesophageal Junction Cancer among Patients in the KEYNOTE-059, KEYNOTE-061, and KEYNOTE-062 Clinical Trials. JAMA oncology. 7. 895?902. 2021**

| Population | Intervention / Comparison | Outcomes/Results | Methodical Notes |
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| **Evidence level:** 3<br>**Study type:** post hoc analysis of the phase 2 KEYNOTE-059 (third-line treatment or higher) single- | **Intervention:** KEYNOTE-059: pembrolizumab monotherapy<br>KEYNOTE-061: pembrolizumab | **Primary:** Overall survival<br>**Secondary:** progression free survival, objective response rate, duration of response<br>**Results:** 7 of 174 patients (4.0%) in | **Funding Sources:** This study and assistance with medical writing were funded by Merck Sharp & Dohme, a subsidiary of Merck, and supported by grant 5K12CA001727-23 from the |

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| arm trial and the phase 3 KEYNOTE-061 (second-line treatment) and KEYNOTE-062 (first-line treatment) randomized trials i<br>**Number of Patients:** Patients who had tumors that were evaluable for microsatellite instability–high status were included:<br>174 of 259 patients enrolled in KEYNOTE-059,<br>514 of 592 patients enrolled in KEYNOTE-061<br>682 of 763 patients enrolled in KEYNOTE-062.<br>**Recruiting Phase:** Patients were enrolled from:<br>March 2, 2015, to March 26, 2016, in KEYNOTE-059;<br>June 4, 2015, to July 26, 2016, in KEYNOTE-061;<br>September 18, 2015, to May 26, 2017, in KEYNOTE-062,<br>with data cutoff dates of | monotherapy<br>KEYNOTE-062: pembrolizumab monotherapy or , pembrolizumab plus chemotherapy (cisplatin and 5-fluorouracil or capecitabine)<br>**Comparison:** KEYNOTE-059: no comparator<br>KEYNOTE-061: paclitaxel<br>KEYNOTE-062: chemotherapy alone | KEYNOTE-059, 27 of 514 patients (5.3%) in KEYNOTE-061, and 50 of 682 patients (7.3%) in KEYNOTE-062 with evaluable tumors had MSI-H gastric or gastroesophageal junction cancer.<br>Among patients with MSI-H tumors, the median OS for pembrolizumab monotherapy was not reached (ie, >50% of patients were still alive at data cutoff) in KEYNOTE-059 (95% CI, 1.1 months to not reached) or KEYNOTE-061 (95% CI, 5.6 months to not reached) compared with a median OS of 8.1 months (95% CI, 2.0-16.7 months) for chemotherapy alone in KEYNOTE-061. In KEYNOTE-062, the median OS was not reached for both pembrolizumab monotherapy (95% CI, 10.7 months to not reached) and pembrolizumab plus chemotherapy (95% CI, 3.6 months to not reached) compared with a median OS of 8.5 months (95% CI, 5.3-20.8 months) for chemotherapy alone<br>The estimated 12-month OS rates for pembrolizumab monotherapy among patients with MSI-H tumors were 71% (95% CI, not available) for KEYNOTE-059 and 73% (95% CI, 44%-89%) for KEYNOTE-061 | National Institutes of Health (Dr Chao).<br>Role of the Funder/Sponsor: Employees of Merck Sharp & Dohme were involved in the design and conduct of the study and in the collection,management, analysis, and interpretation of the data. Drs Chen, Adelberg, Shih, Shah, and Bhagia,employees of Merck, were involved in the review and approval of the manuscript and the decision to submit the manuscript for publication.<br>**COI:** Dr Chao reported receiving manuscript-writing assistance from Merck Sharp & Dohme during the conduct of the study and receiving grants from Brooklyn ImmunoTherapeutics and Merck and personal fees from Amgen, AstraZeneca, Boston Biomedical, Daiichi Sankyo, Foundation Medicine, MacroGenics, Merck, Ono Pharmaceutical, and Taiho Pharmaceutical outside the submitted work.<br>Dr Fuchs reported receiving personal |

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| August 8, 2018; October 26, 2017; and March 26, 2019; respectively<br>**Inclusion Criteria:** patients with advanced G/GEJ cancer<br>**Exclusion Criteria:** | | (compared with 25% [95% CI, 6%-50%] for chemotherapy alone in KEYNOTE-061). In KEYNOTE-062, the estimated 12-month OS rates were 79% (95% CI, 47%-92%) for pembrolizumabmonotherapy, 71% (95% CI, 43%-87%) for pembrolizumab plus chemotherapy, and 47% (95% CI, 24%-67%) for chemotherapy alone.<br>In KEYNOTE059 and KEYNOTE-061, the estimated 24-month OS rates for pembrolizumab monotherapy were 57% (95% CI, not available) and 59% (95% CI, 31%-79%), respectively (24-month OS rate not available for chemotherapy alone in KEYNOTE-061). In KEYNOTE-062, the estimated 24-month OS rates were 71% (95% CI, 41%-88%) for pembrolizumab monotherapy, 65% (95% CI, 38%-82%) for pembrolizumab plus chemotherapy, and 26% (95% CI, 10%-57%) for chemotherapy alone.<br>The median progression-free survival (PFS) for pembrolizumab was NR (95% CI, 1.1 months to NR) in KEYNOTE-059 and 17.8 months (95% CI, 2.7 months to NR) in KEYNOTE-061 (vs 3.5 months [95% CI, 2.0-9.8 months] for chemotherapy). In | fees from Agios Pharmaceuticals, Amylin Pharmaceuticals, Bain Capital, CytomX Therapeutics, Daiichi Sankyo, Eli Lilly, Entrinsic Health, EvolveImmune Therapeutics, Genentech, Merck, Taiho Pharmaceutical, and Unum Therapeutics; owning stock in CytomX Therapeutics and Entrinsic Health; cofounding EvolveImmune Therapeutics; serving as the director of CytomX Therapeutics and EvolveImmune Therapeutics; and providing expert testimony for Amylin Pharmaceuticals and Eli Lilly outside the submitted work.<br>Dr Shitara reported receiving grants from Astellas Pharma, Chugai Pharmaceutical, Daiichi Sankyo, Eli Lilly, Merck, Medi Science, Ono Pharmaceutical, Sumitomo Dainippon Pharma, and Taiho Pharmaceutical and personal fees from AbbVie, Astellas Pharma, Bristol Myers Squibb, Eli Lilly, GlaxoSmithKline, Novartis, Pfizer, Takeda Pharmaceutical, and Yakult Honsha outside the submitted |

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| | | KEYNOTE-062, the median PFS was 11.2 months (95% CI, 1.5 months to NR) for pembrolizumab, NR (95% CI, 3.6 months to NR) for pembrolizumab plus chemotherapy, and 6.6 months (95% CI, 4.4-8.3 months) for chemotherapy.<br>The objective response rate (ORR) for pembrolizumab was 57.1% in KEYNOTE-059 and 46.7% (vs 16.7% for chemotherapy) in KEYNOTE-061. In KEYNOTE-062, the ORR was 57.1% for pembrolizumab , 64.7% for pembrolizumab plus chemotherapy, and 36.8% for chemotherapy.<br>The median duration of response was not reached for pembrolizumab monotherapy in both KEYNOTE059 (range, 20.0-26.8 months) and KEYNOTE-061 (range, 5.5- 26.0 months) and not reached for chemotherapy alone (range, 2.2-12.2 months) in KEYNOTE-061. In KEYNOTE-062, the median duration of response was 21.2 months (range, 1.4+ to 33.6 months, with + indicating no progressive disease at last assessment) for pembrolizumab monotherapy, not reached (range, 1.6+ to 34.5+ months) for pembrolizumab plus chemotherapy, and 7.0 months (range, 2.0-30.4+ months) for | work.<br>Dr Tabernero reported receiving personal fees from Array BioPharma, AstraZeneca, Bayer, BeiGene, Biocartis, Boehringer Ingelheim, Chugai Pharmaceutical, Eli Lilly, F. Hoffmann-La Roche, Foundation Medicine, Genentech, Genmab, HalioDx, Halozyme Therapeutics, Imugene, Inflection Biosciences, Ipsen Biopharmaceuticals, Kura Oncology, Menarini, Merck Serono, Merck Sharp & Dohme, Merrimack Pharmaceuticals, Merus, Molecular Partners, Novartis, Peptomyc, Pfizer, Pharmacyclics, ProteoDesign, Rafael Pharmaceuticals, Roche Diagnostics, Sanofi, SeaGen (formerly Seattle Genetics), Servier Laboratories, Symphogen, Taiho Pharmaceutical, and VCN Biosciences outside the submitted work.<br>Dr Muro reported receiving grants from Merck Sharp & Dohme during the conduct of the study and receiving grants from Amgen, Astellas Pharma, Daiichi Sankyo, Merck Sharp & |

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| | | chemotherapy alone.<br><br>**Author's Conclusion:** The findings of this analysis support MSI-H status as a biomarker for pembrolizumab therapy among patients with advanced gastric or gastroesophageal junction cancer and warrant its prospective validation in ongoing first-line studies. | Dohme, Merck Serono, Ono Pharmaceutical, Parexel, Pfizer, Sanofi, Solasia Pharma, and Taiho Pharmaceutical and personal fees from Amgen, AstraZeneca, Bayer, Bristol Myers Squibb, Chugai Pharmaceutical, Eli Lilly, Ono Pharmaceutical, Sanofi, Takeda Pharmaceutical, and Taiho Pharmaceutical outside the submitted work.<br>Dr Van Cutsem reported receiving grants from Amgen, Bayer, Bristol Myers Squibb, Boehringer Ingelheim, Celgene, Eli Lilly, Ipsen Biopharmaceuticals, Merck KGaA, Merck Sharp & Dohme, Novartis, Roche, and Servier Laboratories and serving on the advisory boards of Array BioPharma, AstraZeneca, Bayer, Biocartis, Bristol Myers Squibb, Celgene, Daiichi Sankyo, Eli Lilly, GlaxoSmithKline, Halozyme Therapeutics, Incyte, Ipsen Biopharmaceuticals, Merck KGaA, Merck Sharp & Dohme, Novartis, Pierre Fabre, Roche, Servier |

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| | | | Laboratories, Sirtex Medical, and Taiho Pharmaceutical outside the submitted work.<br>Dr Bang reported receiving grants from Astellas Pharma, AstraZeneca, Bayer, BeiGene, Boehringer Ingelheim, Boston Biomedical, Bristol Myers Squibb, CKD Pharmaceuticals, Curis, Daiichi Sankyo, Eli Lilly, Five Prime Therapeutics, Genentech, Genexine, GlaxoSmithKline, GC Pharma, MacroGenics, Merck Serono, Merck Sharp & Dohme, Novartis, Ono Pharmaceutical, Pfizer, Taiho Pharmaceutical, and Takeda Pharmaceutical and serving as a consultant or advisor for Astellas Pharma, AstraZeneca, Bayer, BeiGene, Bristol Myers Squibb, Daiichi Sankyo, Eli Lilly, Genentech, Genexine, GC Pharma, Hanmi Pharmaceutical, Merck Serono, Merck Sharp & Dohme, Novartis, Samyang Biopharm, and Taiho Pharmaceutical outside the submitted work.<br>Dr De Vita reported serving as a consultant or advisor for Celgene and |

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| | | | Eli Lilly outside the submitted work.<br>Dr Chau reported receiving grants from Merck Sharp & Dohme during the conduct of the study and receiving grants from Eli Lilly, Janssen-Cilag, and Sanofi Oncology and personal fees from AstraZeneca, Bayer, Bristol Myers Squibb, Eli Lilly, Five Prime Therapeutics, Merck Serono, Merck Sharp & Dohme, Oncologie, Pierre Fabre, and Roche outside the submitted work.<br>Dr Elme reported receiving grants from Merck Sharp & Dohme during the conduct of the study and receiving grants from Roche and personal fees from Amgen, Astra Zeneca, Ipsen Biopharmaceuticals, Merck Sharp & Dohme, and Roche outside the submitted work.<br>Dr ÖzgüroÄŸlu reported receiving grants from Merck Sharp & Dohme during the conduct of the study and receiving personal fees from Astellas Pharma, AstraZeneca, Bristol Myers Squibb, Janssen Pharmaceuticals, Novartis, Roche, and Sanofi outside |

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| | | | the submitted work.<br>Dr Catenacci reported receiving grants from Merck Sharp & Dohme and personal fees from Astellas Pharma, Bristol Myers Squibb, Daiichi Sankyo, Eli Lilly, Five Prime Therapeutics, Foundation Medicine, Genentech, Gritstone Oncology, Guardant Health, Merck, Pieris Pharmaceuticals, Taiho Pharmaceutical, and Tempus Labs during the conduct of the study.<br>Dr Yoon reported receiving grants from Merck and personal fees from BeiGene, Bristol Myers Squibb, and MacroGenics outside the submitted work.<br>Dr Wainberg reported receiving grants from Bristol Myers Squibb, Five Prime Therapeutics, Merck Serono, Novartis, and Ipsen Biopharmaceuticals and personal fees from AstraZeneca, Bayer, Daiichi Sankyo, Eli Lilly, MacroGenics, and Merck outside the submitted work. No other disclosures were reported.<br>**Randomization:**<br>**Blinding:** |

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| | | | **Dropout Rate/ITT-Analysis:**<br>**Notes:** Cochrane risk of bias tool 1 (RoB 1):<br>(6 unclear risks of bias (#1 - #6) were observed)<br>Overall risk of bias: Unclear<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 2 (Randomized trial).<br>Downgrade to evidence level 3 due to high risk of bias. |
| **Fuchs, C. S. et al. Pembrolizumab versus paclitaxel for previously treated PD-L1-positive advanced gastric or gastroesophageal junction cancer: 2-year update of the randomized phase 3 KEYNOTE-061 trial. Gastric cancer. . . 2021** | | | |
| **Population** | **Intervention / Comparison** | **Outcomes/Results** | **Methodical Notes** |
| **Evidence level:** 2<br>**Study type:** randomized phase 3 trial, re-evaluation of data after 2 additional years of follow up (cutof: 10/07/2019)<br>**Number of Patients:** 395 patients<br>**Recruiting Phase:**<br>**Inclusion Criteria:** histologically or cytologically confrmed | **Intervention:** pembrolizumab 200 mg Q3W forâ‰¤35 cycles<br>**Comparison:** standard-dose paclitaxel | **Primary:** OS and PFS (CPS≥1 population)<br>**Secondary:**<br>**Results:** 366/395 patients (92.7%) with CPS≥1 died. Pembrolizumab demonstrated a trend toward improved OS vs paclitaxel in the CPS≥1 population (HR, 0.81); 24-month OS rates: 19.9% vs 8.5%.<br>Pembrolizumab incrementally increased the OS<br>beneft with PD-L1 enrichment (CPS≥5: HR, | **Funding Sources:** Merck Sharp & Dohme Corp, a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA<br>**COI:** Extensive list of fundings and disclosures for the authors<br>**Randomization:** 1:1<br>**Blinding:**<br>**Dropout Rate/ITT-** |

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| adenocarcinoma of the stomach or GEJ that<br>metastatic or locally advanced but unresectable<br>disease progression per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 after frst-line therapy with a platinum and fuoropyrimidine<br>Eastern Cooperative Oncology Group performance status (ECOG PS) 0 or 1.<br>**Exclusion Criteria:** | | 0.72, 24-month rate, 24.2% vs 8.8%; CPS≥10: 0.69, 24-month rate, 32.1% vs 10.9%). There was no diference in median PFS among treatment groups (CPS≥1: HR, 1.25; CPS≥5: 0.98; CPS≥10:<br>0.79). ORR (pembrolizumab vs paclitaxel) was 16.3% vs 13.6% (CPS≥1), 20.0% vs 14.3% (CPS≥5), and 24.5% vs 9.1% (CPS≥10); median DOR was 19.1 months vs 5.2, 32.7 vs 4.8, and NR vs 6.9, respectively. Fewer treatment-related AEs (TRAEs) occurred with pembrolizumab than paclitaxel (53% vs 84%).<br>**Author's Conclusion:** In this long-term analysis, 2L pembrolizumab did not signifcantly improve OS but was associated with higher 24-month OS rates than paclitaxel. Pembrolizumab also increased OS beneft with PD-L1 enrichment among patients with PD-L1-positive gastric/GEJ cancer and led to fewer TRAEs than paclitaxel. | **Analysis:**<br>**Notes:** Cochrane risk of bias tool 1 (RoB 1):<br>(1 high risk of bias was observed (#3 Performance bias: Blinding of participants and personnel)<br>2 unclear risks of bias (#2. Selection bias: Allocation concealment, #6. Reporting bias: Selective reporting) were observed)<br>Overall risk of bias: Low<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 2 (Randomized trial). |

| **Kato, K. et al. Nivolumab versus chemotherapy in patients with advanced oesophageal squamous cell carcinoma refractory or intolerant to previous chemotherapy (ATTRACTION-3): a multicentre, randomised, open-label, phase 3 trial. The lancet. Oncology. 20. 1506?1517. 2019** | | | |
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| **Population** | **Intervention / Comparison** | **Outcomes/Results** | **Methodical Notes** |

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| **Evidence level:** 2<br>**Study type:** randomised, open-label, phase 3 trial<br>**Number of Patients:** 419 patients<br>**Recruiting Phase:** Between Jan 7, 2016, and May 25, 2017<br>**Inclusion Criteria:** 20 years and older with unresectable advanced or recurrent oesophageal squamous cell carcinoma (regardless of PD-L1 expression), at least one measurable or non-measurable lesion per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, a baseline Eastern Cooperative Oncology Group performance status of 0–1, and who were refractory or intolerant to one previous fluoropyrimidine-based and platinum-based chemotherapy and had a life expectancy of at least 3 months.<br>**Exclusion Criteria:** | **Intervention:** nivolumab (240 mg for 30 min every 2 weeks)<br>**Comparison:** investigator's choice of chemotherapy (paclitaxel 100 mg/m2 for at least 60 min once per week for 6 weeks then 1 week off; or docetaxel 75 mg/m2 for at least 60 min every 3 weeks) | **Primary:** overall survival, defined as the time from randomisation until death from any cause, in the intention-to-treat population that included all randomly assigned patients.<br>**Secondary:**<br>**Results:** Between Jan 7, 2016, and May 25, 2017, we assigned 419 patients to treatment: 210 to nivolumab and 209 to chemotherapy.<br>At the time of data cutoff on Nov 12, 2018, median follow-up for overall survival was 10Â·5 months (IQR 4Â·5–19Â·0) in the nivolumab group and 8Â·0 months (4Â·6–15Â·2) in the chemotherapy group. At a minimum follow-up time (ie, time from random assignment of the last patient to data cutoff) of 17Â·6 months, overall survival was significantly improved in the nivolumab group compared with the chemotherapy group (median 10Â·9 months, 95% CI 9Â·2–13Â·3 vs 8Â·4 months, 7Â·2–9Â·9; hazard ratio for death 0Â·77, 95% CI 0Â·62–0Â·96; p=0Â·019). 38 (18%) of 209 patients in the nivolumab group had grade 3 or 4 | **Funding Sources:** ONO Pharmaceutical Company and Bristol-Myers Squibb.<br>**COI:** N/A<br>**Randomization:** 1:1<br>**Blinding:** No, open label<br>**Dropout Rate/ITT-Analysis:**<br>**Notes:** Cochrane risk of bias tool 1 (RoB 1):<br>(1 unclear risks of bias (#6. Reporting bias: Selective reporting) was observed)<br>Overall risk of bias: Low<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 2 (Randomized trial). |

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| | | treatment-related adverse events compared with 131 (63%) of 208 patients in the chemotherapy group. The most frequent grade 3 or 4 treatment-related adverse events were anaemia (four [2%]) in the nivolumab group and decreased neutrophil count (59 [28%]) in the chemotherapy group. Five deaths were deemed treatment-related: two in the nivolumab group (one each of interstitial lung disease and pneumonitis) and three in the chemotherapy group (one each of pneumonia, spinal cord abscess, and interstitial lung disease).<br>**Author's Conclusion:** Nivolumab was associated with a significant improvement in overall survivaland a favourable safety profile compared with chemotherapy in previously treated patients with advanced oesophageal squamous cell carcinoma, and might represent a new standard second-line treatment option for these patients. | |

| **Shitara, K. et al. Molecular determinants of clinical outcomes with pembrolizumab versus paclitaxel in a randomized, open-label, phase III trial in patients with gastroesophageal adenocarcinoma. Annals of oncology : official journal of the european society for medical oncology. 32. 1127?1136. 2021** | | | |
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| **Population** | **Intervention / Comparison** | **Outcomes/Results** | **Methodical Notes** |
| **Evidence level:** 2<br>**Study type:** randomized, open-label, phase III trial<br>**Number of Patients:** 592 patients<br>**Recruiting Phase:** 4 June 2015 - 26 July 2016<br>**Inclusion Criteria:** Histologically- or cytologically-confirmed diagnosis of gastric or gastroesophageal junction adenocarcinoma. Confirmed metastatic or locally advanced, unresectable disease (by computed tomography [CT] scan or clinical evidence). Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Progression on or after prior first-line therapy containing any platinum/fluoropyrimidine doublet. Willing to provide tumor tissue for PD-L1 biomarker analysis (new or archived specimens with agreement of Sponsor). As of 20 March 2016, participants must be | **Intervention:** Pembrolizumab<br>**Comparison:** Paclitaxel | **Primary:** Progression-free Survival (PFS) According to Response Criteria in Solid Tumors Version 1.1 (RECIST 1.1) Based on Blinded Independent Central Review (BICR) in Programmed Death-Ligand 1 (PD-L1) Positive Participants [ Time Frame: Up to 30 months (through database cut-off date of 26 Oct 2017) ] Overall Survival (OS) in PD-L1 Positive Participants [ Time Frame: Up to 30 months (through database cut-off date of 26 Oct 2017) ]<br>**Secondary:** Progression-free Survival (PFS), Time to Tumor Progression (TTP), Objective Response Rate (ORR), Duration of Response (DOR) According to RECIST 1.1 Based on BICR and Investigator Assessment in PD-L1 Positive Participants and All Participants. OS in All Participants [ Time Frame: Up to 30 months (through database cut-off | **Funding Sources:**<br>**COI:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout Rate/ITT-Analysis:**<br>**Notes:** Cochrane risk of bias tool 1 (RoB 1): (2 unclear risks of bias (#1. Selection bias: Random sequence generation, #6. Reporting bias: Selective reporting) were observed)<br>Overall risk of bias: Low<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence |

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| PD-L1 positive to be enrolled. Human epidermal growth factor receptor 2 (HER-2/neu) status known and participants with HER2/neu positive tumors show documentation of disease progression on treatment containing trastuzumab. Female participants of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of pembrolizumab or through 180 days after the last dose of paclitaxel. Male participants should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of pembrolizumab or through 180 days after the last dose of paclitaxel. Adequate organ function.<br>**Exclusion Criteria:** Currently participating and receiving study therapy, or participated in a study of an investigational agent and received study therapy or used an investigation device within 4 weeks of the first dose of | | date of 26 Oct 2017)]<br>Percentage of All Participants Who Experienced an AE [ Time Frame: Up to 30 months (through database cut-off date of 26 Oct 2017) ]<br>Percentage of PD-L1 Positive Participants That Discontinued Study Treatment Due to AE [ Time Frame: Up to 30 months (through database cut-off date of 26 Oct 2017) ]<br>Percentage of All Participants That Discontinued Study Treatment Due to AE [ Time Frame: Up to 30 months (through database cut-off date of 26 Oct 2017) ]<br><br>**Results:** WES-tTMB was significantly associated with ORR, PFS, and OS in pembrolizumab-treated (all P < 0.001) but not paclitaxel-treated patients (all P > 0.6) in univariate analysis. The area under the receiver operating characteristics curve for WES-tTMB and response was 0.68 [95% confidence interval (CI) 0.56-0.81] for pembrolizumab and 0.51 (95% CI 0.39-0.63) for paclitaxel in univariate analysis. There was low correlation between | (Treatment benefits): 2 (Randomized trial). |

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| medication. Squamous cell or undifferentiated gastric cancer. Active autoimmune disease that has required systemic treatment in past 2 years (replacement therapy is not considered a form of systemic treatment. Diagnosis of immunodeficiency or receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of study medication. Prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study Day 1 or not recovered from AEs due to agents administered more than 4 weeks earlier. Prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or not recovered from adverse events due to a previously administered agent or surgery. Known additional malignancy that is progressing or requires active treatment (with the exception of basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy). Known active central nervous system (CNS) metastases and/or carcinomatous | | WES-tTMB and CPS in both treatment groups (r 0.16). WES-tTMB remained significantly associated with all clinical endpoints with pembrolizumab after adjusting for CPS and with PFS and OS after excluding known MSI-H tumors (n Â¼ 26). FoundationOneÂ®CDx-tTMB demonstrated a positive association with ORR, PFS, and OS in pembrolizumab-treated patients (all P 0.003) but not PFS or OS in paclitaxel-treated patients (P > 0.1).<br>**Author's Conclusion:** This exploratory analysis from KEYNOTE-061 is the first to demonstrate a strong association between tTMB and efficacy with pembrolizumab but not paclitaxel in patients with gastric/GEJ adenocarcinoma in a randomized setting. Data further suggest tTMB is a significant and independent predictor beyond PD-L1 status. | |

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| meningitis. History of (noninfectious) pneumonitis that required steroids or current pneumonitis. Active infection requiring systemic therapy. Known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial. Pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 120 days after the last dose of pembrolizumab or through 180 days after the last dose of paclitaxel. Prior immunotherapy including anti-PD-1, anti-PD-L1, or anti-PD-L2 agent, or previously participated in Merck pembrolizumab (MK-3475) clinical trial. Known history of human immunodeficiency virus (HIV). Known active Hepatitis B or Hepatitis C. Live vaccine within 30 days of planned start of study therapy. Known allergy or hypersensitivity to paclitaxel or any components used in the paclitaxel preparation or other contraindication for taxane therapy. | | | |

## 3.20 Schlüsselfrage 12.2: Stellenwert der Immuntherapie – Zweitlinie

**Schlüsselfrage:**

**12.2 Stellenwert der Immuntherapie - Zweitlinie (PICO s.o.)**
P: Patienten im Stadium IV und mit lokoregionär fortgeschrittenen, primär inoperablen Plattenepithel- und Adenokarzinomen des Ösophagus und Adenokarzinomen des gastroösophagealen Übergangs 1-3
I: 1) palliative Chemotherapie, 2) Zweitlinienchemo therapie palliativ , 3) Radiotherapie palliativ, 4) Brachytherapie palliativ, 5) Radiochemotherapie palliativ, 6) Stentimplantation palliativ, 7) palliative OP 8) Immuntherapie (Pembrolizumab, Nivolumab, Tislelizumab, Cambrelizumab..)
C: Die jeweils anderen Verfahren
O: Patientenrelevante Endpunkte: Lebensqualität (QoL), Nutzen, Schaden (Therapienebenwirkungen/Toxizität), Perforation, Blutung, Todesfall), Remissionsrate, Progressionsfreies Überleben, symptomfreies Überleben (symptomfree survival) (time without signs and symptoms), Gesamtüberlebensrate/ Überlebenszeit, Speziell für 6) Stentimplantation zusätzlich: Dysphagiefreies Überleben ohne Stentverschluss, Dysphagieminderung

***Inhalt:*** *5 Literaturstellen*

| Literaturstelle | Evidenzlevel | Studientyp |
|---|---|---|
| Cao, Y. 2022 | 3 | randomized, open-label, phase III trial |
| Chao, J. 2021 | 3 | post hoc analysis of the phase 2 KEYNOTE-059 (third-line treatment or higher) single-arm trial and the phase 3 KEYNOTE-061 (second-line treatment) and KEYNOTE-062 (first-line treatment) randomized trials i |
| Fuchs, C. S. 2021 | 2 | randomized phase 3 trial, re-evaluation of data after 2 additional years of follow up (cutof: 10/07/2019) |

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| Kato, K. 2019 | 2 | randomised, open-label, phase 3 trial |
| Shitara, K. 2021 | 2 | randomized, open-label, phase III trial |

***Cochrane Risk of Bias Tool 1 (RCT):*** *5 Bewertung(en)*

| **Cao, Y. et al. Pembrolizumab versus chemotherapy for patients with esophageal squamous cell carcinoma enrolled in the randomized KEYNOTE-181 trial in Asia. ESMO Open. 7. . 2022** | | | |
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| **Population** | **Intervention / Comparison** | **Outcomes/Results** | **Methodical Notes** |
| **Evidence level:** 3<br>**Study type:** randomized, open-label, phase III trial<br>**Number of Patients:** 340 Asian patients<br>**Recruiting Phase:**<br>**Inclusion Criteria:** histologically confirmed SCC or adenocarcinoma of the esophagus, including human epidermal growth factor receptor 2/neu-negative Siewert type I adenocarcinoma of the esophagogastric junction documented radiographic or clinical progression on one previous line of standard therapy<br>**Exclusion Criteria:** | **Intervention:** pembrolizumab 200 mg every 3 weeks<br>**Comparison:** investigatorâ€™s choice of standard-of-care chemotherapy [paclitaxel (80-100 mg/m2 on days 1, 8, and 15 of each 28-day cycle), docetaxel (75 mg/m2 on day 1 of each 21-day cycle), or irinotecan (180 mg/m2 on day 1 of each 14-day cycle)] | **Primary:** overall survival (OS) in patients with programmed death-ligand 1 (PD-L1) combined positive score (CPS) 10, in patients with esophageal SCC (ESCC), and in all patients.<br>**Secondary:**<br>**Results:** In Asian patients with ESCC, median OS was 10.0 months with pembrolizumab and 6.5 months with chemotherapy [hazard ratio (HR), 0.63; 95% CI 0.50-0.80; nominal P < 0.0001]. Median progression-free survival was 2.3 months with pembrolizumab and 3.1 months with chemotherapy (HR, 0.79; 95% CI 0.63-0.99; nominal P = 0.020). Objective response rate was 17.1% with pembrolizumab and 7.1% with chemotherapy; median duration of response was 10.5 months and 7.7 months, respectively.<br>In patients with PD-L1 CPS 1 [CPS ≥1, | **Funding Sources:** Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA<br>**COI:** Extensive list of fundings and disclosures for the authors.<br>**Randomization:** 1:1<br>**Blinding:** No, open label<br>**Dropout Rate/ITT-Analysis:**<br>**Notes:** Cochrane risk of bias tool 1 (RoB 1):<br>(3 unclear risks of bias (#1. Selection bias: Random sequence generation, 2. Selection bias: Allocation concealment, #6. Reporting bias: Selective reporting) were observed) |

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| | | 0.57 (0.44-0.75); CPS ≥5, 0.56 (0.41-0.76); CPS ≥10, 0.53 (0.37-0.75)]. Treatment-related adverse events were reported in 71.8% of patients in the pembrolizumab group and 89.8% in the chemotherapy group; grade 3-5 events were reported in 20.0% and 44.6%, respectively. **Author's Conclusion:** Pembrolizumab monotherapy demonstrated promising efficacy in Asian patients with ESCC, with fewer treatment-related adverse events than chemotherapy. PD-L1 CPS ≥1 is an appropriate cut-off and a predictive marker of pembrolizumab efficacy in Asian patients with ESCC. | Overall risk of bias: Unclear<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 2 (Randomized trial). Downgrade to evidence level 3 due to high risk of bias. |

**Chao, J. et al. Assessment of Pembrolizumab Therapy for the Treatment of Microsatellite Instability-High Gastric or Gastroesophageal Junction Cancer among Patients in the KEYNOTE-059, KEYNOTE-061, and KEYNOTE-062 Clinical Trials. JAMA oncology. 7. 895?902. 2021**

| Population | Intervention / Comparison | Outcomes/Results | Methodical Notes |
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| **Evidence level:** 3<br>**Study type:** post hoc analysis of the phase 2 KEYNOTE-059 (third-line treatment or higher) single- | **Intervention:** KEYNOTE-059: pembrolizumab monotherapy<br>KEYNOTE-061: pembrolizumab | **Primary:** Overall survival<br>**Secondary:** progression free survival, objective response rate, duration of response<br>**Results:** 7 of 174 patients (4.0%) in | **Funding Sources:** This study and assistance with medical writing were funded by Merck Sharp & Dohme, a subsidiary of Merck, and supported by grant 5K12CA001727-23 from the |

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| arm trial and the phase 3 KEYNOTE-061 (second-line treatment) and KEYNOTE-062 (first-line treatment) randomized trials i<br>**Number of Patients:** Patients who had tumors that were evaluable for microsatellite instability–high status were included:<br>174 of 259 patients enrolled in KEYNOTE-059,<br>514 of 592 patients enrolled in KEYNOTE-061<br>682 of 763 patients enrolled in KEYNOTE-062.<br>**Recruiting Phase:** Patients were enrolled from:<br>March 2, 2015, to March 26, 2016, in KEYNOTE-059;<br>June 4, 2015, to July 26, 2016, in KEYNOTE-061;<br>September 18, 2015, to May 26, 2017, in KEYNOTE-062,<br>with data cutoff dates of | monotherapy<br>KEYNOTE-062: pembrolizumab monotherapy or , pembrolizumab plus chemotherapy (cisplatin and 5-fluorouracil or capecitabine)<br>**Comparison:** KEYNOTE-059: no comparator<br>KEYNOTE-061: paclitaxel<br>KEYNOTE-062: chemotherapy alone | KEYNOTE-059, 27 of 514 patients (5.3%) in KEYNOTE-061, and 50 of 682 patients (7.3%) in KEYNOTE-062 with evaluable tumors had MSI-H gastric or gastroesophageal junction cancer.<br>Among patients with MSI-H tumors, the median OS for pembrolizumab monotherapy was not reached (ie, >50% of patients were still alive at data cutoff) in KEYNOTE-059 (95% CI, 1.1 months to not reached) or KEYNOTE-061 (95% CI, 5.6 months to not reached) compared with a median OS of 8.1 months (95% CI, 2.0-16.7 months) for chemotherapy alone in KEYNOTE-061. In KEYNOTE-062, the median OS was not reached for both pembrolizumab monotherapy (95% CI, 10.7 months to not reached) and pembrolizumab plus chemotherapy (95% CI, 3.6 months to not reached) compared with a median OS of 8.5 months (95% CI, 5.3-20.8 months) for chemotherapy alone<br>The estimated 12-month OS rates for pembrolizumab monotherapy among patients with MSI-H tumors were 71% (95% CI, not available) for KEYNOTE-059 and 73% (95% CI, 44%-89%) for KEYNOTE-061 | National Institutes of Health (Dr Chao).<br>Role of the Funder/Sponsor: Employees of Merck Sharp & Dohme were involved in the design and conduct of the study and in the collection,management, analysis, and interpretation of the data. Drs Chen, Adelberg, Shih, Shah, and Bhagia,employees of Merck, were involved in the review and approval of the manuscript and the decision to submit the manuscript for publication.<br>**COI:** Dr Chao reported receiving manuscript-writing assistance from Merck Sharp & Dohme during the conduct of the study and receiving grants from Brooklyn ImmunoTherapeutics and Merck and personal fees from Amgen, AstraZeneca, Boston Biomedical, Daiichi Sankyo, Foundation Medicine, MacroGenics, Merck, Ono Pharmaceutical, and Taiho Pharmaceutical outside the submitted work.<br>Dr Fuchs reported receiving personal |

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| August 8, 2018; October 26, 2017; and March 26, 2019; respectively<br>**Inclusion Criteria:** patients with advanced G/GEJ cancer<br>**Exclusion Criteria:** | | (compared with 25% [95% CI, 6%-50%] for chemotherapy alone in KEYNOTE-061). In KEYNOTE-062, the estimated 12-month OS rates were 79% (95% CI, 47%-92%) for pembrolizumabmonotherapy, 71% (95% CI, 43%-87%) for pembrolizumab plus chemotherapy, and 47% (95% CI, 24%-67%) for chemotherapy alone.<br>In KEYNOTE059 and KEYNOTE-061, the estimated 24-month OS rates for pembrolizumab monotherapy were 57% (95% CI, not available) and 59% (95% CI, 31%-79%), respectively (24-month OS rate not available for chemotherapy alone in KEYNOTE-061). In KEYNOTE-062, the estimated 24-month OS rates were 71% (95% CI, 41%-88%) for pembrolizumab monotherapy, 65% (95% CI, 38%-82%) for pembrolizumab plus chemotherapy, and 26% (95% CI, 10%-57%) for chemotherapy alone.<br>The median progression-free survival (PFS) for pembrolizumab was NR (95% CI, 1.1 months to NR) in KEYNOTE-059 and 17.8 months (95% CI, 2.7 months to NR) in KEYNOTE-061 (vs 3.5 months [95% CI, 2.0-9.8 months] for chemotherapy). In | fees from Agios Pharmaceuticals, Amylin Pharmaceuticals, Bain Capital, CytomX Therapeutics, Daiichi Sankyo, Eli Lilly, Entrinsic Health, EvolveImmune Therapeutics, Genentech, Merck, Taiho Pharmaceutical, and Unum Therapeutics; owning stock in CytomX Therapeutics and Entrinsic Health; cofounding EvolveImmune Therapeutics; serving as the director of CytomX Therapeutics and EvolveImmune Therapeutics; and providing expert testimony for Amylin Pharmaceuticals and Eli Lilly outside the submitted work.<br>Dr Shitara reported receiving grants from Astellas Pharma, Chugai Pharmaceutical, Daiichi Sankyo, Eli Lilly, Merck, Medi Science, Ono Pharmaceutical, Sumitomo Dainippon Pharma, and Taiho Pharmaceutical and personal fees from AbbVie, Astellas Pharma, Bristol Myers Squibb, Eli Lilly, GlaxoSmithKline, Novartis, Pfizer, Takeda Pharmaceutical, and Yakult Honsha outside the submitted |

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| | | KEYNOTE-062, the median PFS was 11.2 months (95% CI, 1.5 months to NR) for pembrolizumab, NR (95% CI, 3.6 months to NR) for pembrolizumab plus chemotherapy, and 6.6 months (95% CI, 4.4-8.3 months) for chemotherapy.<br>The objective response rate (ORR) for pembrolizumab was 57.1% in KEYNOTE-059 and 46.7% (vs 16.7% for chemotherapy) in KEYNOTE-061. In KEYNOTE-062, the ORR was 57.1% for pembrolizumab , 64.7% for pembrolizumab plus chemotherapy, and 36.8% for chemotherapy.<br>The median duration of response was not reached for pembrolizumab monotherapy in both KEYNOTE059 (range, 20.0-26.8 months) and KEYNOTE-061 (range, 5.5- 26.0 months) and not reached for chemotherapy alone (range, 2.2-12.2 months) in KEYNOTE-061. In KEYNOTE-062, the median duration of response was 21.2 months (range, 1.4+ to 33.6 months, with + indicating no progressive disease at last assessment) for pembrolizumab monotherapy, not reached (range, 1.6+ to 34.5+ months) for pembrolizumab plus chemotherapy, and 7.0 months (range, 2.0-30.4+ months) for | work.<br>Dr Tabernero reported receiving personal fees from Array BioPharma, AstraZeneca, Bayer, BeiGene, Biocartis, Boehringer Ingelheim, Chugai Pharmaceutical, Eli Lilly, F. Hoffmann-La Roche, Foundation Medicine, Genentech, Genmab, HalioDx, Halozyme Therapeutics, Imugene, Inflection Biosciences, Ipsen Biopharmaceuticals, Kura Oncology, Menarini, Merck Serono, Merck Sharp & Dohme, Merrimack Pharmaceuticals, Merus, Molecular Partners, Novartis, Peptomyc, Pfizer, Pharmacyclics, ProteoDesign, Rafael Pharmaceuticals, Roche Diagnostics, Sanofi, SeaGen (formerly Seattle Genetics), Servier Laboratories, Symphogen, Taiho Pharmaceutical, and VCN Biosciences outside the submitted work.<br>Dr Muro reported receiving grants from Merck Sharp & Dohme during the conduct of the study and receiving grants from Amgen, Astellas Pharma, Daiichi Sankyo, Merck Sharp & |

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| | | chemotherapy alone.<br><br>**Author's Conclusion:** The findings of this analysis support MSI-H status as a biomarker for pembrolizumab therapy among patients with advanced gastric or gastroesophageal junction cancer and warrant its prospective validation in ongoing first-line studies. | Dohme, Merck Serono, Ono Pharmaceutical, Parexel, Pfizer, Sanofi, Solasia Pharma, and Taiho Pharmaceutical and personal fees from Amgen, AstraZeneca, Bayer, Bristol Myers Squibb, Chugai Pharmaceutical, Eli Lilly, Ono Pharmaceutical, Sanofi, Takeda Pharmaceutical, and Taiho Pharmaceutical outside the submitted work.<br>Dr Van Cutsem reported receiving grants from Amgen, Bayer, Bristol Myers Squibb, Boehringer Ingelheim, Celgene, Eli Lilly, Ipsen Biopharmaceuticals, Merck KGaA, Merck Sharp & Dohme, Novartis, Roche, and Servier Laboratories and serving on the advisory boards of Array BioPharma, AstraZeneca, Bayer, Biocartis, Bristol Myers Squibb, Celgene, Daiichi Sankyo, Eli Lilly, GlaxoSmithKline, Halozyme Therapeutics, Incyte, Ipsen Biopharmaceuticals, Merck KGaA, Merck Sharp & Dohme, Novartis, Pierre Fabre, Roche, Servier |

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| | | | Laboratories, Sirtex Medical, and Taiho Pharmaceutical outside the submitted work.<br>Dr Bang reported receiving grants from Astellas Pharma, AstraZeneca, Bayer, BeiGene, Boehringer Ingelheim, Boston Biomedical, Bristol Myers Squibb, CKD Pharmaceuticals, Curis, Daiichi Sankyo, Eli Lilly, Five Prime Therapeutics, Genentech, Genexine, GlaxoSmithKline, GC Pharma, MacroGenics, Merck Serono, Merck Sharp & Dohme, Novartis, Ono Pharmaceutical, Pfizer, Taiho Pharmaceutical, and Takeda Pharmaceutical and serving as a consultant or advisor for Astellas Pharma, AstraZeneca, Bayer, BeiGene, Bristol Myers Squibb, Daiichi Sankyo, Eli Lilly, Genentech, Genexine, GC Pharma, Hanmi Pharmaceutical, Merck Serono, Merck Sharp & Dohme, Novartis, Samyang Biopharm, and Taiho Pharmaceutical outside the submitted work.<br>Dr De Vita reported serving as a consultant or advisor for Celgene and |

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| | | | Eli Lilly outside the submitted work.<br>Dr Chau reported receiving grants from Merck Sharp & Dohme during the conduct of the study and receiving grants from Eli Lilly, Janssen-Cilag, and Sanofi Oncology and personal fees from AstraZeneca, Bayer, Bristol Myers Squibb, Eli Lilly, Five Prime Therapeutics, Merck Serono, Merck Sharp & Dohme, Oncologie, Pierre Fabre, and Roche outside the submitted work.<br>Dr Elme reported receiving grants from Merck Sharp & Dohme during the conduct of the study and receiving grants from Roche and personal fees from Amgen, Astra Zeneca, Ipsen Biopharmaceuticals, Merck Sharp & Dohme, and Roche outside the submitted work.<br>Dr ÖzgüroÄŸlu reported receiving grants from Merck Sharp & Dohme during the conduct of the study and receiving personal fees from Astellas Pharma, AstraZeneca, Bristol Myers Squibb, Janssen Pharmaceuticals, Novartis, Roche, and Sanofi outside |

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| | | | the submitted work.<br>Dr Catenacci reported receiving grants from Merck Sharp & Dohme and personal fees from Astellas Pharma, Bristol Myers Squibb, Daiichi Sankyo, Eli Lilly, Five Prime Therapeutics, Foundation Medicine, Genentech, Gritstone Oncology, Guardant Health, Merck, Pieris Pharmaceuticals, Taiho Pharmaceutical, and Tempus Labs during the conduct of the study.<br>Dr Yoon reported receiving grants from Merck and personal fees from BeiGene, Bristol Myers Squibb, and MacroGenics outside the submitted work.<br>Dr Wainberg reported receiving grants from Bristol Myers Squibb, Five Prime Therapeutics, Merck Serono, Novartis, and Ipsen Biopharmaceuticals and personal fees from AstraZeneca, Bayer, Daiichi Sankyo, Eli Lilly, MacroGenics, and Merck outside the submitted work. No other disclosures were reported.<br>**Randomization:**<br>**Blinding:** |

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| | | | **Dropout Rate/ITT-Analysis:**<br>**Notes:** Cochrane risk of bias tool 1 (RoB 1):<br>(6 unclear risks of bias (#1 - #6) were observed)<br>Overall risk of bias: Unclear<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 2 (Randomized trial).<br>Downgrade to evidence level 3 due to high risk of bias. |
| **Fuchs, C. S. et al. Pembrolizumab versus paclitaxel for previously treated PD-L1-positive advanced gastric or gastroesophageal junction cancer: 2-year update of the randomized phase 3 KEYNOTE-061 trial. Gastric cancer. . . 2021** | | | |
| **Population** | **Intervention / Comparison** | **Outcomes/Results** | **Methodical Notes** |
| **Evidence level:** 2<br>**Study type:** randomized phase 3 trial, re-evaluation of data after 2 additional years of follow up (cutof: 10/07/2019)<br>**Number of Patients:** 395 patients<br>**Recruiting Phase:**<br>**Inclusion Criteria:** histologically or cytologically confrmed | **Intervention:** pembrolizumab 200 mg Q3W forâ‰¤35 cycles<br>**Comparison:** standard-dose paclitaxel | **Primary:** OS and PFS (CPS≥1 population)<br>**Secondary:**<br>**Results:** 366/395 patients (92.7%) with CPS≥1 died. Pembrolizumab demonstrated a trend toward improved OS vs paclitaxel in the CPS≥1 population (HR, 0.81); 24-month OS rates: 19.9% vs 8.5%.<br>Pembrolizumab incrementally increased the OS<br>beneft with PD-L1 enrichment (CPS≥5: HR, | **Funding Sources:** Merck Sharp & Dohme Corp, a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA<br>**COI:** Extensive list of fundings and disclosures for the authors<br>**Randomization:** 1:1<br>**Blinding:**<br>**Dropout Rate/ITT-** |

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| adenocarcinoma of the stomach or GEJ that<br>metastatic or locally advanced but unresectable<br>disease progression per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 after frst-line therapy with a platinum and fuoropyrimidine<br>Eastern Cooperative Oncology Group performance status (ECOG PS) 0 or 1.<br>**Exclusion Criteria:** | | 0.72, 24-month rate, 24.2% vs 8.8%; CPS≥10: 0.69, 24-month rate, 32.1% vs 10.9%). There was no diference in median PFS among treatment groups (CPS≥1: HR, 1.25; CPS≥5: 0.98; CPS≥10:<br>0.79). ORR (pembrolizumab vs paclitaxel) was 16.3% vs 13.6% (CPS≥1), 20.0% vs 14.3% (CPS≥5), and 24.5% vs 9.1% (CPS≥10); median DOR was 19.1 months vs 5.2, 32.7 vs 4.8, and NR vs 6.9, respectively. Fewer treatment-related AEs (TRAEs) occurred with pembrolizumab than paclitaxel (53% vs 84%).<br>**Author's Conclusion:** In this long-term analysis, 2L pembrolizumab did not signifcantly improve OS but was associated with higher 24-month OS rates than paclitaxel. Pembrolizumab also increased OS beneft with PD-L1 enrichment among patients with PD-L1-positive gastric/GEJ cancer and led to fewer TRAEs than paclitaxel. | **Analysis:**<br>**Notes:** Cochrane risk of bias tool 1 (RoB 1):<br>(1 high risk of bias was observed (#3 Performance bias: Blinding of participants and personnel)<br>2 unclear risks of bias (#2. Selection bias: Allocation concealment, #6. Reporting bias: Selective reporting) were observed)<br>Overall risk of bias: Low<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 2 (Randomized trial). |

| **Kato, K. et al. Nivolumab versus chemotherapy in patients with advanced oesophageal squamous cell carcinoma refractory or intolerant to previous chemotherapy (ATTRACTION-3): a multicentre, randomised, open-label, phase 3 trial. The lancet. Oncology. 20. 1506?1517. 2019** | | | |
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| **Population** | **Intervention / Comparison** | **Outcomes/Results** | **Methodical Notes** |

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| **Evidence level:** 2<br>**Study type:** randomised, open-label, phase 3 trial<br>**Number of Patients:** 419 patients<br>**Recruiting Phase:** Between Jan 7, 2016, and May 25, 2017<br>**Inclusion Criteria:** 20 years and older with unresectable advanced or recurrent oesophageal squamous cell carcinoma (regardless of PD-L1 expression), at least one measurable or non-measurable lesion per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, a baseline Eastern Cooperative Oncology Group performance status of 0–1, and who were refractory or intolerant to one previous fluoropyrimidine-based and platinum-based chemotherapy and had a life expectancy of at least 3 months.<br>**Exclusion Criteria:** | **Intervention:** nivolumab (240 mg for 30 min every 2 weeks)<br>**Comparison:** investigator's choice of chemotherapy (paclitaxel 100 mg/m2 for at least 60 min once per week for 6 weeks then 1 week off; or docetaxel 75 mg/m2 for at least 60 min every 3 weeks) | **Primary:** overall survival, defined as the time from randomisation until death from any cause, in the intention-to-treat population that included all randomly assigned patients.<br>**Secondary:**<br>**Results:** Between Jan 7, 2016, and May 25, 2017, we assigned 419 patients to treatment: 210 to nivolumab and 209 to chemotherapy.<br>At the time of data cutoff on Nov 12, 2018, median follow-up for overall survival was 10Â·5 months (IQR 4Â·5–19Â·0) in the nivolumab group and 8Â·0 months (4Â·6–15Â·2) in the chemotherapy group. At a minimum follow-up time (ie, time from random assignment of the last patient to data cutoff) of 17Â·6 months, overall survival was significantly improved in the nivolumab group compared with the chemotherapy group (median 10Â·9 months, 95% CI 9Â·2–13Â·3 vs 8Â·4 months, 7Â·2–9Â·9; hazard ratio for death 0Â·77, 95% CI 0Â·62–0Â·96; p=0Â·019). 38 (18%) of 209 patients in the nivolumab group had grade 3 or 4 | **Funding Sources:** ONO Pharmaceutical Company and Bristol-Myers Squibb.<br>**COI:** N/A<br>**Randomization:** 1:1<br>**Blinding:** No, open label<br>**Dropout Rate/ITT-Analysis:**<br>**Notes:** Cochrane risk of bias tool 1 (RoB 1):<br>(1 unclear risks of bias (#6. Reporting bias: Selective reporting) was observed)<br>Overall risk of bias: Low<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 2 (Randomized trial). |

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| | | treatment-related adverse events compared with 131 (63%) of 208 patients in the chemotherapy group. The most frequent grade 3 or 4 treatment-related adverse events were anaemia (four [2%]) in the nivolumab group and decreased neutrophil count (59 [28%]) in the chemotherapy group. Five deaths were deemed treatment-related: two in the nivolumab group (one each of interstitial lung disease and pneumonitis) and three in the chemotherapy group (one each of pneumonia, spinal cord abscess, and interstitial lung disease).<br>**Author's Conclusion:** Nivolumab was associated with a significant improvement in overall survivaland a favourable safety profile compared with chemotherapy in previously treated patients with advanced oesophageal squamous cell carcinoma, and might represent a new standard second-line treatment option for these patients. | |

| **Shitara, K. et al. Molecular determinants of clinical outcomes with pembrolizumab versus paclitaxel in a randomized, open-label, phase III trial in patients with gastroesophageal adenocarcinoma. Annals of oncology : official journal of the european society for medical oncology. 32. 1127?1136. 2021** | | | |
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| **Population** | **Intervention / Comparison** | **Outcomes/Results** | **Methodical Notes** |
| **Evidence level:** 2<br>**Study type:** randomized, open-label, phase III trial<br>**Number of Patients:** 592 patients<br>**Recruiting Phase:** 4 June 2015 - 26 July 2016<br>**Inclusion Criteria:** Histologically- or cytologically-confirmed diagnosis of gastric or gastroesophageal junction adenocarcinoma. Confirmed metastatic or locally advanced, unresectable disease (by computed tomography [CT] scan or clinical evidence). Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Progression on or after prior first-line therapy containing any platinum/fluoropyrimidine doublet. Willing to provide tumor tissue for PD-L1 biomarker analysis (new or archived specimens with agreement of Sponsor). As of 20 March 2016, participants must be | **Intervention:** Pembrolizumab<br>**Comparison:** Paclitaxel | **Primary:** Progression-free Survival (PFS) According to Response Criteria in Solid Tumors Version 1.1 (RECIST 1.1) Based on Blinded Independent Central Review (BICR) in Programmed Death-Ligand 1 (PD-L1) Positive Participants [ Time Frame: Up to 30 months (through database cut-off date of 26 Oct 2017) ] Overall Survival (OS) in PD-L1 Positive Participants [ Time Frame: Up to 30 months (through database cut-off date of 26 Oct 2017) ]<br>**Secondary:** Progression-free Survival (PFS), Time to Tumor Progression (TTP), Objective Response Rate (ORR), Duration of Response (DOR) According to RECIST 1.1 Based on BICR and Investigator Assessment in PD-L1 Positive Participants and All Participants. OS in All Participants [ Time Frame: Up to 30 months (through database cut-off | **Funding Sources:**<br>**COI:**<br>**Randomization:**<br>**Blinding:**<br>**Dropout Rate/ITT-Analysis:**<br>**Notes:** Cochrane risk of bias tool 1 (RoB 1): (2 unclear risks of bias (#1. Selection bias: Random sequence generation, #6. Reporting bias: Selective reporting) were observed)<br>Overall risk of bias: Low<br>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence |

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| PD-L1 positive to be enrolled. Human epidermal growth factor receptor 2 (HER-2/neu) status known and participants with HER2/neu positive tumors show documentation of disease progression on treatment containing trastuzumab. Female participants of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of pembrolizumab or through 180 days after the last dose of paclitaxel. Male participants should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of pembrolizumab or through 180 days after the last dose of paclitaxel. Adequate organ function.<br>**Exclusion Criteria:** Currently participating and receiving study therapy, or participated in a study of an investigational agent and received study therapy or used an investigation device within 4 weeks of the first dose of | | date of 26 Oct 2017)]<br>Percentage of All Participants Who Experienced an AE [ Time Frame: Up to 30 months (through database cut-off date of 26 Oct 2017) ]<br>Percentage of PD-L1 Positive Participants That Discontinued Study Treatment Due to AE [ Time Frame: Up to 30 months (through database cut-off date of 26 Oct 2017) ]<br>Percentage of All Participants That Discontinued Study Treatment Due to AE [ Time Frame: Up to 30 months (through database cut-off date of 26 Oct 2017) ]<br><br>**Results:** WES-tTMB was significantly associated with ORR, PFS, and OS in pembrolizumab-treated (all P < 0.001) but not paclitaxel-treated patients (all P > 0.6) in univariate analysis. The area under the receiver operating characteristics curve for WES-tTMB and response was 0.68 [95% confidence interval (CI) 0.56-0.81] for pembrolizumab and 0.51 (95% CI 0.39-0.63) for paclitaxel in univariate analysis. There was low correlation between | (Treatment benefits): 2 (Randomized trial). |

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| medication. Squamous cell or undifferentiated gastric cancer. Active autoimmune disease that has required systemic treatment in past 2 years (replacement therapy is not considered a form of systemic treatment. Diagnosis of immunodeficiency or receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of study medication. Prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study Day 1 or not recovered from AEs due to agents administered more than 4 weeks earlier. Prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or not recovered from adverse events due to a previously administered agent or surgery. Known additional malignancy that is progressing or requires active treatment (with the exception of basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy). Known active central nervous system (CNS) metastases and/or carcinomatous | | WES-tTMB and CPS in both treatment groups (r 0.16). WES-tTMB remained significantly associated with all clinical endpoints with pembrolizumab after adjusting for CPS and with PFS and OS after excluding known MSI-H tumors (n Â¼ 26). FoundationOneÂ®CDx-tTMB demonstrated a positive association with ORR, PFS, and OS in pembrolizumab-treated patients (all P 0.003) but not PFS or OS in paclitaxel-treated patients (P > 0.1).<br>**Author's Conclusion:** This exploratory analysis from KEYNOTE-061 is the first to demonstrate a strong association between tTMB and efficacy with pembrolizumab but not paclitaxel in patients with gastric/GEJ adenocarcinoma in a randomized setting. Data further suggest tTMB is a significant and independent predictor beyond PD-L1 status. | |

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| meningitis. History of (noninfectious) pneumonitis that required steroids or current pneumonitis. Active infection requiring systemic therapy. Known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial. Pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 120 days after the last dose of pembrolizumab or through 180 days after the last dose of paclitaxel. Prior immunotherapy including anti-PD-1, anti-PD-L1, or anti-PD-L2 agent, or previously participated in Merck pembrolizumab (MK-3475) clinical trial. Known history of human immunodeficiency virus (HIV). Known active Hepatitis B or Hepatitis C. Live vaccine within 30 days of planned start of study therapy. Known allergy or hypersensitivity to paclitaxel or any components used in the paclitaxel preparation or other contraindication for taxane therapy. | | | |

# 4 Literaturverzeichnis

1. Group, O.L.o.E.W. *The Oxford Levels of Evidence 2*. 2011; Available from: https://www.cebm.ox.ac.uk/resources/levels-of-evidence/ocebm-levels-of-evidence.
2. Jeremy Howick, et al. *Explanation of the 2011 Oxford Centre for Evidence-Based Medicine (OCEBM) Levels of Evidence (Background Document)*. 2011.
3. *Cochrane Handbook for Systematic Reviews of Interventions. Version 5.0.0. The Cochrane Collaboration*, ed. J.P.T. Higgins and S. Green. 2008: Wiley.
4. GA Wells, B.S., D O'Connell, J Peterson, V Welch, M Losos, P Tugwell,. *The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses*. Available from: https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
5. *CEBM (Centre for Evidence-Based Medicine) Critical Appraisal tools* 2017; Available from: https://www.cebm.ox.ac.uk/resources/ebm-tools/critical-appraisal-tools