Cluster Oesofagus- en maagcarcinoom: Richtlijnmodules mei 2024

INITIATIEF
Cluster Oesofagus- en Maagcarcinoom

IN SAMENWERKING MET
Nederlandse Internisten Vereniging
Nederlandse Vereniging voor Heelkunde
Nederlandse Vereniging voor Keel-Neus-Oorheelkunde
Nederlandse Vereniging voor Maag-Darm-Leverartsen
Nederlandse Vereniging voor Nucleaire Geneeskunde
Nederlandse Vereniging voor Pathologie
Nederlandse Vereniging voor Radiologie
Nederlandse Vereniging voor Radiotherapie en Oncologie
Stichting voor Patiënten met Kanker aan het Spijsverteringskanaal

MET ONDERSTEUNING VAN
Kennisinstituut van de Federatie Medisch Specialisten

FINANCIERING
De richtlijnontwikkeling werd gefinancierd uit de Kwaliteitsgelden Medisch Specialisten (SKMS).

Colofon

CLUSTER OESOFAGUS- EN MAAGCARCINOOM: RICHTLIJNMODULES MEI

Inhoudsopgave

Verantwoording

Leeswijzer
De verantwoording zal worden geplaatst op de Richtlijnendatabase (Richtlijnendatabase.nl) bij elke geprioriteerde module die is ontwikkeld binnen dit cluster. De betrokken expertiseleden, de kwalitatieve raming van mogelijke financiële gevolgen in het kader van de Wet kwaliteiten, klachten en geschillen zorg (Wkkgz) en de autoriserende partijen kunnen variëren per module.

Autorisatie en geldigheid

Autorisatiedatum:	[volgt later]
Laatst beoordeeld:	[volgt later]
Geplande herbeoordeling:	[volgt later]
Initiatief:	Cluster oesofagus- en maagcarcinoom

Onderstaande vijf modules zijn ontwikkeld:
Richtlijn oesofaguscarcinoom

- Module 1: Minimaal invasieve chirurgie
  Geautoriseerd door: *[volgt]*
  - [Vereniging 1]
  - [Vereniging 2]

- Module 2: Nacontrole na definitieve chemoradiatie
  Geautoriseerd door: *[volgt]*
  - [Vereniging 1]
  - [Vereniging 2]

- Module 3: Palliatie van dysfagie
  Geautoriseerd door: *[volgt]*
  - [Vereniging 1]
  - [Vereniging 2]

- Module 4: Palliatieve immuuntherapie
  Geautoriseerd door: *[volgt]*
  - [Vereniging 1]
  - [Vereniging 2]

Richtlijn maagcarcinoom

- Module 5: Chirurgische resectie na endoscopische behandeling vroegcarcinoom maag
  Geautoriseerd door: *[volgt]*
  - [Vereniging 1]
  - [Vereniging 2]

Algemene gegevens
De ontwikkeling/herziening van deze richtlijnmodule werd ondersteund door het Kennisinstituut van de Federatie Medisch Specialisten (www.demedischspecialist.nl/kennisinstituut) en werd gefinancierd uit de Kwaliteitsgelden Medisch Specialisten (SKMS). De financier heeft geen enkele invloed gehad op de inhoud van de richtlijnmodule.

Samenstelling cluster
Voor het ontwikkelen van de richtlijnmodule is in 2021 een multidisciplinair cluster ingesteld, bestaande uit vertegenwoordigers van alle relevante specialismen (zie hiervoor de Samenstelling van het cluster) die betrokken zijn bij de zorg voor patiënten met oesofagus- en maagcarcinoom.

Het cluster oesofagus- en maagcarcinoom bestaat uit meerdere richtlijnen, zie hier voor de actuele clusterindeling. De stuurgroep bewaakt het proces van modulair onderhoud binnen het cluster. De expertisegroepsleden worden indien nodig gevraagd om hun expertise in te zetten voor een specifieke richtlijnmodule. Het cluster oesofagus- en maagcarcinoom bestaat uit de volgende personen:

Clusterstuurgroep
- Prof. dr. P.D. (Peter) Siersema (voorzitter), maag-darm-leverarts, Erasmus MC, Rotterdam; NVMDL
- Dr. R.E. (Roos) Pouw (voorzitter), maag-darm-leverarts, Amsterdam UMC, Amsterdam; NVMDL
- Dr. A. (Annemarieke) Bartels – Rutten, radioloog, NKI-AVL, Amsterdam; NVvR
- Prof. dr. M.I. (Mark) van Berge Henegouwen, chirurg, Amsterdam UMC, Amsterdam; NVvH
- Prof. dr. R. (Richard) van Hillegersberg, chirurg, UMC Utrecht, Utrecht; NVvH
- Dr. H.W.M. (Hanneke) van Laarhoven, internist, Amsterdam UMC, Amsterdam; NIV
- Dr. E.M. (Liesbeth) Timmermans, bestuurslid Stichting voor Patiënten met Kanker aan het Spijsverteringskanaal (SPKS) *(tot 1 december 2023)*
- Dr. E. (Erik) Vegt, nucleair geneeskundige, Erasmus MC, Rotterdam; NVNG

Clusterexpertisegroep
- Drs. W.W. (Weibel) Braunius, keel-neus-oorarts, UMC Utrecht, Utrecht; NVKNO
- Dr. M.J. (Marc) van Det, chirurg, Ziekenhuisgroep Twente, Almelo; NVvH
- Dr. S.S. (Suzanne) Gisbertz, chirurg, Amsterdam UMC, Amsterdam; NVvH
- Dr. N.C.T. (Nicole) van Grieken, patholoog, Amsterdam UMC, Amsterdam; NVVP
- Dr. R. (Ronald) Hoekstra, internist, Ziekenhuisgroep Twente, Almelo; NIV
- R. (Remco) Huiszoon, MBA, ervaringsdeskundige en bestuurslid Stichting voor Patiënten met kanker aan het Spijsverteringskanaal excl. darmkanker (SPKS)
- Dr. P.M. (Paul) Jeene, radiotherapeut, Radiotherapiegroep, Deventer; NVRO
- Dr. S.M. (Sjoerd) Lagarde, chirurg, Erasmus MC, Rotterdam; NVvH
- Dr. R.W.F. (Roelof) van Leeuwen, ziekenhuisapotheker, Erasmus MC, Rotterdam; NVZA
- Dr. S.L. (Sybren) Meijer, patholoog, Amsterdam UMC, Amsterdam; NVVP
- Dr. B. (Bianca) Mostert, internist, Erasmus MC, Rotterdam; NIV
- Dr. C.T. (Kristel) Muijs, radiotherapeut, UMCG, Groningen; NVRO
- Dr. L. (Liudmila) Peppelenbosch – Kodach, patholoog, NKI-AVL, Amsterdam; NVVP
- Drs. H. (Heidi) Rütten, radiotherapeut, Radboud UMC, Nijmegen; NVRO
- Dr. M. (Marije) Slingerland, internist, LUMC, Leiden; NIV
- Prof. Dr. V.M.C.W. (Manon) Spaander, maag-darm-leverarts, Erasmus MC, Rotterdam; NVMDL
- M.E. (Manon) Dik, verpleegkundig specialist, Ziekenhuisgroep Twente; V&VN
- C.C.G. (Carlo) Schippers, verpleegkundig specialist, UMC Utrecht, Utrecht; V&VN

Met ondersteuning van:

- Drs. S.N. (Sarah) van Duijn, adviseur, Kennisinstituut van de Federatie Medisch Specialisten
- Drs. M. (Miriam) te Lintel Hekkert, adviseur, Kennisinstituut van de Federatie Medisch Specialisten
- Dr. C.M.W. (Charlotte) Gaasterland, adviseur, Kennisinstituut van de Federatie Medisch Specialisten

Belangenverklaringen
De Code ter voorkoming van oneigenlijke beïnvloeding door belangenverstrengeling is gevolgd. Alle clusterleden hebben schriftelijk verklaard of zij in de laatste drie jaar directe financiële belangen (betrekking bij een commercieel bedrijf, persoonlijke financiële belangen, onderzoeksfinanciering) of indirecte belangen (persoonlijke relaties, reputatiemanagement) hebben gehad. Gedurende de ontwikkeling of herziening van een module worden wijzigingen in belangen aan de voorzitter doorgegeven. De belangenverklaring wordt opnieuw bevestigd tijdens de commentaarfase.

Een overzicht van de belangen van de clusterleden en het oordeel over het omgaan met eventuele belangen vindt u in onderstaande tabel. De ondertekende belangenverklaringen zijn op te vragen bij het secretariaat van het Kennisinstituut van de Federatie Medisch Specialisten.

Clusterstuurgroep

Clusterlid	Functie	Nevenfuncties	Gemelde belangen	Ondernomen actie
Siersema (Voorzitter)	Hoogleraar gastro-intestinale endoscopie met focus op innovatie en duurzaamheid Erasmus MC, Rotterdam	Editor in Chief, *Endoscopy*	Research funding/advisory board zonder invloed op deze richtlijn	*Geen restrictie*
Pouw (tijdelijke voorzitter)	MDL-arts Amsterdam UMC	Bestuurslid DUCG - onbetaald. Bestuurslid young ISDE - onbetaald. Bestuurslid Barrett Expertise Centra - onbetaald. Lid beoordelingscommissie ontwikkeling en implementatie KWF - onbetaald. Nationaal afgevaardigde NVMDL voor UEG - onbetaald. Projectleider KWF (PREFER studie). Studie protocol (inclusief inclusie criteria) PREFER studie staat vast. Publicatie resultaten worden pas over vijf jaar verwacht, ruim na datum publicatie richtlijnmodule endoscopische behandeling vroegcarcinoom maag.	Betaalde deelname aan onderwijscursus georganiseerd door Medtronic Betaald adviseurschap voor Medtronic BV. (scholing en webminar endoscopische behandeling vroege afwijking in slokdarm, geen belang bij gebruik producten) Betaald adviseurschap voor MicroTech Europe (webminar, symposium, m.n. behandeling van lekkages na slokdarmoperaties)	a) Werkgroeplid werkt niet als enige inhoudsdeskundige aan de module; b) Werkgroeplid werkt tenminste samen met een ander werkgroeplid met vergelijkbare expertise in alle fasen (studieselectie, data-extractie, evidence synthese, evidence-to-decision, aanbevelingen formuleren) van het ontwikkelproces; c) In alle fasen van het ontwikkelproces is een onafhankelijk methodoloog betrokken; d) Overwegingen en aanbevelingen worden besproken en vastgesteld tijdens een werkgroepvergadering onder leiding van een onafhankelijk voorzitter (zonder gemelde belangen)
Timmermans	- Bestuurslid SPKS (Stichting voor Patiënten met kanker aan het Spijsverteringskanaal) 5 uur per week	Onbetaald vrijwilligerswerk Bestuurslid SPKS (15 uur per week)	Geen	*Neemt geen deel meer aan cluster - Geen restrictie*

	- Gedragswetenschappelijk docent huisartsenopleiding Eerstelijnsgeneeskunde Radboudumc			
Van Laarhoven	Hoofd afdeling medische oncologie, Amsterdam UMC	- Wetenschappelijke raad KWF (onbetaald) - Voorzitter ESMO upper GI faculty (onbetaald) - Lid ESMO Leadership Generation programme (onbetaald) - Lid EORTC upper GI strategy commiittee (onbetaald)	- Consultant or advisory role: Amphera, AstraZeneca, Beigene, BMS, Daiichy-Sankyo, Dragonfly, Eli Lilly, MSD, Nordic Pharma, Servier - Research funding and/or medication supply: Bayer, BMS, Celgene, Janssen, Incyte, Eli Lilly, MSD, Nordic Pharma, Philips, Roche, Servier - Speaker role: Astellas, Benecke, Daiichy-Sankyo, JAAP, Medtalks, Novartis, Travel Congress Management B.V Employment and leadership: Amsterdam UMC, the Netherlands (head of the department of medical oncology) Honorary: ESMO (chair upper GI faculty)	*Geen restrictie*
Bartels	Radioloog, Antoni van Leeuwenhoek	Geen	Geen	*Geen restrictie*
Van Berge Henegouwen	Chirurg slokdarm en maagchirurgie Amsterdam UMC Hoogleraar slokdarm en maagchirurgie Universiteit van Amsterdam	- bestuur DUCA, DICA en voorzitter werkgroep Upper GI (allen onbetaald).	- Olympus financiering studie (researcher initiated grant) Stryker financiering studie (researcher initiated grant) uitkomsten richtlijn geen invloed op deze bedrijven of studies - Consultancy voor meerdere bedrijven (B. Braun en Viatris) (uitbetaling aan Amsterdam UMC), niet gerelateerd aan richtlijn.	*Geen restrictie*

Hulshof	Radiotherapeut oncoloog Amsterdam UMC	Geen	Geen	*Neemt geen deel meer aan cluster - Geen restrictie*
Van Hillegersberg	Chirurg, UMC Utrecht	Proctor Intuitive Surgical Consultant Medtronic	- Bestuur DUCA, DICA	*Geen restrictie*
Vegt	Nucleair geneeskundige, Afdeling Radiologie en Nucleaire Geneeskunde, Erasmus MC, Rotterdam	Geen	- ZonMW-subsidie voor de PLASTIC-studie, programma doelmatigheid van zorg, naar de kosten-effectiviteit van FDG-PET/CT en laparoscopie bij maagcarcinoom.	*Geen restrictie*
Van Rossum	*[volgt]*	*[volgt]*	*[volgt]*	*[volgt]*

Clusterexpertisegroep

Clusterlid	Functie	Nevenfuncties	Gemelde belangen	Ondernomen actie
Huiszoon	ING Bank N.V. Agile coach expert, full-time	Buddy voor slokdarmkanker patiënten bij het SPKS, onbetaald. Vanuit persoonlijke ervaring 'klankbord' zijn voor patiënten die nu dezelfde ziekte hebben als ik in 2017 heb gehad	Neemt deel namens SPKS en hoopt vanuit dat perspectief als ervaringsdeskundige bij te kunnen dragen. Geen boegbeeldfunctie of ander belang	*Geen restrictie*
Braunius	Oncologisch Hoofd-Halschirurg UMC Utrecht Cancer Center	Geen	Geen	*Geen restrictie*
Van Leeuwen	Ziekenhuisapotheker - Erasmus MC Afdelingen Apotheek (80%) en Interne Oncologie (20%)	SIG Oncologie NVZA - onbetaald Werkgroep Geneesmiddel Interacties NVZA/KNMP (betaald "onkosten") Onderwijs PAO Farmacie (betaald "onkosten")	Industrie: Geneesmiddelen onderzoek i.s.m. Roche, Astellas, BMS, Servier, Boehringer (unrestricted research grants) Fondsen: Stichting Coolsingel, Stichting de Merel, Stichting Mitialto Geen conflict of interest	a) Werkgroeplid werkt niet als enige inhoudsdeskundige aan de module; b) Werkgroeplid werkt tenminste samen met een ander werkgroeplid met vergelijkbare expertise in alle fasen (studieselectie, data-extractie, evidence synthese, evidence-to-decision, aanbevelingen formuleren) van het ontwikkelproces; c) In alle fasen van het ontwikkelproces is een onafhankelijk methodoloog betrokken; d) Overwegingen en aanbevelingen worden besproken en vastgesteld tijdens een werkgroepvergadering onder leiding van een

				onafhankelijk voorzitter (zonder gemelde belangen)
Jeene	Radiotherapeut - Oncoloog bij Radiotherapiegroep PhD candidate - AmsterdamUMC (0 uren aanstelling)	Bestuurslid DUCG - onbetaald	Studie coördinator en eerste auteur POLDER trail (effectiviteit kortdurende uitwendige radiotherapie, geen externe financiering). PICO is anders dan studie	*Geen restrictie*
Gisbertz	Slokdarmkanker en maagkanker chirurg - Amsterdam UMC	Bestuur ESDE, NVGIC, ISDE, research commitee EAES, de Groene OK: allen onbetaald	Extern gefinancierd onderzoek: KWF: SQA n observational studies (projectleider) CCA: USPIO enhanced MRI in esophageal cancer (projectleider)	*Geen restrictie*
Lagarde	Chirug, Erasmus MC, Rotterdam	- lid wetenschappelijke commissie DKCA - bestuurslid werkgroep Upper Gi beiden onbetaald	Geen	*Geen restrictie*
Hoekstra	Internist-oncoloog, Ziekenhuisgroep Twente (ZGT)	Lid Concillium Medicinae Internae (onbetaald)	- Als internist-oncoloog betrokken bij inclusie van patiënten in klinische studies bij oesofagus- en maagcarcinoom. Op dit moment Critics-2 studie en Lyrics studie	*Geen restrictie*
Van Det	Gastro-intestinaal chirurg Ziekenhuis groep Twente (ZGT)	- Proctor/Instructor voor Intuitive Surgical betreffende Robot-Assisted operaties in de upper-GI zoals: - Slokdarm resecties - Maagresecties - Hernia diafragmatica.	Geen	*Geen restrictie*
Rütten	Radiotherapeut, Radboud UMC	Geen	Geen	*Geen restrictie*
Van Grieken	Patholoog, Amsterdam UMC (locatie Vumc), Amsterdam	Detachering Expertisepanel poliepen BVO-DK, Screeningsorganisatie BVO darmkanker (3 uur/week)	- KWF - Identificatie van markers voor response op immunotherapie - projectleider - KWF - CRITICS-II klinische trial voor resectabel maagcarcinoom - ZonMW - Effect van chemotherapie bij patienten met microsatelliet instabiel resectabel maagcarcinoom. – projectleider - advisory boards van BMS, MSD	a) Werkgroeplid werkt niet als enige inhoudsdeskundige aan de module; b) Werkgroeplid werkt tenminste samen met een ander werkgroeplid met vergelijkbare expertise in alle fasen (studieselectie, data-extractie, evidence synthese, evidence-to-decision, aanbevelingen formuleren) van het ontwikkelproces; c) In alle fasen van het ontwikkelproces is een onafhankelijk methodoloog betrokken; d) Overwegingen en aanbevelingen worden besproken en

				vastgesteld tijdens een werkgroepvergadering onder leiding van een onafhankelijk voorzitter (zonder gemelde belangen)
Mostert	Internist-oncoloog, Erasmus MC	Consultancy voor: BMS, Lilly, Servier	- BMS: fase 2 studie: nivolumab tijdens actieve surveillance slokdarmcarcinoom Sanofi: cabazitaxel bij AR-v7 positieve prostaatcarcinoom patiënten Pfizer: DLA bij mammacarcinoompatiënten behandeld met CDK4/6 De f1/2 studie betreft research support`; investigator initiated studie waarvoor BMS de medicatie "schenkt" Astra zeneca betreft advisory board.	a) Werkgroeplid werkt niet als enige inhoudsdeskundige aan de module; b) Werkgroeplid werkt tenminste samen met een ander werkgroeplid met vergelijkbare expertise in alle fasen (studieselectie, data-extractie, evidence synthese, evidence-to-decision, aanbevelingen formuleren) van het ontwikkelproces; c) In alle fasen van het ontwikkelproces is een onafhankelijk methodoloog betrokken; d) Overwegingen en aanbevelingen worden besproken en vastgesteld tijdens een werkgroepvergadering onder leiding van een onafhankelijk voorzitter (zonder gemelde belangen)
Slingerland	Internist-oncoloog LUMC	Geen	- Advisory board Lilly, Astra Zeneca en BMS	a) Werkgroeplid werkt niet als enige inhoudsdeskundige aan de module; b) Werkgroeplid werkt tenminste samen met een ander werkgroeplid met vergelijkbare expertise in alle fasen (studieselectie, data-extractie, evidence synthese, evidence-to-decision, aanbevelingen formuleren) van het ontwikkelproces; c) In alle fasen van het ontwikkelproces is een onafhankelijk methodoloog betrokken; d) Overwegingen en aanbevelingen

				worden besproken en vastgesteld tijdens een werkgroepvergadering onder leiding van een onafhankelijk voorzitter (zonder gemelde belangen)
Spaander	MDL-arts 1.0 Fte in Erasmus Universiteit MC (betaald) Voor 6 uur per week gedetacheerd aan de screeningorganisatie voor het BVO darmkanker (betaald)	Voorzitter NVMDL en NVGE oncologie commissie (onbetaald) Editor in Chief Best Practice & Research Clinical Gastroenterology (betaald) Co-editor Endoscopy (betaald) Voorzitter Stichting Lever en Maag-darm onderzoek (onbetaald) Editorial board Oncology-Up- to- date (onbetaald) Taskforce member ESGE richtlijn Barrett slokdarm (onbetaald) Lid van de werkgroep voor de Nederlandse richtlijn poliep surveillance	ZonMW: Gender differencees in Barrett Surveillance, projectleidersrol. Capsulomics: Biomarkers in Barrett slokdarm, projectleidersrol. Lucid: Non-ionvasive tool for Barrett surveillance. Microtech: New Esophageal stent. CELTIC: Blood test bij FIT +patiënten	*Geen restrictie*
Meijer	Patholoog, Amsterdam UMC	Geen	Geen	*Geen restrictie*
Peppelenbosch - Kodach	Patholoog, NKI/AVL	Geen	Deelname studie inter-observer variabiliteit voor PD-L1 CPS in maagcarcinomen, gefinancierd door BMS, fee naar de werkgever AVL/NKI	*Geen restrictie*
Muijs	Radiotherapeut-Oncoloog Universitaire Medisch Centrum Groningen	Lid wetenschapscommissie DUCA (Gemandateerde NVRO) Lid werkgroep indicatie protocol protonen radiotherapie (NVRO)	Project Leider Models Project (KWf funded): ontwikkelen en valideren predictiemodellen voor complicaties na CRT en resectie Principle investigator CLARIFY studie (KWF funded): Observationeel onderzoek naar pulmonale hupertensie als complicatie na thoracale RT Participatie in PROTECT studie (EU funded): RCT fase 3: fotonen vs protonen bij nCRT voor oesofaguscarcinoom Voortrekker protonen RT bij het oesofaguscarcinoom	*Geen restrictie*
Dik	*[volgt]*	*[volgt]*	*[volgt]*	*[volgt]*
Schippers	*[volgt]*	*[volgt]*	*[volgt]*	*[volgt]*

Inbreng patiëntenperspectief
Er werd aandacht besteed aan het patiëntenperspectief door de afvaardiging van de Stichting voor Patiënten met kanker aan het Spijsverteringskanaal (SPKS). De verkregen input is meegenomen bij het opstellen van de uitgangsvragen, de keuze voor de uitkomstmaten en bij het opstellen van de overwegingen. De conceptmodule is tevens voor commentaar voorgelegd aan SPKS en de eventueel aangeleverde commentaren zijn bekeken en verwerkt.

Kwalitatieve raming van mogelijke financiële gevolgen in het kader van de Wkkgz
Bij de richtlijn is conform de Wet kwaliteit, klachten en geschillen zorg (Wkkgz) een kwalitatieve raming uitgevoerd of de aanbevelingen mogelijk leiden tot substantiële financiële gevolgen. Bij het uitvoeren van deze beoordeling zijn richtlijnmodules op verschillende domeinen getoetst (zie het stroomschema op de Richtlijnendatabase).
Uit de kwalitatieve raming blijkt dat er waarschijnlijk geen substantiële financiële gevolgen zijn, zie onderstaande tabel.

Module	Uitkomst raming	Toelichting
'Minimaal invasieve chirurgie' (oesofaguscarcinoom)	Geen financiële gevolgen	Hoewel uit de toetsing volgt dat de aanbeveling(en) breed toepasbaar zijn (5.000-40.000 patiënten), volgt ook uit de toetsing dat [het overgrote deel (±90%) van de zorgaanbieders en zorgverleners al aan de norm voldoet OF het geen nieuwe manier van zorgverlening of andere organisatie van zorgverlening betreft]. Er worden daarom geen financiële gevolgen verwacht.

Module	Uitkomst raming	Toelichting
'Nacontrole na definitieve chemoradiatie' (oesofaguscarcinoom)	Geen financiële gevolgen	Hoewel uit de toetsing volgt dat de aanbeveling(en) breed toepasbaar zijn (5.000-40.000 patiënten), volgt ook uit de toetsing dat [het overgrote deel (±90%) van de zorgaanbieders en zorgverleners al aan de norm voldoet OF het geen nieuwe manier van zorgverlening of andere organisatie van zorgverlening betreft]. Er worden daarom geen financiële gevolgen verwacht.

Module	Uitkomst raming	Toelichting
'Palliatie van dysfagie' (oesofaguscarcinoom)	Geen financiële gevolgen	Hoewel uit de toetsing volgt dat de aanbeveling(en) breed toepasbaar zijn (5.000-40.000 patiënten), volgt ook uit de toetsing dat [het overgrote deel (±90%) van de zorgaanbieders en zorgverleners al aan de norm voldoet OF het geen nieuwe manier van zorgverlening of andere organisatie van zorgverlening betreft]. Er worden daarom geen financiële gevolgen verwacht.

Module	Uitkomst raming	Toelichting
'Palliatieve immuuntherapie' (oesofagus- en maagcarcinoom)	Geen financiële gevolgen	Hoewel uit de toetsing volgt dat de aanbeveling(en) breed toepasbaar zijn (5.000-40.000 patiënten), volgt ook uit de toetsing dat [het overgrote deel (±90%) van de zorgaanbieders en zorgverleners al aan de norm voldoet OF het geen nieuwe manier van zorgverlening of andere organisatie van zorgverlening betreft]. Er worden daarom geen financiële gevolgen verwacht.

Module	Uitkomst raming	Toelichting
'Chirurgische resectie na endoscopische behandeling vroegcarcinoom maag' (maagcarcinoom)	Geen financiële gevolgen	Hoewel uit de toetsing volgt dat de aanbeveling(en) breed toepasbaar zijn (5.000-40.000 patiënten), volgt ook uit de toetsing dat [het overgrote deel (±90%) van de zorgaanbieders en zorgverleners al aan de norm voldoet OF het geen nieuwe manier

		van zorgverlening of andere organisatie van zorgverlening betreft]. Er worden daarom geen financiële gevolgen verwacht.

De kwalitatieve raming volgt na de commentaarfase.

Werkwijze

AGREE

Deze richtlijnmodule is opgesteld conform de eisen vermeld in het rapport Medisch Specialistische Richtlijnen 2.0 van de adviescommissie Richtlijnen van de Raad Kwaliteit. Dit rapport is gebaseerd op het AGREE II instrument (Appraisal of Guidelines for Research & Evaluation II; Brouwers, 2010).

Need-for-update, prioritering en uitgangsvragen

Tijdens de need-for-update fase inventariseerde het cluster de geldigheid van de modules binnen het cluster. Naast de betrokken wetenschappelijke verenigingen en patiëntenorganisaties zijn hier ook andere stakeholders voor benaderd in juni 2021.
Per module is aangegeven of deze geldig is, kan worden samengevoegd met een andere module, obsoleet is en kan vervallen of niet meer geldig is en moet worden herzien. Ook was er de mogelijkheid om nieuwe onderwerpen voor modules aan te dragen die aansluiten bij één (of meerdere) richtlijn(en) behorend tot het cluster. De modules die door één of meerdere partijen werden aangekaart als 'niet geldig' zijn meegegaan in de prioriteringsfase. Deze module is geprioriteerd door het cluster.

Voor de geprioriteerde modules zijn door het cluster concept-uitgangsvragen herzien of opgesteld en definitief vastgesteld.

Uitkomstmaten

Na het opstellen van de zoekvraag behorende bij de uitgangsvraag inventariseerde het cluster welke uitkomstmaten voor de patiënt relevant zijn, waarbij zowel naar gewenste als ongewenste effecten werd gekeken. Hierbij werd een maximum van acht uitkomstmaten gehanteerd. Het cluster waardeerde deze uitkomstmaten volgens hun relatieve belang bij de besluitvorming rondom aanbevelingen als cruciaal (kritiek voor de besluitvorming), belangrijk (maar niet cruciaal) en onbelangrijk. Het cluster definieerde klinisch (patiënt) relevante verschillen, tenminste voor de cruciale uitkomstmaten.

Methode literatuursamenvatting

Een uitgebreide beschrijving van de strategie voor zoeken en selecteren van literatuur is te vinden onder 'Zoeken en selecteren' onder Onderbouwing. Indien mogelijk werd de data uit verschillende studies gepoold in een random-effects model. Review Manager 5.4 werd gebruikt voor de statistische analyses. De beoordeling van de kracht van het wetenschappelijke bewijs wordt hieronder toegelicht.

Beoordelen van de kracht van het wetenschappelijke bewijs

De kracht van het wetenschappelijke bewijs werd bepaald volgens de GRADE-methode. GRADE staat voor 'Grading Recommendations Assessment, Development and Evaluation' (zie http://www.gradeworkinggroup.org/). De basisprincipes van de GRADE-methodiek zijn: het benoemen en prioriteren van de klinisch (patiënt) relevante uitkomstmaten, een systematische review per uitkomstmaat, en een beoordeling van de bewijskracht per uitkomstmaat op basis van de acht GRADE-domeinen (domeinen voor downgraden: risk of bias, inconsistentie, indirectheid, imprecisie, en publicatiebias; domeinen voor upgraden: dosis-effect relatie, groot effect, en residuele plausibele confounding).

GRADE onderscheidt vier gradaties voor de kwaliteit van het wetenschappelijk bewijs: hoog, redelijk, laag en zeer laag. Deze gradaties verwijzen naar de mate van zekerheid die er bestaat over de literatuurconclusie, in het bijzonder de mate van zekerheid dat de literatuurconclusie de aanbeveling adequaat ondersteunt (Schünemann, 2013; Hultcrantz, 2017).

GRADE	Definitie
Hoog	• er is hoge zekerheid dat het ware effect van behandeling dichtbij het geschatte effect van behandeling ligt; • het is zeer onwaarschijnlijk dat de literatuurconclusie klinisch relevant verandert wanneer er resultaten van nieuw grootschalig onderzoek aan de literatuuranalyse worden toegevoegd.
Redelijk	• er is redelijke zekerheid dat het ware effect van behandeling dichtbij het geschatte effect van behandeling ligt; • het is mogelijk dat de conclusie klinisch relevant verandert wanneer er resultaten van nieuw grootschalig onderzoek aan de literatuuranalyse worden toegevoegd.
Laag	• er is lage zekerheid dat het ware effect van behandeling dichtbij het geschatte effect van behandeling ligt; • er is een reële kans dat de conclusie klinisch relevant verandert wanneer er resultaten van nieuw grootschalig onderzoek aan de literatuuranalyse worden toegevoegd.
Zeer laag	• er is zeer lage zekerheid dat het ware effect van behandeling dichtbij het geschatte effect van behandeling ligt; • de literatuurconclusie is zeer onzeker.

Bij het beoordelen (graderen) van de kracht van het wetenschappelijk bewijs in richtlijnen volgens de GRADE-methodiek spelen grenzen voor klinische besluitvorming een belangrijke rol (Hultcrantz, 2017). Dit zijn de grenzen die bij overschrijding aanleiding zouden geven tot een aanpassing van de aanbeveling. Om de grenzen voor klinische besluitvorming te bepalen moeten alle relevante uitkomstmaten en overwegingen worden meegewogen.

De grenzen voor klinische besluitvorming zijn daarmee niet één op één vergelijkbaar met het minimaal klinisch relevant verschil (Minimal Clinically Important Difference, MCID).

Met name in situaties waarin een interventie geen belangrijke nadelen heeft en de kosten relatief laag zijn, kan de grens voor klinische besluitvorming met betrekking tot de effectiviteit van de interventie bij een lagere waarde (dichter bij het nuleffect) liggen dan de MCID (Hultcrantz, 2017).

<u>Overwegingen (van bewijs naar aanbeveling)</u>
Om te komen tot een aanbeveling zijn naast (de kwaliteit van) het wetenschappelijke bewijs ook andere aspecten belangrijk en deze worden meegewogen, zoals aanvullende argumenten uit bijvoorbeeld de biomechanica of fysiologie, waarden en voorkeuren van patiënten, kosten (middelenbeslag), aanvaardbaarheid, haalbaarheid en implementatie. Deze aspecten zijn systematisch vermeld en beoordeeld (gewogen) onder het kopje ‘Overwegingen’ en kunnen (mede) gebaseerd zijn op expert opinion. Hierbij is gebruik gemaakt van een gestructureerd format gebaseerd op het evidence-to-decision framework van de internationale GRADE Working Group (Alonso-Coello, 2016a; Alonso-Coello 2016b). Dit evidence-to-decision framework is een integraal onderdeel van de GRADE methodiek.

<u>Formuleren van aanbevelingen</u>
De aanbevelingen geven antwoord op de uitgangsvraag en zijn gebaseerd op het beschikbare wetenschappelijke bewijs en de belangrijkste overwegingen, en een weging van de gunstige en ongunstige effecten van de relevante interventies. De kracht van het wetenschappelijk bewijs en het gewicht dat door het cluster wordt toegekend aan de overwegingen, bepalen samen de sterkte van de aanbeveling. Conform de GRADE-

methodiek sluit een lage bewijskracht van conclusies in de systematische literatuuranalyse een sterke aanbeveling niet a priori uit, en zijn bij een hoge bewijskracht ook zwakke aanbevelingen mogelijk (Agoritsas, 2017; Neumann, 2016). De sterkte van de aanbeveling wordt altijd bepaald door weging van alle relevante argumenten tezamen. Het cluster heeft bij elke aanbeveling opgenomen hoe zij tot de richting en sterkte van de aanbeveling zijn gekomen.

In de GRADE-methodiek wordt onderscheid gemaakt tussen sterke en zwakke (of conditionele) aanbevelingen. De sterkte van een aanbeveling verwijst naar de mate van zekerheid dat de voordelen van de interventie opwegen tegen de nadelen (of vice versa), gezien over het hele spectrum van patiënten waarvoor de aanbeveling is bedoeld. De sterkte van een aanbeveling heeft duidelijke implicaties voor patiënten, behandelaars en beleidsmakers (zie onderstaande tabel). Een aanbeveling is geen dictaat, zelfs een sterke aanbeveling gebaseerd op bewijs van hoge kwaliteit (GRADE gradering HOOG) zal niet altijd van toepassing zijn, onder alle mogelijke omstandigheden en voor elke individuele patiënt.

Implicaties van sterke en zwakke aanbevelingen voor verschillende richtlijngebruikers		
	Sterke aanbeveling	*Zwakke (conditionele) aanbeveling*
Voor patiënten	De meeste patiënten zouden de aanbevolen interventie of aanpak kiezen en slechts een klein aantal niet.	Een aanzienlijk deel van de patiënten zouden de aanbevolen interventie of aanpak kiezen, maar veel patiënten ook niet.
Voor behandelaars	De meeste patiënten zouden de aanbevolen interventie of aanpak moeten ontvangen.	Er zijn meerdere geschikte interventies of aanpakken. De patiënt moet worden ondersteund bij de keuze voor de interventie of aanpak die het beste aansluit bij zijn of haar waarden en voorkeuren.
Voor beleidsmakers	De aanbevolen interventie of aanpak kan worden gezien als standaardbeleid.	Beleidsbepaling vereist uitvoerige discussie met betrokkenheid van veel stakeholders. Er is een grotere kans op lokale beleidsverschillen.

<u>Organisatie van zorg</u>
Bij de ontwikkeling van de richtlijnmodule is expliciet aandacht geweest voor de organisatie van zorg: alle aspecten die randvoorwaardelijk zijn voor het verlenen van zorg (zoals coördinatie, communicatie, (financiële) middelen, mankracht en infrastructuur). Randvoorwaarden die relevant zijn voor het beantwoorden van deze specifieke uitgangsvraag zijn genoemd bij de overwegingen. Meer algemene, overkoepelende, of bijkomende aspecten van de organisatie van zorg worden behandeld in de module Organisatie van zorg.

<u>Commentaar- en autorisatiefase</u>
De conceptrichtlijnmodule werd aan de betrokken (wetenschappelijke) verenigingen en (patiënt) organisaties voorgelegd ter commentaar. De commentaren werden verzameld en besproken met het cluster. Naar aanleiding van de commentaren werd de conceptrichtlijnmodule aangepast en definitief vastgesteld door het cluster. De definitieve richtlijnmodule werd aan de deelnemende (wetenschappelijke) verenigingen en (patiënt)organisaties voorgelegd voor autorisatie en door hen geautoriseerd dan wel geaccordeerd.

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Startpagina richtlijn oesofaguscarcinoom

Deze richtlijn valt onder het cluster oesofagus- en maagcarcinoom.

Waar gaat deze richtlijn over?
Deze richtlijn richt zich op wat volgens de huidige maatstaven de beste zorg is voor patiënten met oesofaguscarcinoom. In de richtlijn komen de volgende onderwerpen aan de orde:

- Epidemiologie van oesofaguscarcinoom
- Diagnostiek van oesofaguscarcinoom
- Pathologie van oesofaguscarcinoom
- Neoadjuvante behandeling
- Chirurgische behandeling en technieken
- Niet chirurgische behandeling van grote tumoren
- Perioperatieve maatregelen zoals voeding, selectieve darmdecontaminatie (SDD), normotherapie, glucoseregulatie, vochtbeleid en analgesie
- Nacontrole en nazorg
- De rol van psychosociale zorg bij patiënten met oesofaguscarcinoom
- Palliatieve zorg
- De organisatie van zorg rondom patiënten met oesofaguscarcinoom

Voor wie is deze richtlijn bedoeld?
Deze richtlijn is bestemd voor alle zorgverleners in de tweede (en derde) lijn die betrokken zijn bij de zorg voor patiënten met oesofaguscarcinoom.

Voor patiënten
Oesofaguscarcinoom is kanker van de slokdarm ofwel slokdarmkanker. Er zijn twee typen slokdarmkanker die vaak voorkomen: Adenocarcinoom en plaveiselcelcarcinoom. Een adenocarcinoom is een tumor die ontstaat in klierweefsel en een plaveiselcelcarcinoom ontstaat in cellen van het slijmvlies. In Nederland krijgen per jaar ongeveer 2000 mensen slokdarmkanker waarbij de meeste patiënten tussen de 50 en 70 jaar zijn. Bij mannen komt de ziekte driemaal vaker voor als bij vrouwen.

- Meer informatie over slokdarmkanker is te vinden op Thuisarts: https://www.thuisarts.nl/slokdarmkanker.
- Meer informatie over slokdarmkanker is ook te vinden op de website van de Stichting voor Patiënten met Kanker aan het Spijsverteringskanaal (SPKS): https://spks.nl/.
- Bij deze richtlijn is een keuzekaart ontwikkeld. Een keuzekaart kan helpen bij het maken van keuzes over screening, diagnose en behandeling in het kader van samen beslissen. Meer informatie over palliatieve opties bij slokdarmkanker kunt u vinden op de keuzekaart slokdarmkanker.

Hoe is de richtlijn tot stand gekomen?
Het initiatief voor deze richtlijn is afkomstig van Nederlandse Vereniging voor Maag-Darm-Leverartsen (NVMDL) en wordt vanaf 2022 modulair herzien door het cluster Oesofagus- en maagcarcinoom.

De richtlijn is opgesteld door een multidisciplinaire commissie met vertegenwoordigers vanuit internisten, maag-darm-leverartsen, medisch-oncologen, chirurgen, anesthesiologen,

pathologen, radiologen, radiotherapeuten, oncologen, nucleair geneeskundigen en keel-neus-oorartsen. De samenstelling van het cluster kunt u hier (link) vinden. Er werd aandacht besteed aan het patiëntenperspectief door inbreng van de patiëntenvereniging SPKS.

Onderhoudsplan

De richtlijnen in het cluster oesofagus- en maagcarcinoom worden modulair onderhouden. Het cluster oesofagus- en maagcarcinoom omvat de richtlijn oesofaguscarcinoom en de richtlijn maagcarcinoom. In onderstaande tabel is te zien wat de geldigheid is van de richtlijnmodules voor oesofaguscarcinoom. Tevens zijn de aandachtspunten vermeld die van belang zijn voor een herziening. Het cluster Oesofagus- en maagcarcinoom is als houder van deze richtlijn de eerstverantwoordelijke voor de actualiteit van deze richtlijn.

Richtlijn oesofaguscarcinoom	Geautoriseerd in	Laatst beoordeeld in[1]	Geplande herbeoordeling[2]	Wijzigingen meest recente versie
1. Startpagina – Oesofaguscarcinoom			1 jaar	Geüpdatet
2. Algemeen	2015	2021	2023	n.v.t.
3. Epidemiologie	2010	2021	2023	n.v.t.
4. Diagnostiek	2018	2021	2023	n.v.t.
5. Pathologie	2010	2021	2023	n.v.t.
6. Behandeling	2010	2021	2023	
6.3.5 Nieuwe update module: **Module 1**: Minimaal invasieve chirurgie				Update module vervangt oude module 6.3.5
7. Specifieke perioperatieve maatregelen	2010	2021	2023	n.v.t.
8. Follow-up	2010	2021	2023	
8.1 Nieuwe update module: **Module 2**: Nacontrole na definitieve chemoradiatie				Update module vervangt oude module 8.1
8.2 Nieuwe update module: Nacontrole na resectie *[volgende commentaarfase]*				Update module vervangt oude module 8.1
8.3 Nieuwe update module: Nazorg *[volgende commentaarfase]*				Update module vervangt oude module 8.1
9. Spreiding, concentratie en infrastructuur	2015	2021	2023	n.v.t.
10. Psychosociale zorg	2005	2021	2023	Links naar verwijsmogelijkheden geüpdatet
11. Palliatieve zorg	2005	2021	2023	
11.1 Nieuwe update module: **Module 3**: Palliatie van dysfagie				Update module vervangt oude module 11.1
11.2 Nieuwe module: **Module 4**: Palliatieve immuuntherapie				Nieuwe module
12. Implementatie en richtlijnevaluatie	2005	2021	2023	n.v.t.
13. TNM	2010	2021	2023	n.v.t.

[1] Jaartal waarin de richtlijnmodule is meegenomen in de need-for-update.

[2] Jaartal waarin de richtlijnmodule weer moet worden meegenomen in de need-for-update.

Module 1 Minimaal invasieve chirurgie

Uitgangsvraag
Wat is de rol van minimaal invasieve chirurgie bij patiënten met een oesofaguscarcinoom?
De uitgangsvraag omvat de volgende deelvragen:

1. Wat is de rol van minimaal invasieve chirurgie (Robot, video-geassisteerde, conventionele minimaal invasieve chirurgie) versus open chirurgie bij patiënten met een oesofaguscarcinoom?
2. Wat is de rol van hybride chirurgie (minimaal invasief gecombineerd met open) versus open chirurgie bij patiënten met een oesofaguscarcinoom?

Introduction
Minimally invasive surgery for esophageal cancer was first introduced in 1992 and has since then gradually gained more widespread use, especially in the Netherlands, following the publication of the Dutch TIME trial in 2012 (Straatman, 2017; Cuschieri, 1994). Currently, more than 80% of esophagectomies in the Netherlands is performed minimally invasively (DUCA registration). This chapter investigates the available evidence comparing minimally invasive with open esophagectomy.

Search and select
A systematic review of the literature was performed to answer the following question: What is the effect of minimally invasive surgery compared with open surgery on complications, pain, time to recovery, length of hospital stay, R0 resection, lymph node yield, quality of life, and overall survival in patients undergoing esophagectomy for esophageal carcinoma?

PICO 1
P: patients with an esophageal carcinoma;
I: minimally invasive surgery (MIE, RAMIE, conventional minimally invasive surgery);
C: open surgery;
O: complications, pain, time to recovery, length of hospital stay, R0 resection, lymph node yield, quality of life and overall survival.

PICO 2
P: patients with an esophageal carcinoma;
I: hybrid surgery (Minimally invasive surgery combined with open surgery);
C: open surgery;
O: complications, pain, time to recovery, length of hospital stay, R0 resection, lymph node yield, quality of life and overall survival.

<u>Relevant outcome measures</u>
The guideline development group considered complications, quality of life and overall survival as a critical outcome measure for decision making and pain, time to recovery, length of hospital stay, R0 resection and lymph node yield as an important outcome measure for decision making.

A priori, the working group did not define the outcome measures listed above but used the definitions used in the studies.

The working group defined the following differences as a minimal clinically (patient) important:

- Complications: Absolute difference ≥1% for lethal complications, or ≥5% for severe complications
- Pain: Change of 10 on 100mm (1 on 10) Visual Analogue Scale (VAS) (Myles, 2017)
- Time to recovery: > 1 week
- Length of hospital stay: > 1 day
- R0 resection: Absolute difference >5% or absolute difference >3% and Hazard Ratio (HR) <0.7
- Lymph node yield: Number of resected lymph nodes >10% difference
- Quality of life: A difference of 10 points on the quality of life instrument EORTC QLQ-C30 or a difference of a similar magnitude on other quality of life instruments.
- Overall survival: >5% or >3% and HR<0.70

Search and select (Methods)

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until June 22nd 2023. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 499 hits. The systematic review was selected based on the following criteria:

- Minimum of two databases searched;
- Detailed search strategy with search date;
- In- and exclusion criteria;
- Evidence table for included studies;
- Risk of bias assessment per study.

Additional studies were selected based on the following criteria:

- The study population had to meet the criteria as defined in the PICO;
- The intervention and comparison had to be as defined in the PICO;
- Outcomes had to be as defined in the PICO;
- Research type: Randomized-controlled trial (RCT);
- Articles written in English or Dutch.

30 studies were initially selected based on title and abstract screening. After reading the full text, 19 studies were excluded (see the table with reasons for exclusion under the tab Methods), and one systematic review (together with the included RCTs) and three additional RCTs were included.

Results

One systematic review and three additional studies were included in the analysis of the literature. Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables.

Summary of literature

Description of studies

The systematic review by Muller-Stich (2021) was included as the basis for the literature analysis. In this review, six RCTs with eight publications in total (Biere, 2012; Maas, 2015; Straatman, 2017; Guo, 2013; Ma, 2018; Mariette, 2019; Paireder, 2018; van der Sluis, 2019) were included. Additionally, three RCT (Nuytens, 2021; Song, 2022; Wan, 2020) were included that were published after the systematic review by Muller-Stich (2021). Table 1 lists the types of intervention and total sample size of each study. All studies used open esophagectomy as the control treatment.

Table 1. Study characteristics

Study	Intervention	Sample size (n)
Biere, Maas, Straatman*	Totally minimally invasive	115
Guo	Totally minimally invasive	221
Ma	Totally minimally invasive	144
Van der Sluis	Totally minimally invasive (robot-assisted)	109
Paireder	Hybrid (abdominal part laporoscopic)	26
Mariette, Nuytens*	Hybrid (abdominal part laporoscopic)	205
Song	Totally minimally invasive	122
Wan	Totally minimally invasive	120

* studies are describing the same trial population

Results

The systematic review by Muller-Stich (2021) was used as the basis for this literature analysis, but due to incomplete reporting, most data was extracted from the individual studies. Survival data had to be extracted for a few studies because no event data was given.

Overall survival

One-year survival

Four studies reported the overall survival after one year (Guo, 2013; Maas, 2015; Paireder, 2018; Mariette, 2019). Guo (2013) and Maas (2015) both used a totally minimally invasive approach, whereas Paireder (2018) and Mariette (2019) both used a hybrid invasive approach. For Guo (2013) and Paireder (2018), the data was extracted using WebPlotDigitizer.

In total, there were 49 events (17%) in the intervention group and 60 events (21%) in the control group. This resulted in a relative risk of 0.80 (95% CI; 0.57 to 1.13) (figure 1). This difference is not clinically relevant.

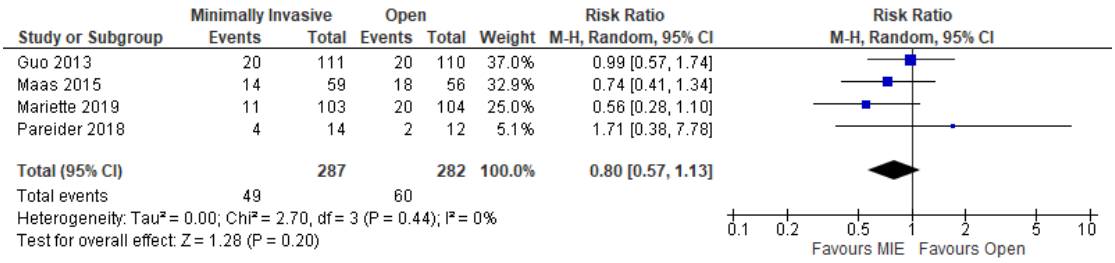

Figure 1. One-year survival

Minimally invasive versus open

Two studies used a minimally invasive approach (Guo, 2013; Maas, 2015). In total, there were 34 events in 170 patients in the intervention group and 38 events in the 166 patients in the control group (.

Hybrid versus open

Two studies used a minimally invasive approach (Paireder, 2018; Mariette, 2019). In total, there were 15 events in 117 patients in the intervention group and 22 events in the 116 patients in the control group.

Three-year survival

Four studies reported the overall survival after three years (Guo, 2013; Straatman, 2017; Paireder, 2018; Mariette, 2019). Guo (2013) and Straatman (2017) both used a totally minimally invasive approach, whereas Paireder (2018) and Mariette (2019) both used a hybrid invasive approach. For Guo (2013), Straatman (2017), and Paireder (2018), the data was extracted using WebPlotDigitizer. Straatman (2017) reported two different populations

and, in concurrence with the data from Maas (2015), the full responder data was used for this analysis. In total, there were 113 events (39%) in the intervention group and 129 events (45%) in the control group. This resulted in a relative risk of 0.88 (95% CI; 0.63 to 1.02), which is a clinically relevant difference.

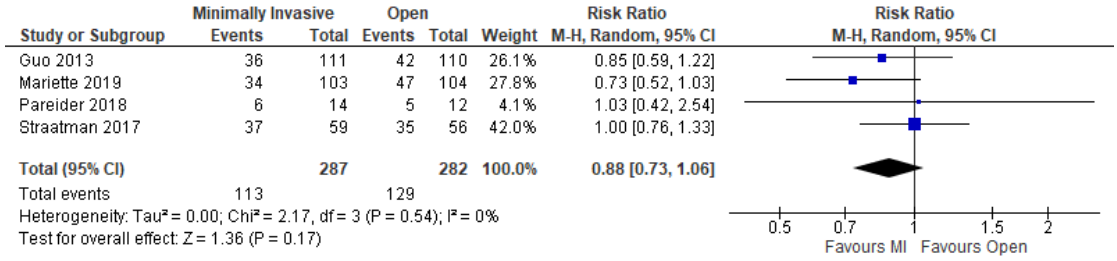

Figure 2. Three-year survival

Minimally invasive versus open
Two studies used a minimally invasive approach (Guo, 2013; Straatman, 2017). In total, there were 73 events in 170 patients in the intervention group and 77 events in the 166 patients in the control group.

Hybrid versus open
Two studies used a minimally invasive approach (Paireder, 2018; Mariette, 2019). In total, there were 40 events in 117 patients in the intervention group and 52 events in the 116 patients in the control group.

Five-year survival
Two studies reported the overall survival after five years (Paireder, 2018; Nuytens, 2021). Both studies used a hybrid invasive approach. In the study of Paireder (2018), there were 7 events (50%) in the intervention group, compared to 5 events (42%) in the control group. In the study of Nuytens (2021), there were 42 events (41%) in the intervention group compared to 55 events (53%) in the control group. This results in a total number of 49 events (42%) in 117 patients in the intervention group compared to 60 events in the control group (52%). This difference is clinically relevant.

Complications
Complications were split up in three categories: anastomotic leakage, cardiac complications, and pulmonary complications. All individual cardiac and pulmonary complications reported in the studies were added to these two main groups.

Anastomotic leakage
Six studies reported on anastomotic leakage (Biere, 2012; Guo, 2013; Ma, 2018; Paireder, 2018; Mariette, 2019; Van der Sluis, 2019). In total, there were 38 events (10%) in the intervention group, compared to 32 events (7%) in the control group. This resulted in a relative risk ratio of 1.29 (95% CI; 0.83 to 2.02). This is not clinically relevant.

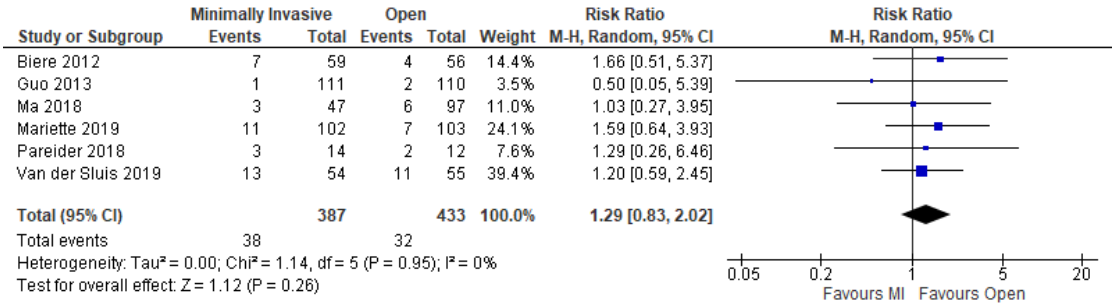

Figure 3. Anastomotic leakage – minimally invasive and hybrid versus open

Minimally invasive versus open

Four studies used a minimally invasive approach (Biere, 2012; Guo, 2013; Ma, 2018; Van der Sluis, 2019). In total, there were 24 events (9%) in the intervention group and 23 events (7%) in the control group. This resulted in a relative risk ratio of 1.20 (95%CI; 0.70 to 2.06) which is not clinically relevant.

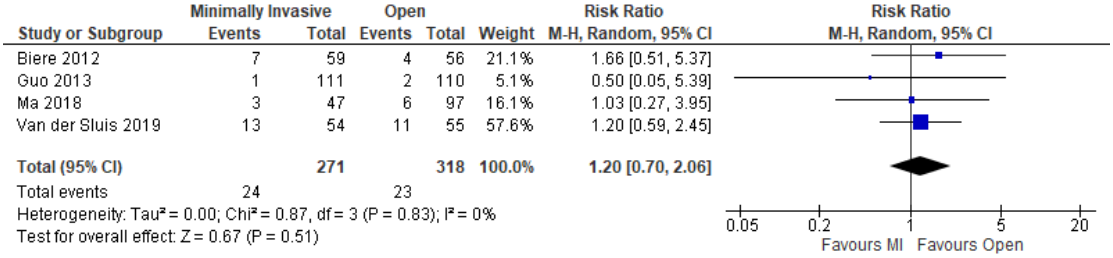

Figure 4. Anastomotic leakage - totally minimally invasive only versus open

Hybrid versus open

Two studies used a minimally invasive approach (Paireder, 2018; Mariette, 2019). In total, there were 14 events (12%) in the intervention group and 9 events (7%) in the control group. This is clinically relevant.

Cardiac complications

Three studies reported on cardiac complications (Ma, 2018; Mariette, 2019; Van der Sluis, 2019). In total, there were 29 events (14%) in the intervention group, compared to 52 events (20%) in the control group. This resulted in a relative risk ratio of 0.64 (95% CI; 0.42 to 0.98), which is a clinically relevant difference in favor of minimally invasive surgery.

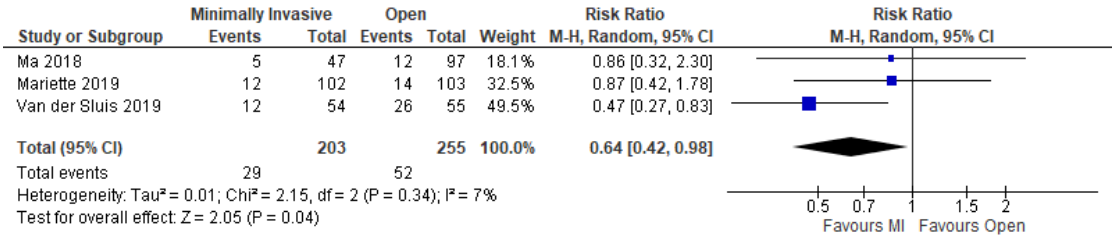

Figure 5. Cardiac complications – minimally invasive and hybrid versus open

Minimally invasive versus open

Ma (2018) and Van der Sluis (2019) used a totally minimally invasive approach, where Van der Sluis' was a robot-assisted trial. In total, there were 17 events (17%) in the intervention group and 38 events (25%) in the control group. This is clinically relevant.

Hybrid versus open
Mariette (2019) used a hybrid minimally invasive approach. There were 12 events (12%) in the intervention group and 14 events (14%) in the control group. This difference is not clinically relevant.

Pulmonary complications
Six studies reported on anastomotic leakage (Biere, 2012; Guo, 2013; Ma, 2018; Paireder, 2018; Mariette, 2019; Van der Sluis, 2019). In total, there were 62 events in 387 patients (16%) in the intervention group, compared to 123 events in the 433 patients (28%) in the control group. This resulted in a relative risk ratio of 0.68 (95% CI; 0.49 to 0.94), which is a clinically relevant difference in favor of minimally invasive surgery.

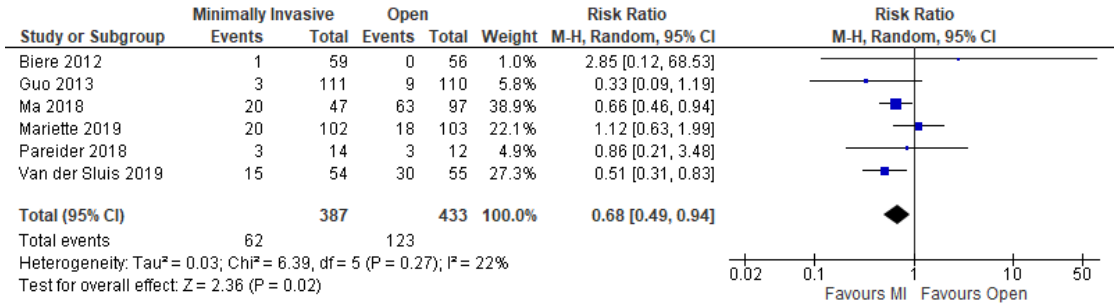

Figure 6. Pulmonary complications - minimally invasive and hybrid versus open

Minimally invasive versus open
Four studies used a minimally invasive approach (Biere, 2012; Guo, 2013; Ma, 2018; Van der Sluis, 2019). In total, there were 39 events in 271 patients (14%) in the intervention group and 102 events in the 318 patients (32%) in the control group. This difference is clinically relevant.

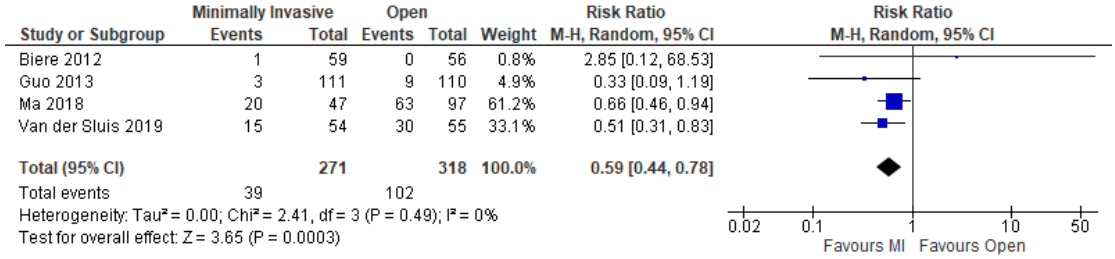

Figure 7. Pulmonary complications - totally minimally invasive only versus open

Hybrid versus open
Two studies used a minimally invasive approach (Paireder, 2018; Mariette, 2019). In total, there were 23 events in 116 patients (20%) in the intervention group and 21 events in the 115 patients (18%) in the control group. This difference is not clinically relevant.

The study of Wan (2020) reported overall complications. Nine complications (15%) were reported in the intervention group and 28 (46.7%) in the control group. This difference is clinically relevant.

Quality of life
Four studies reported quality of life (Biere, 2012; Van der Sluis, 2019; Song, 2021; Wan, 2020). All studies used a minimally invasive approach, where Van der Sluis' (2019) was robot-assisted.

Biere (2012) reported the physical and mental component summary score of the SF-36, the EORTC C30 Global health score, and the OES 18 Talking and Pain scores six weeks post-surgery. Van der Sluis reported the health-related quality of life and the physical functioning six weeks post-surgery. Song (2021) reported quality of life using the Quality of Life Questionnaire-Lung which includes five domains. A higher score represents a better quality of life. Wan (2020) reported quality of live using the EORTC C30 Global health score.

For the SF-36 and the C30 questionnaires, a higher value means a better quality of life; for the OES18, a lower value means a better quality of life. In Biere (2012), the intervention group consisted of 59 patients and the control group of 56 patients. In Van der Sluis (2019), the intervention group consisted of 31 patients and the control group of 33 patients.

The average physical component summary score of the SF-36 as used in Biere (2012) for the intervention group was 42 (95% CI; 39 to 46) compared to the control group which scored 36 (95% CI; 34 to 39). The average mental component of the SF-36 for the intervention group was 46 (95% CI; 41 to 50) compared to the control group which scored 45 (95% CI; 40 to 50). These differences are not clinically relevant.

For the talking section of the OES 18 in Biere (2012), the intervention group scores on average 18 (95% CI; 10 to 26) compared to the control group which scores 37 (95% CI; 25 to 49). For the pain section of the OES 18, the intervention group scores on average 8 (95% CI; 5 to 11) compared to the control group which scores 19 (95% CI; 13 to 26). These differences are clinically relevant.

For the C30 Global health score in Biere (2012), the intervention group scores on average 61 (95% CI; 56 to 67) compared to the control group which scores on average 51 (95% CI; 45 to 58). This difference is clinically relevant.

For the C30 Global health score in Van der Sluis (2019), the intervention group scores on average 68.7 (95% CI; 51.5 to 75.9) compared to the control group which scores on average 57.6 (95% CI; 50.6 to 64.6). This difference is not clinically relevant.

The physical functioning score in the intervention group was on average 69.3 (95% CI; 61.6 to 76.9) and in the control group 58.6 (95% CI; 51.1 to 66.0). This difference is clinically relevant.

Song (2021) reported QOL score on the domain ‘role function’ of 61.56 (2.01 SD) in the intervention group and 50.34 (2.12 SD) in the control group. Regarding the domain ‘emotional functioning’ mean score in the intervention group was 61.71 (2.12 SD) and in the control group 49.80 (2.03). Mean score on the domain ‘physical function’ was 60.88 (2.07 SD) in the intervention group and 51.36 (2.12 SD) in the control group. Mean score on the domain ‘cognitive function’ in the intervention group was 63.57 (2.91 SD) and 50.22 (2.76) in the control group. Regarding the final domain ‘social function’ mean score in the intervention group was 60.16 (2.05 SD) and 51.41 (2.35 SD) in the control group. These differences are clinically relevant.

Wan (2020) reported mean C30 Gobal health score of 88.04 (18.64 SD) in the intervention group and 80.78 (15.76 SD) in the control group. This difference is not clinically relevant.

Pain
Three studies reported pain (Biere, 2012; Ma, 2018; Van der Sluis, 2019). Biere (2012) and Van der Sluis (2019) both uses the Visual Analog Scale (VAS), whereas Ma (2018) used the Numerical Rating Scale (NRS). All three studies used a totally minimally invasive approach, where Van der Sluis' was robot-assisted.

Biere (2012) reported the mean VAS ten days post-operation. The intervention group of 56 patients had a mean VAS score of 2 (SD 2) compared to the 59 patients in the control group who had a mean VAS score of 3 (SD 2). This difference is clinically relevant.

Van der Sluis (2019) also used the VAS, but they reported the mean average scores of the first fourteen days post-surgery. The intervention group of 54 patients had a mean VAS score of 1.86 compared to the 55 patients in the control group who had a mean VAS score of 2.62. Ma (2018) reported the average NRS score of the first seven days post-surgery. The intervention group of 72 patients reported an NRS score of 1.88 (SD 0.54), compared to the control group of 72 patients who reported an NRS score of 2.16 (SD 0.58). These differences are not clinically relevant.

Time to recovery
Van der Sluis (2019) was the only study that reported on the time to recovery, which was the median day that patients were functionally recovered. This study investigated a robot-assisted minimally invasive approach. In the 54 patients of the intervention group consisted of 54 patients and the control group of patients. The median number of days that patients were functionally recovered was 10 (IQR; 9 to 13) compared to the control group where the median number of days was 13 (IQR; 9 to 34). This difference is not clinically relevant.

Length of hospital stay
Three studies reported length of hospital stay (Biere, 2012; Guo, 2013; Song, 2021).

Biere (2012) reported median intensive care unit stay. Median stay in the intervention group was 1 day (range 0-50) and 1 day (range 0-106) in the control group. This difference is not clinically relevant.

Guo (2013) used a minimally invasive approach and consisted of 110 patients in the intervention group and 111 patients in the control group. The mean length of hospital stay in the intervention group was 9.6 days (SD 1.7) compared to the control group who were in the hospital for an average of 11.4 days (SD 2.3). We then calculated a mean difference which resulted in -1.80 (95% CI; -2.33 to -1.27), which is a clinically relevant difference in favor of minimally invasive surgery.

Song (2021) reported mean length of hospital stay. Mean length of stay in the intervention group was 14.82 days (2.33 SD) and in the control group 20.03 days (2.21 SD). The calculated mean difference is -5.21 (95%CI -6.01 to -4.40), which is clinically relevant in favor of minimally invasive surgery.

R0 resection margin
Three studies reported on R0 resection margins (Biere, 2012; Mariette, 2019; Van der Sluis, 2019). Biere (2012) and Van der Sluis (2019) used a totally minimally invasive approach, where Van der Sluis' investigated a robot-assisted esophagectomy; Mariette (2019) investigated a hybrid minimally invasive approach. In total, an R0 resection was performed in 201 out of 215 patients (93%) in the intervention group, compared to 201 cases in the 214

patients (94%) in the control group. We then calculated a relative risk ratio which resulted in 1.18 (95% CI; 0.40 to 3.42) (figure 8). This difference is not clinically relevant.

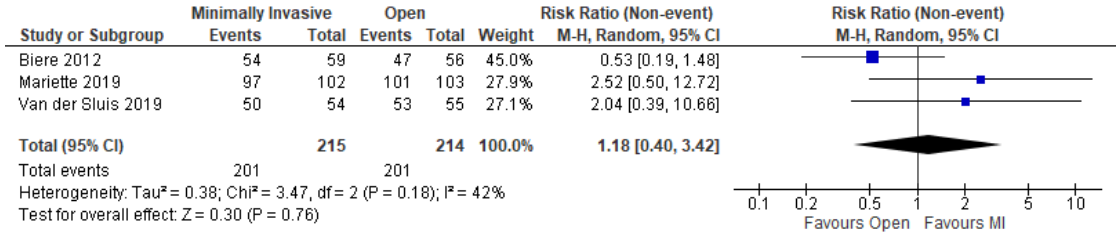

Figure 8+. R0 resection margin

Lymph node yield

Five studies reported lymph node yield (Biere, 2012; Guo, 2013; Mariette, 2019; Van der Sluis, 2019; Song, 2021). Biere (2012), Guo (2013), and Van der Sluis (2019) investigated a totally minimally invasive approach, where Van der Sluis' was robot-assisted. Mariette (2019) investigated a hybrid minimally invasive approach. Guo (2013) reported the mean number of resected lymph nodes, where Biere (2012), Mariette (2019), and Van der Sluis (2019) reported the median number of resected lymph nodes.

Guo (2013) reported a mean of 24.3 (SD 21.0) in the intervention group of 111 patients, compared to a mean of 19.2 (SD 12.5) in the control group of 110 patients, which is clinically relevant.

Biere (2012) reported a median of 20 (IQR; 3 to 44) in the intervention group of 59 patients, compared to 21 (IQR; 7 to 47) in the control group of 56 patients. Mariette (2019) reported a median of 21 (IQR; 7 to 76) in the intervention group of 102 patients, compared to 22 (IQR; 9 to 64) in the control group of 103 patients. These differences are not clinically relevant.

Van der Sluis reported a median of 27 (IQR; 17 to 33) in the intervention group of 54 patients, compared to 25 (IQR; 17 to 31) in the control group of 55 patients, which is clinically relevant.

Song (2021) reported mean lymph node dissections of 15.36 (2.21 SD) in the intervention group of 61 patients and 11.86 (3.01 SD) in the control group of 61 patients.

<u>Level of evidence of the literature</u>

Critical outcomes

Overall survival

The level of evidence regarding the outcome measure **overall survival** was downgraded by two levels to Low GRADE because of study limitations (risk of bias, -1) and number of included patients (imprecision, -1).

Anastomotic leakage

The level of evidence regarding the outcome measure **anastomotic leakage** was downgraded by one level to Moderate GRADE because of number of included patients (imprecision, -1).

Cardiac complications

The level of evidence regarding the outcome measure **cardiac complications** was downgraded by one level to Moderate GRADE because of number of included patients (imprecision, -1).

Pulmonary complications
The level of evidence regarding the outcome measure **pulmonary complications** was downgraded by one level to Moderate GRADE because of number of included patients (imprecision, -1).

Quality of life
The level of evidence regarding the outcome measure **quality of life** was downgraded by two levels to Low GRADE because of study limitations (risk of bias, -2).

Important outcomes
Pain
The level of evidence regarding the outcome measure **pain** was downgraded by two levels to Low GRADE because of study limitations (risk of bias, -1) and number of included patients (imprecision, -1).

Time to recovery
The level of evidence regarding the outcome measure **time to recovery** was downgraded by three levels to Very Low GRADE because of study limitations (risk of bias, -1) and number of included patients (imprecision, -2).

Length of hospital stay
The level of evidence regarding the outcome measure **length of hospital stay** was downgraded by three levels to Very Low GRADE because of study limitations (risk of bias, -1), applicability (bias due to indirectness, -1) and number of included patients (imprecision, -1).

R0 resection margin
The level of evidence regarding the outcome measure **R0 resection margin** was downgraded by two levels to Low GRADE because of conflicting results (inconsistency, -1) and number of included patients (imprecision, -1).

Lymph node yield
The level of evidence regarding the outcome measure **lymph node yield** was downgraded by three levels to Very Low GRADE because of study limitations (risk of bias, -1), conflicting results (inconsistency, -1) and number of included patients (imprecision, -1).

Conclusions
Critical

Low GRADE	Minimally invasive esophagectomy may increase **overall survival** when compared with open esophagectomy in patients with esophageal cancer. *Source: Guo, 2013; Maas, 2015; Mariette, 2019; Nuytens, 2021; Paireder, 2018; Straatman, 2017*

Moderate GRADE	Minimally invasive esophagectomy probably results in little to no difference in **anastomotic leakage** when compared with open esophagectomy in patients with esophageal cancer. *Source: Biere, 2012; Guo, 2013; Ma, 2018; Mariette, 2019; Paireder, 2018; Van der Sluis, 2019*

Moderate GRADE	Minimally invasive esophagectomy probably reduces **cardiac complications** when compared with open esophagectomy in patients with esophageal cancer. *Source: Biere, 2012; Guo, 2013; Ma, 2018; Mariette, 2019; Paireder, 2018; Van der Sluis, 2019*

Moderate GRADE	Minimally invasive esophagectomy probably reduces **pulmonary complications** when compared with open esophagectomy in patients with esophageal cancer. *Source: Biere, 2012; Guo, 2013; Ma, 2018; Mariette, 2019; Paireder, 2018; Van der Sluis, 2019*

Low GRADE	Minimally invasive esophagectomy may increase **quality of life** when compared with open esophagectomy in patients with esophageal cancer. *Source: Biere, 2012; Van der Sluis, 2019; Song, 2021; Wan, 2020*

Important

Low GRADE	Minimally invasive esophagectomy may result in little to no difference regarding **pain** when compared with open esophagectomy in patients with esophageal cancer. *Source: Biere, 2012; Ma, 2018; Van der Sluis, 2019*

Very low GRADE	The evidence is very uncertain about the effect of minimally invasive esophagectomy on **time to recovery** when compared with open esophagectomy in patients with esophageal cancer. *Source: Van der Sluis, 2019*

Very low GRADE	The evidence is very uncertain about the effect of minimally invasive esophagectomy on the **length of hospital stay** when compared with open esophagectomy in patients with esophageal cancer. *Source: Biere, 2012; Guo, 2013; Song, 2021*

Low GRADE	Minimally invasive esophagectomy may result in little to no difference in **R0 resection margin** when compared with open esophagectomy in patients with esophageal cancer. *Source: Biere, 2012; Mariette, 2019; Van der Sluis, 2019*

Very low GRADE	The evidence is very uncertain about the effect of minimally invasive esophagectomy on **lymph node yield** when compared with open esophagectomy in patients with esophageal cancer. *Source: Biere, 2012; Guo, 2013; Mariette, 2019; Van der Sluis, 2019*

Overwegingen – van bewijs naar aanbeveling

Voor- en nadelen van de interventie en de kwaliteit van het bewijs

Er is literatuuronderzoek gedaan naar de rol van minimaal invasieve chirurgie (MIC) als behandeling van patiënten met slokdarmkanker, waarbij nog specifiek onderscheid werd gemaakt voor volledig MIC en hybride MIC.

Er lijkt een effect te zijn in het voordeel van MIC op overall survival. Dit effect was waarneembaar één, drie en vijf jaar na de operatie, maar vanwege de imprecisie rond deze data, tezamen met een risico op bias, is de bewijskracht voor deze bevinding laag. Bij het beschouwen van de onderverdeling tussen volledig minimaal invasief en hybride benaderingen lijkt het verschil vooral te wijten aan het lagere aantal gebeurtenissen in de hybride benadering, maar er is onvoldoende data om hieruit een definitieve conclusie te trekken.

De complicaties zijn onderverdeeld in een drietal groepen: lekkage anastomose, cardiale complicaties en pulmonale complicaties. Er werd geen duidelijk klinisch relevant voordeel gevonden voor lekkage van de anastomose, behalve voor hybride versus open benadering. Bij de open benadering was er minder sprake van lekkage dan bij de hybride benadering.

Met betrekking tot de cardiale en pulmonale complicaties is er een klinisch relevant voordeel voor minimaal invasieve chirurgie, met uitzondering van de vergelijking tussen de hybride versus open benadering. Over de hele breedte genomen kan dus niet worden bepaald welke van de twee operatieve benaderingen tot minder complicaties leidt, omdat de bewijskracht voor deze bevindingen laag zijn.

Kwaliteit van leven werd in minder artikelen gerapporteerd en ook alleen maar in studies die volledig MIC hebben toegepast. In beide global health scores van de C30 vragenlijst, het fysiek functioneren van de C30 vragenlijst en de praten en pijn subdomeinen van de OES18 vragenlijst werd een klinisch relevant verschil in het voordeel van MIC gezien; de fysiek en mentale domeinen van de SF-36 vragenlijst lieten geen klinisch relevant verschil zien. Er lijkt een voordeel voor een (volledig) MIC te zijn op de kwaliteit van leven, maar de bewijskracht hiervan is laag. Er is niets bekend over hybride MIC en kwaliteit van leven.

Waarden en voorkeuren van patiënten (en evt. hun verzorgers)

Voor patiënten zou een minimaal invasieve benadering voordeel kunnen hebben, mits deze wordt uitgevoerd in een centrum met deze expertise. Patiënten hebben dan minder grote littekens, wat ook op de lange termijn voordelen kan hebben, aangezien er minder littekenbreuken voorkomen na minimaal invasieve chirurgie. Ook is het cosmetisch resultaat fraaier. Het chirurgisch trauma is kleiner, wat zou kunnen resulteren in een minder diepe dip in de immuunrespons na chirurgie.

Kosten (middelenbeslag)

Ondanks dat de primaire kosten voor minimaal invasieve chirurgie hoger zijn dan die voor open chirurgie, blijkt uit enkele studies dat de IC-opnameduur en ook de opnameduur korter zijn na minimaal invasieve chirurgie (link). Ook zijn pulmonale en cardiale complicaties minder, wat ook tot lagere kosten leidt. Dit kan de hogere procedure kosten weer opheffen (Lee, 2013).

Aanvaardbaarheid, haalbaarheid en implementatie

De meeste Nederlandse centra voeren reeds minimaal invasieve oesophagusresecties uit, waarbij momenteel > 80% minimaal invasief wordt geopereerd (DUCA registratie). Er

worden dan ook geen belemmerende factoren gevonden voor aanvaardbaarheid, haalbaarheid en implementatie.

Aanbeveling

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies

1. De belangrijkste voordelen die worden gevonden voor minimaal invasieve vergeleken met open oesophagusresectie zijn het minder voorkomen van postoperatieve pulmonale en cardiale complicaties met een moderate grade of evidence. Het voorkomen van naadlekkages, de lymfeklieropbrengst en het R0 resectie percentage lijken vergelijkbaar, ook al is de level of evidence laag. Er wordt ook mogelijk een overlevingsvoordeel gezien en een betere kwaliteit van leven, echter met een low grade of evidence.
2. Minimaal invasieve oesophaguschirurgie wordt reeds in de meeste Nederlandse centra toegepast. Er is echter, gezien de moderate tot very low grades of evidence, geen reden om geen open chirurgie aan te bevelen. Het gaat hierbij vooral om de lokale expertise. Het belangrijkste doel van de operatie is een radicale resectie met adequate lymphadenectomie. Indien echter de expertise voor minimaal invasieve chirurgie aanwezig is, kan dit voordelen hebben voor de patient, met minder complicaties en mogelijk een overlevingsvoordeel en betere kwaliteit van leven.

Een minimaal invasieve oesophagusresectie wordt geadviseerd wanneer de expertise daarvoor aanwezig is, omdat dit kan leiden tot minder pulmonale en cardiale complicaties en mogelijk een betere kwaliteit van leven en overleving

Verricht een minimaal invasieve oesofagus resectie indien expertise hiervoor aanwezig is.

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Bijlagen bij module 'Minimaal invasieve chirurgie'

Evidence tables

Research question: What is the effect of minimally invasive surgery compared with open surgery on complications, pain, time to recovery, length of hospital stay, R0 resection, lymph node yield, quality of life, and overall survival in patients undergoing esophagectomy for esophageal carcinoma?

Study reference	Study characteristics	Patient characteristics [2]	Intervention (I)	Comparison / control	Follow-up	Outcome measures and effect size	Comments
Nuytens, 2021	Type of study: RCT Setting and country: Thirteen hospitals in France Funding: The Multicentre Randomized Controlled Phase III Trial was funded by the PHRC. This follow-up study received no additional funding. Conflict of interest: Dr Mabrut reported receiving grants from the National Cancer Research Project during the conduct of the study. Dr Piessen reported receiving grants from Institut National du Cancer during the conduct of the study; nonfinancial support in the past from Medtronic;	Inclusion criteria: - Clinical stage I-III (cT1-T3, N1-2, M0) tumors - Receipt or nonreceipt of neoadjuvant radiotherapy, chemotherapy or a combination of both - World Health Organization performance- status score of 0, 1 or 2 and the ability to undergo the proposed surgical procedure. - Ability to provide a written informed consent - Ability to attend to the scheduled follow-up consultations Exclusion criteria: - Partial pressure of arterial oxygen of ≤60 mm Hg in ambient air - Partial pressure of arterial carbon dioxide of ≥ 45 mmHg - Forced expiratory volume in 1 second ≤1000 ml - Liver cirrhosis - Myocardial infarction or progressive coronary artery disease - Peripheral arterial occlusive diseases (Leriche-Fontaine stage ≥ II) - Weight loss of > 15 % in the 6 months prior to cancer diagnosis - Presence of another synchronous malignancy - Simultaneous inclusion in any other experimental treatment protocol.	Hybrid minimally invasive esophagectomy	Open esophagectomy	Length of follow-up: Median 58.2 months (95% CI; 56.5 to 63.8) Loss-to-follow-up: Intervention: N=1 (1%) Reasons: Excluded from analysis of intraoperative and postoperative morbidity because of no resection Control: N=1 (1%) Reasons: Excluded from analysis of intraoperative and postoperative morbidity because of no resection Incomplete outcome data: Intervention: 0 Control: 0	*Overall survival after 5 years (hazard ratio with CI)* 0.71 (95% CI; 0.48 to 1.06)	

	and personal fees from Bristol-Myers Squibb, Stryker, and Nestle as well as personal fees in the past from Amgen, Hoffmann-La Roche, and MSD outside the submitted work. No other disclosures were reported.	- Histological subtype of esophageal cancer other than squamous-cell carcinoma or adenocarcinoma - Tumor located at the level of the pharyngoesophageal junction, the cervical oesophagus, the upper third of the oesophagus or the gastroesophageal junction (Siewert type II and III) - Distant metastases including peritoneal carcinomatosis, metastasis to supraclavicular and coeliac lymph nodes - Recurrent laryngeal nerve palsy or tumor involvement into adjacent mediastinal structures - Patients not eligible for laparoscopy - Previous history of a supra-umbilical laparotomy <u>N total at baseline</u>: Intervention: 103 Control: 104 <u>Important prognostic factors</u>[2]: Median age (range): I: 59 (23-75) C: 62 (41-78) Sex: I: 85% M / 15% F C: 84% M / 16% F Groups comparable at baseline? Yes					
Song, 2021	Type of study: RCT Setting and country:	<u>Inclusion criteria</u>1) Patients diagnosed with EC by pathological diagnosis and met the surgical criteria; (2) Patients with pathological stages i-IIb; and (3) Patients aged 45-75 years.	Minimally invasive esophagectomy	Open esophagectomy	<u>Length of follow-up</u>: <u>Loss-to-follow-up</u>:	*Length of hospital stay Mean (SD)* I: 14.82 (2.33)	

	Hospital, China Funding: Not reported Conflicts of interest: None	<u>Exclusion criteria:</u> 1) Patients with malignant tumors other than EC; (2) Patients with severe hepatorenal dysfunction or surgical contraindications; (3) Patients who underwent chemoradiotherapy before surgery; (4) Patients with lymph node metastasis, communication impairment or cognitive dysfunction; and (5) Patients who could not cooperate with the study. <u>N total at baseline</u>: Intervention: 61 Control: 61 <u>Important prognostic factors</u>[2]: age ± SD: 62.4 ± 7.4 Sex: I: 57% M/ 43% F C: 54% M/ 46% F Groups comparable at baseline? Yes			Intervention: 0 Control: 0 <u>Incomplete outcome data</u>: Intervention: 0 Control: 0	C: 20.03 (2.21) *Quality of life (Mean (SD)* *Intervention* Role function: 61.56 (2.01) Emotional function: 61.71 (2.12) Physical function: 60.88 (2.07) Cognitive function: 63.57 (2.91) Social function: 60.16 (2.05) *Control* Role function: 50.34 (2.12) Emotional function: 49.80 (2.03) Physical function: 51.36 (2.11) Cognitive function: 50.22 (2.76) Social function: 51.41 (2.35) *Lymph node dissections* *Mean (SD)* I: 15.36 (2.21)	

						C: 11.86 (3.01)	
Wan, 2020	Type of study: RCT Setting and country: Hospital, China Funding: Not reported Conflicts of interest: None	<u>Inclusion criteria:</u> 1) Confirmed by pathological biopsy. (2) No contraindication to the methods used in this study. (3) All patients underwent thoracoscopic esophagectomy alone. (4) With complete clinical data. (5) No cognitive impairment. (6) TNM clinical stage I-III. (7) No abnormal coagulation. <u>Exclusion criteria:</u> 1) Withdrawal from the study halfway. (2) Those who cannot follow the doctor's instructions and do not cooperate with the treatment. (3) Heart and lung function intolerant. (4) Those with other malignant tumors. (5) Immune system disorders. (6) Patients who have been treated with chemotherapy and radiotherapy before operation. <u>N total at baseline</u>: Intervention: 60 Control: 60 <u>Important prognostic factors</u>: Age ± SD: I: 50.2 ± 3.7 C: 50.3 ± 3.6 Sex: I: 57% % M/ 43% F C: 58% M / 42% F Groups comparable at baseline? Yes	Minimally invasive esophagectomy	Open esophagectomy	<u>Length of follow-up</u>: 7 days <u>Loss-to-follow-up</u>: Intervention: 0 Control: 0 <u>Incomplete outcome data</u>: Intervention: 0 Control: 0	*Quality of life (EORTC QLQ-C30)* *Mean (SD)* I: 88.04 (18.64) C: 80.78 (15.76) *Complications (N)* I: 9 (15%) C: 28 (46.7%)	

Risk of bias table for intervention studies (randomized controlled trials; based on Cochrane risk of bias tool and suggestions by the CLARITY Group at McMaster University)

Research question: **Research question: What is the effect of minimally invasive surgery compared with open surgery in patients undergoing esophagectomy for esophageal carcinoma?**

Study reference (first author, publication year)	**Was the allocation sequence adequately generated?** Definitely yes Probably yes Probably no Definitely no	**Was the allocation adequately concealed?** Definitely yes Probably yes Probably no Definitely no	**Blinding: Was knowledge of the allocated interventions adequately prevented?** **Were patients blinded?** **Were healthcare providers blinded?** **Were data collectors blinded?** **Were outcome assessors blinded?** **Were data analysts blinded?** Definitely yes Probably yes Probably no Definitely no	**Was loss to follow-up (missing outcome data) infrequent?** Definitely yes Probably yes Probably no Definitely no	**Are reports of the study free of selective outcome reporting?** Definitely yes Probably yes Probably no Definitely no	**Was the study apparently free of other problems that could put it at a risk of bias?** Definitely yes Probably yes Probably no Definitely no	**Overall risk of bias** **If applicable/necessary, per outcome measure** **LOW** **Some concerns** **HIGH**
Nuytens, 2021	Definitely yes Reason: Randomization was performed centrally by means of a stratified-field	Probably yes Reason: Prepared numbers envelopes were used	Definitely no Reason: Surgeons and patients could not be blinded due to the nature of the intervention; other personnel not reported	Definitely yes Reason: No loss to follow-up	Definitely yes Reason: All relevant outcomes were reported	Definitely yes Reason: No other problems noted	Some concerns

	block randomization (blocks of 4) for each participating center.						
Song, 2022	Probably no Reason: Study only mentions 'randomly divided'	Definitely no Reason: not reported	Definitely no Reason: Surgeons and patients could not be blinded due to the nature of the intervention; other personnel not reported	Definitely yes Reason: No loss to follow-up	Definitely yes Reason: All relevant outcomes were reported	Definitely yes Reason: No other problems noted	**HIGH**
Wan, 2020	Probably no Reason: Study only mentions 'digital random table'	Definitely no Reason: not reported	Definitely no Reason: Surgeons and patients could not be blinded due to the nature of the intervention; other personnel not reported	Definitely yes Reason: No loss to follow-up	Definitely yes Reason: All relevant outcomes were reported	Definitely yes Reason: No other problems noted	**HIGH**

Table of excluded studies

Reference	Reason for exclusion
Booka E, Tsubosa Y, Haneda R, Ishii K. Ability of Laparoscopic Gastric Mobilization to Prevent Pulmonary Complications After Open Thoracotomy or Thoracoscopic Esophagectomy for Esophageal Cancer: A Systematic Review and Meta-analysis. World J Surg. 2020 Mar;44(3):980-989. doi: 10.1007/s00268-019-05272-9. PMID: 31722075.	Wrong comparison
Dantoc M, Cox MR, Eslick GD. Evidence to support the use of minimally invasive esophagectomy for esophageal cancer: a meta-analysis. Arch Surg. 2012 Aug;147(8):768-76. doi: 10.1001/archsurg.2012.1326. PMID: 22911078.	Systematic review only includes retrospective case-control studies
Huang L, Onaitis M. Minimally invasive and robotic Ivor Lewis esophagectomy. J Thorac Dis. 2014 May;6 Suppl 3(Suppl 3):S314-21. doi: 10.3978/j.issn.2072-1439.2014.04.32. PMID: 24876936; PMCID: PMC4037415.	Narrative review
Khan O, Nizar S, Vasilikostas G, Wan A. Minimally invasive versus open oesophagectomy for patients with oesophageal cancer: a multicentre, open-label, randomised controlled trial. J Thorac Dis. 2012 Oct;4(5):465-6. doi: 10.3978/j.issn.2072-1439.2012.08.16. PMID: 23050109; PMCID: PMC3461074.	Wrong design
Manigrasso M, Vertaldi S, Marello A, Antoniou SA, Francis NK, De Palma GD, Milone M. Robotic Esophagectomy. A Systematic Review with Meta-Analysis of Clinical Outcomes. J Pers Med. 2021 Jul 6;11(7):640. doi: 10.3390/jpm11070640. PMID: 34357107; PMCID: PMC8306060.	Wrong comparison: RAMIE versus OE or RAMIE versus Laparoscopic
Patel K, Askari A, Moorthy K. Long-term oncological outcomes following completely minimally invasive esophagectomy versus open esophagectomy. Dis Esophagus. 2020 Jun 15;33(6):doz113. doi: 10.1093/dote/doz113. PMID: 31950180.	No RCT's in SR
Ramjit SE, Ashley E, Donlon NE, Weiss A, Doyle F, Heskin L. Safety, efficacy, and cost-effectiveness of minimally invasive esophagectomies versus open esophagectomies: an umbrella review. Dis Esophagus. 2022 Dec 14;35(12):doac025. doi: 10.1093/dote/doac025. PMID: 35596955.	No data extraction from only RCT's possible
Siaw-Acheampong K, Kamarajah SK, Gujjuri R, Bundred JR, Singh P, Griffiths EA. Minimally invasive techniques for transthoracic oesophagectomy for oesophageal cancer: systematic review and network meta-analysis. BJS Open. 2020 Oct;4(5):787-803. doi: 10.1002/bjs5.50330. Epub 2020 Sep 7. PMID: 32894001; PMCID: PMC7528517.	Wrong comparisons: Open versus laparoscopic, open versus MIE, MIE versus laparoscopic
Sugimura K, Miyata H, Kanemura T, Takeoka T, Sugase T, Masuzawa T, Katsuyama S, Motoori M, Takeda Y, Murata K, Yano M. Patterns of Recurrence and Long-Term Survival of Minimally Invasive Esophagectomy Versus Open Esophagectomy for Locally Advanced Esophageal Cancer Treated with Neoadjuvant Chemotherapy: a Propensity Score-Matched Analysis. J Gastrointest Surg. 2023 Jun;27(6):1055-1065. doi: 10.1007/s11605-023-05615-x. Epub 2023 Feb 7. PMID: 36749557.	Wrong study design
Szakó L, Németh D, Farkas N, Kiss S, Dömötör RZ, Engh MA, Hegyi P, Eross B, Papp A. Network meta-analysis of randomized controlled trials on esophagectomies in esophageal cancer: The superiority of minimally invasive surgery. World J Gastroenterol. 2022 Aug 14;28(30):4201-4210. doi: 10.3748/wjg.v28.i30.4201. PMID: 36157121; PMCID: PMC9403425.	Includes comparisons that are not relevant to our PICO
Taioli E, Schwartz RM, Lieberman-Cribbin W, Moskowitz G, van Gerwen M, Flores R. Quality of Life after Open or Minimally Invasive Esophagectomy in Patients With Esophageal Cancer-A Systematic Review. Semin Thorac Cardiovasc Surg. 2017 Autumn;29(3):377-390. doi: 10.1053/j.semtcvs.2017.08.013. Epub 2017 Aug 24. PMID: 28939239.	No direct comparison between MIE and OE
Wang B, Zuo Z, Chen H, Qiu B, Du M, Gao Y. The comparison of thoracoscopic-laparoscopic esophagectomy and open esophagectomy: A meta-analysis. Indian J Cancer. 2017 Jan-Mar;54(1):115-119. doi: 10.4103/ijc.IJC_192_17. PMID: 29199673.	Does not meet quality SR criteria
Yibulayin W, Abulizi S, Lv H, Sun W. Minimally invasive oesophagectomy versus open esophagectomy for resectable esophageal cancer: a meta-analysis. World J Surg Oncol. 2016 Dec 8;14(1):304. doi: 10.1186/s12957-016-1062-7. PMID: 27927246; PMCID: PMC5143462.	No clear distinction between RCTs and observations studies in SR
Biere SS, van Berge Henegouwen MI, Bonavina L, Rosman C, Roig Garcia J, Gisbertz SS, van der Peet DL, Cuesta MA. Predictive factors for post-operative respiratory infections after esophagectomy for esophageal cancer: outcome of randomized trial. J Thorac Dis. 2017 Jul;9(Suppl 8):S861-S867. doi: 10.21037/jtd.2017.06.61. PMID: 28815084; PMCID: PMC5538980.	Wrong comparison; factors influencing risk of pneumonia or other complications

Cuesta MA, Biere SS, van Berge Henegouwen MI, van der Peet DL. Randomised trial, Minimally Invasive Oesophagectomy versus open oesophagectomy for patients with resectable oesophageal cancer. J Thorac Dis. 2012 Oct;4(5):462-4. doi: 10.3978/j.issn.2072-1439.2012.08.12. PMID: 23050108; PMCID: PMC3461077.	Narrative review
Wan J, Che Y, Kang N, Zhang R. Surgical Method, Postoperative Complications, and Gastrointestinal Motility of Thoraco-Laparoscopy 3-Field Esophagectomy in Treatment of Esophageal Cancer. Med Sci Monit. 2016 Jun 16;22:2056-65. doi: 10.12659/msm.895882. PMID: 27310399; PMCID: PMC4913812.	Wrong design: Retrospective study
Yang ZQ, Lu HX, Zhang JH, Wang J. Comparative study on long-term survival results between minimally invasive surgery and traditional resection for esophageal squamous cell carcinoma. Eur Rev Med Pharmacol Sci. 2016 Aug;20(16):3368-72. PMID: 27608894.	Probably no RCT (randomization unclear)
Yang J, Chen L, Ge K, Yang JL. Efficacy of hybrid minimally invasive esophagectomy vs open esophagectomy for esophageal cancer: A meta-analysis. World J Gastrointest Oncol. 2019 Nov 15;11(11):1081-1091. doi: 10.4251/wjgo.v11.i11.1081. PMID: 31798787; PMCID: PMC6883181.	Wrong comparison
Yu Y, Han Y. Clinical Effect and Postoperative Pain of Laparo-Thoracoscopic Esophagectomy in Patients with Esophageal Cancer. Evid Based Complement Alternat Med. 2022 Jun 26;2022:4507696. doi: 10.1155/2022/4507696. Retraction in: Evid Based Complement Alternat Med. 2023 Dec 6;2023:9790841. PMID: 35795286; PMCID: PMC9251098.	No/unclear randomization

Literature search strategy

Uitgangsvraag 3: Wat is de plaats van minimaal invasieve chirurgie ten opzichte van open chirurgie bij patiënten met een oesofaguscarcinoom?	
Database(s): Medline, Embase	Datum: 22-6-2023
Periode: >2011	

Zoekverantwoording

Ontdubbelen

Database	Aantallen treffers	Aantallen treffers na ontdubbelen
Medline 22 jun 2023	355	353
Embase 22 jun 2023	450	146
Totaal	805	499

Aantal SRs: 244; aantal RCT's: 255.

OVID/Medline 22 juni 2023
Ovid MEDLINE(R) ALL <1946 to June 21, 2023>

1	exp Esophageal Neoplasms/ or ((carcinoma* or neoplas* or adenoma* or adenocarcinoma* or tumor* or tumour* or cancer* or oncolog* or malignan* or carcinogen* or oncogen* or anticarcinogen* or squamous*) adj3 (oesophag* or esophag* or gastroesophag* or gastrooesophag* or oesogastr* or esogastr*)).ti,ab,kf.	**79323**
2	"Minimally Invasive Surgical Procedures"/ or exp Laparoscopy/ or Laparoscopes/ or (laparoscop* or (mini* adj2 invasive*) or (minimal* adj3 (surg* or procedure* or access or esophagectom* or oesophagectom*))).ti,ab,kf.	**263979**
3	1 and 2	**3619**
4	3 not ((Adolescent/ or Child/ or Infant/) not Adult/)	**3613**
5	4 not ((exp animals/ or exp models, animal/) not humans/)	**3595**
6	5 not (comment/ or editorial/ or letter/ or Case Reports/)	**3004**
7	limit 6 to yr="2011 -Current"	**2265**
8	(systematic-review.pt. or (meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data extraction" or "data source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data	**640341**

	synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.)) not (comment/ or editorial/ or letter/ or ((exp animals/ or exp models, animal/) not humans/))	
9	7 and 8	**155**
10	exp randomized controlled trial/ or random*.ti,ab,kf. or ((pragmatic or practical) adj clinical trial*).ti,ab,kf. or ((non-inferiority or noninferiority or superiority or equivalence) adj3 trial*).ti,ab,kf.	**1561064**
11	(7 and 10) not 9	**200**

Embase.com 22 juni 2023

No.	Query	Results
#11	#7 AND #10 NOT #9	**220**
#10	'randomized controlled-'trial'/exp OR random*:ti,ab,kw OR (((pragmatic OR practical) NEAR/1 'clinical trial*'):ti,ab,kw) OR ((('non inferiority' OR noninferiority OR superiority OR equivalence) NEAR/3 trial*):ti,ab,kw)	**2061670**
#9	#7 AND #8	**230**
#8	('meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab) NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp) NOT ('conference abstract'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it)	**714935**
#7	#5 NOT ('conference abstract'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'case report'/exp) AND [2011-2023]/py	**2676**
#6	#5 NOT ('conference abstract'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'case report'/exp)	**3624**
#5	#4 NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	**6356**
#4	#3 NOT (('adolescent'/exp OR 'child'/exp) NOT ('adult'/exp OR 'aged'/exp OR 'middle aged'/exp))	**6391**
#3	#1 AND #2	**6408**
#2	'minimally invasive procedure'/exp OR 'laparoscopy'/exp OR 'laparoscope'/exp OR laparoscop*:ti,ab,kw OR ((mini* NEAR/2 invasive*):ti,ab,kw) OR ((minimal* NEAR/3 (surg* OR procedure* OR access OR esophagectom* OR oesophagectom*)):ti,ab,kw)	**429412**
#1	'esophagus tumor'/exp OR (((oesophag* OR esophag* OR gastroesophag* OR gastrooesophag* OR oesogastr* OR esogastr*) NEAR/3 (carcinoma* OR neoplas* OR tumour* OR adenoma* OR adenocarcinoma* OR tumor* OR cancer* OR oncolog* OR malignan* OR carcinogen* OR oncogen* OR anticarcinogen* OR squamous*)):ti,ab,kw)	**126627**

Module 2 Nacontrole na definitieve chemoradiatie

Uitgangsvraag
Wat is de optimale nacontrole voor patiënten met oesofaguscarcinoom na definitieve chemoradiatie?

Introduction
Definitive chemoradiation is a curative treatment modality that should be considered for patients with irresectable esophageal tumors or patients that are medically inoperable. However, recurrences after definitive chemoradiation are frequent. Selected patients may benefit from aggressive, curative-intent treatment in case of relapse after definitive chemoradiation. Currently, varying follow-up schedules are used and do or do not include imaging or endoscopy. This leads to insufficient national real-world data on the efficacy of definitive chemoradiation and may lead to too many or, in case of curative options, too little diagnostic procedures.

Search and select
A systematic review of the literature was performed to answer the following questions:

1. *What is the effect of (5-year) follow-up on overall survival, number of re-interventions, quality of life, locoregional recurrence and distant metastasis compared with no follow-up in patients with esophageal- or gastro-esophageal cancer after definitive chemoradiotherapy?*

P: patients with esophageal- or gastro-esophageal cancer after definitive chemoradiotherapy;
I: (5-year) follow-up with endoscopy, (FDG/PET) CT or MRI;
C: no follow-up;
O: overall survival, number of re-interventions, quality of life, (locoregional) recurrence, distant metastasis.

2. What are the recurrence rates or time to recurrences in patients with esophageal- or gastro-esophageal cancer after definitive chemoradiotherapy?

P: patients with esophageal- or gastro-esophageal cancer after definitive chemoradiotherapy;
O: (Locoregional) recurrence, time to recurrence.

Relevant outcome measures
The guideline development group considered overall survival, re-interventions and quality of life, as a critical outcome measure for decision making and locoregional recurrence, distant metastasis, recurrence rate and time to recurrence as important outcome measures for decision making.

A priori, the working group did not define the outcome measures listed above but used the definitions used in the studies.

The working group defined the following differences (per outcome measure) as minimal clinically (patient) important difference:
- Overall survival:
- Number of re-interventions: >5% absolute difference

- Quality of life: ≥ 10 points on the EORTC QLQ-C30 or a difference of a similar magnitude on other quality of life instruments
- (Locoregional) recurrence: >5% absolute difference
- Distant metastasis: >5% absolute difference
- Time to recurrence: >5% absolute difference

Search and select (Methods)
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until 27-05-2023. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 81 systematic reviews, 180 RCT's and 110 recurrence rate studies hits. Studies were selected based on the following criteria:
- The study population had to meet the criteria as defined in the PICO;
- The intervention and comparison had to be as defined in the PICO or reported at least one of the outcomes as defined in the PICO;
- Full text available;
- Articles written in English or Dutch.

47 studies were initially selected based on title and abstract screening. After reading the full text, 45 studies were excluded (see the table with reasons for exclusion under the tab Methods), and two studies were included.

Results
Two studies were included in the analysis of the literature. Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables.

Summary of literature
Description of studies
Du (2017) performed a systematic review including studies reporting response rate, survival, failure pattern and toxicity on the definitive concurrent chemoradiotherapy with elective node irradiation (ENI) in patients with esophageal cancer between 1990 and 2015. Studies were excluded if neoadjuvant or adjuvant chemoradiotherapy was combined with surgery, if there was palliative chemoradiotherapy, if radiotherapy was delivered by Co-60 or by unconventional fractions, if it was a phase I study if results of ENI and conventional radiotherapy were mixed or if there were other sites of cancer included.

In total, 22 studies were included. Regarding the scope of this summary and the outcomes, only data regarding patterns of failure was reported. Fifteen studies in the systematic review of Du (2017) reported patterns of failure (Cooper, 1999; Nishimura, 2009; Yamashita, 2011; Onozawa, 2009; Ishikura, 2003; Kato, 2013; Poplin, 1996; Roca, 1996; Jefford, 2002; Ishida, 1996; Liu, 2014; Morota, 2009; Ohtsu, 1999; Kodaira, 2006; Hironaka, 2003) with a total of 1163 patients.

Follow-up period in which patterns of failure should occur, were not reported by Du (2017).

Sudo (2018) performed a retrospective cohort study including patients with stage II or III esophageal squamous cell carcinoma who received definitive chemoradiotherapy.
Patients with a complete therapy response (CRT) (defined as the disappearance of all lesions as well as secondary changes associated with the tumors according to the Japanese classification of esophageal cancer, 10th edition), were under evaluation by CT and

esophagogastroduoscopy. These examinations were repeated every three to six months for at least five years after achieving CRT, until relapse or death.

In total, 204 patients received CRT with a median age of 65 years (range 42-81) and 83% was male. Of the included patients, 184 (90%) received 5-FU and cisplatin as chemotherapy during radiation treatment, 9 patients (4%) received 5-FU and nedaplatin, 9 patients (4%) received S-1 and cisplatin and two patients (1%) received docetaxel. Regarding radiation dose, 57 patients (28%) received 50.4 Gy and 147 patients (72%) received 60.0 Gy.

The median follow-up time was 75.7 months. Sudo (2018) reported locoregional relapses and annual odds of luminal relapse, regional relapse and new cancer found with esophagogastroduodenoscopy.

Results

Overall survival

None of the included studies reported overall survival.

Number of re-interventions

None of the included studies reported number of re-interventions.

Quality of life

None of the included studies reported quality of life.

(Locoregional) recurrence

The systematic review of **Du (2017)** reported local-regional recurrence and distant failure rate. The local-regional recurrence rates of individual studies in the review of Du (2017) are presented in table 1. The pooled local-regional recurrence rate is 21% (95%CI 16-26).

Table 1. Local-regional recurrence rates (Du, 2017)

Study	Local-regional recurrence rate (95%CI)
Cooper (1999) – Randomized group	13% (5-22)
Cooper (1999) – Non-randomized group	20% (11-30)
Nishimura (2009) – Arm B	13% (3-23)
Yamashita (2011)	16% (9-22)
Onozawa (2009)	11% (5-17)
Ishikura (2003)	11% (6-16)
Kato (2013)	27% (15-40)
Poplin (1996)	6% (-2-15)
Jefford (2002)	22% (5-39)
Roca (1996)	38% (25-51)
Ishida (1996)	18% (7-30)
Liu (2014)	37% (29-44)
Morota (2009)	17% (8-26)
Ohtsu (1999)	35% (22-48)
Kodaira (2006)	24% (7-41)
Hironaka (2003)	36% (23-49)

The distant failure rates of individual studies from the review of Du (2017) are presented in table 2. The pooled distant failure rate is 11% (95%CI 9-14).

Table 2. Distant failure rates (Du, 2017)

Study	Distant failure rate (95%CI)
Cooper (1999) – Randomized group	8% (1-15)
Cooper (1999) – Non-randomized group	16% (7-25)
Yamashita (2011)	10% (4-15)

Onozawa (2009)	9% (3-14)
Ishikura (2003)	9% (5-14)
Kato (2013)	16% (6-26)
Poplin (1996)	6% (-2-15)
Jefford (2002)	13% (-1-27)
Roca (1996)	16% (7-26)
Ishida (1996)	36% (22-51)
Liu (2014)	9% (5-13)
Morota (2009)	7% (1-13)
Ohtsu (1999)	17% (7-27)
Kodaira (2006)	24% (7-41)
Hironaka (2003)	8% (0-15)

The pooled distant failure rate and both local-regional recurrence plus distant failure rate is 7% (95%CI 4-11%).

Sudo (2018) reported luminal relapse, regional relapse and distant metastasis in the follow-up period with a median follow-up time of 75.7 months. Sudo (2018) reported luminal relapse in 28 patients (13.7%), regional relapse in 13 patients (6.4%) and distant metastases in 39 patients (19.1%). In 34 patients (7.8%) a new-found cancer was detected by the esophagogastroduodenoscopy.

Distant metastasis
None of the included studies reported distant metastasis.

Time to recurrence
Sudo (2018) reported the annual odds for developing luminal relapse, regional relapse and new-found cancer detected by the esophagogastroduodenoscopy, see table 3.

Table 3. Timing of relaps patterns and new-found cancer (Sudo, 2018)

		≤ 12 months	12-24 months	24-36 months	36-48 months	48-60 months	≥ 60 months	Total
Luminal relapse	Number (n)	20	3	3	1	0	1	28
	Annual odds	9.8%	2.1%	2.7%	1.1%	0%	3.6%	-
Regional relapse	Number (n)	6	7	0	0	0	0	13
	Annual odds	2.9%	4.8%	0%	0%	0%	0%	-
New-found cancer detected by esophagogastroduodenoscopy	Number (n)	7	6	5	3	7	6	34
	Annual odds	3.4%	4.1%	4.5%	3.3%	9.1%	17.6%	-

Level of evidence of the literature
The level of evidence of observational cohort studies is considered low according to the GRADE methodology. Therefore, the level of evidence of these cohort studies starts at low GRADE.

The level of evidence regarding the outcome measure **(locoregional) recurrence** was downgraded to very low because of study limitations (-1; risk of bias).

The level of evidence regarding the outcome measure **time to recurrence** was downgraded by to very low because of study limitations (-1; risk of bias) and number of included patients (-1; imprecision because of small sample size).

Conclusions

- Grade	No evidence was found regarding the effect of follow-up on **overall survival, number of re-interventions, quality of life and distant metastasis** when compared with no follow-up in patients with esophageal- or gastro-esophageal cancer after definitive chemoradiotherapy.

Very low GRADE	The evidence is very uncertain about the risk of **(locoregional) recurrence** in patients with esophageal cancer treated with definitive chemoradiotherapy. *Source: Du, 2017; Sudo, 2018*

Very low GRADE	The evidence is very uncertain about the **time to recurrence** of patients with esophageal cancer treated with definitive chemoradiotherapy. *Source: Sudo, 2018*

Overwegingen – van bewijs naar aanbeveling

<u>Voor- en nadelen van de interventie en de kwaliteit van het bewijs</u>

Voor de drie cruciale uitkomstmaten (algehele overleving, her-interventies en kwaliteit van leven) zijn geen uitkomsten gerapporteerd.

Er is één systematic review (Du, 2017) en een aanvullende observationele studie (Sudo, 2018) die uitkomsten rapporteren voor recurrence rate en tijd tot recurrence. De systematic review van Du (2017) heeft verschillende studie designs geïncludeerd waarbij patiënten verschillende typen chemotherapie ontvingen evenals verschillende doses radiotherapie gecombineerd met electieve lymfeklier bestraling. Echter wordt in de studie niet duidelijk of dit gerapporteerde uitkomsten op 1, 2 of 3 jaar betreft. Daardoor geeft deze studie geen verheldering van de situatie van dCRT patiënten. Bovendien wordt er een pooled local-regional recurrence rate en distant metastasis rate genoemd, waarbij niet duidelijk is op hoeveel jaar dit is.

De observationele studie van Sudo (2018) keek naar recurrences en tijd tot recurrences bij patiënten na definitieve chemoradiotherapy. Patiënten in deze studie werden elke 3 tot 6 maanden middels CT-scan en gastroduodenoscopie onderzocht voor een minimum van vijf jaar.
Vanwege het observationele studie design van de meeste geïncludeerde studies, is er sprake van zeer lage bewijskracht.

Het recidiefpatroon na definitieve chemoradiatie is wezenlijk anders dan na neoadjuvante chemoradiatie gevolgd door een resectie (Versteijne, 2015; Hulshof, 2021; Oppedijk, 2014).

Patiënten hebben na definitieve chemoradiatie een recidiefkans van 45-54% (Versteijne, 2015; Hulshof, 2021; Pape, 2022). Van alle eerste recidieven is 34-55% alleen locoregionaal, 27-41% alleen op afstand en 20-32% zowel locoregionaal als op afstand (Versteijne, 2015; Hulshof, 2021; Pape, 2022).

Verreweg de meeste recidieven treden op binnen 2-3 jaar. De kans op een eerste locoregionaal recidief >3 jaar na behandeling is <2% (Versteijne, 2015). Onderscheid dient te worden gemaakt tussen verschillende groepen patiënten, die allen een andere behandeling vereisen (salvage dCRT, salvage chirurgie of palliatieve systeemtherapie). Voor eventuele salvage behandelingen dient altijd een complete herstadiëring te worden verricht (inclusief

tenminste ^{18}F FDG/PET-CT), alvorens zo mogelijk tot in-opzet curatieve therapie over te gaan.

1. **Locoregionale recidief binnen het bestralingsgebied.** Hiervoor is de enige curatieve optie een salvage resectie. Veelal is in de primaire setting al bewust gekozen voor definitieve chemoradiatie. Slechts bij patiënten waarbij een ingrijpende resectie alsnog haalbaar kan zijn na definitieve chemoradiatie heeft intensievere follow-up therapeutische consequenties. Bij een lokaal recidief in de slokdarm (86% van alle locoregionale recidieven) (Versteijne, 2015), al dan niet in combinatie met recidief in regionale klieren, zullen patiënten zich snel presenteren met dysfagieklachten. Bij een recidief in alleen regionale klieren (14% van alle locoregionale recidieven) (Versteijne, 2015) zullen minder snel symptomen ontstaan. Of screening op een locoregionaal recidief invloed heeft op de overleving is twijfelachtig en onbekend. Hoewel zelden toegepast, is een salvage slokdarmresectie een haalbare therapeutische optie voor zorgvuldig geselecteerde patiënten met een beperkt locoregionaal recidief na dCRT (Borghesi S, 2008; Gardner-Thorpe, 2007; Farinella, 2016). Salvage resectie na dCRT kent een hogere morbiditeit in vergelijking met oesofagusresectie na neo-adjuvante CRT (Nishimura, 2007; Swisher 2002; D'Journo XB, 2008; Miyata, 2009). De beste manier om patiënten voor deze benadering te selecteren is niet vastgesteld. Zeker is dat er alleen een poging tot resectie dient te worden gedaan indien een R0-resectie technisch haalbaar is en afstandsmetastasen zijn uitgesloten (Booka, 2020). In het geval van alleen een klein lokaal residu of recidief dat zich niet dieper dan de (sub)mucosa lijkt uit te breiden kan in zeer geselecteerde gevallen een endoscopische resectie worden overwogen (Al-Kaabi, 2021)Teneinde patiënten voor wie een salvage resectie mogelijk is, tijdig te identificeren en te vervolgen, adviseren we om bij indicatiestelling voor definitieve chemoradiatie, direct in het MDO te bepalen of patiënt potentieel in aanmerking komt voor salvage resectie (chirurgische resectabiliteit). De minimale voorwaarden voor het potentieel mogelijk zijn van een salvage resectie zijn:
    - Chirurgisch resectabel recidief of residu
    - WHO performance status ≤ 1 en medisch operabele patiënt (o.a. bepaald middels spirometrie)
    - Behandelwens bij patiënt, zowel voorafgaand aan als na afronding van definitieve chemoradiatie. Bij een proximaal recidief met betrokkenheid of nabijheid van de bovenste slokdarmsfincter is een larynx-farynx extirpatie nodig; het is belangrijk dat patiënt hier uitgebreid over gecounseld wordt.

De operabiliteit van patiënt dient na dCRT en tijdens follow-up steeds heroverwogen te worden, en indien patiënt niet langer operabel is, de follow-up daarop aangepast.

2. **Locoregionaal recidief buiten het bestralingsgebied**. Dit betreffen meestal regionale klierrecidieven zonder recidief in de slokdarm. Van de circa 50% van alle patiënten die een recidief krijgt, krijgt ongeveer 40% (20% van totaal) alleen een locoregionaal recidief. Bij diegenen met een locoregionaal recidief is in 14% (circa 2-3% van totaal) sprake van een geïsoleerd regionaal klierrecidief, waarvan de meesten zich buiten het eerdere bestralingsveld bevinden (Versteijne, 2015). Voor deze patiënten kan definitieve chemoradiatie een goede salvage behandeling zijn (Jeene, 2017), maar gezien de lage incidentie lijkt het niet aan te bevelen hier actief op te screenen.

3. **Oligometastatische recidiefziekte.** Internationaal neemt de neiging toe om oligometastatische ziekte radicaal te behandelen, ook voor het slokdarmcarcinoom, bijvoorbeeld door naast palliatieve systeemtherapie ook op metastase(n) gerichte

chirurgie, ablatie of stereotactische radiotherapie te overwegen.(Kroese, 2022; Kroese, 2023). Een voltooide gerandomiseerde fase II trial bij patiënten met een oligogemetastaseerd plaveiselcelcarcinoom van de oesofagus (waarvan een kleine meerderheid een metachroon oligorecidief had en status na definitieve chemoradiatie), observeerde een verbeterde progressie-vrije overleving na additie van metastase-gerichte radicale behandeling bovenop systeemtherapie alleen (Liu, 2024). Aanvullend fase III onderzoek en dergelijke studies bij adenocarcinoom zijn nodig om deze bevindingen te ondersteunen of weerleggen. Het is onduidelijk of screening ter vroege identificatie van (oligo)gemetastaseerde ziekte een overlevingsvoordeel biedt en screening met dat doel kan derhalve heden niet worden aanbevolen.

Aanbevelingen

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies

Samenvattend is er geen onderzoek van goede kwaliteit dat het ziektebeloop of de overleving wordt beïnvloed door screening. Gezien het recidiefpatroon waarbij de meeste recidieven optreden binnen 2 tot 3 jaar na behandeling, dient eventuele screening zich tot 3 jaar te beperken.

Studies naar de waarde van diagnostische modaliteiten voor screening in de follow-up periode na definitieve chemoradiatie zijn zeer beperkt. De werkgroep is van mening dat het intensiveren van de frequentie van endoscopische evaluatie (met biopten alleen indien zichtbare afwijkingen) meer kans geeft om een geschikte patiënt voor salvage behandeling op te sporen dan het intensiveren van de frequentie van beeldvorming.

Verricht geen standaard follow-up met beeldvorming of endoscopie bij patiënten met definitieve chemo-radiatie. Overweeg screening alleen bij patiënten voor wie een salvage behandeling haalbaar en wenselijk is, en alleen in de eerste drie jaar na behandeling. Overweeg daarbij het volgende schema:

Screeningsschema na einde chemoradiatie

Endoscopische follow-up na	3 tot 6m-9m-12m-18m-24m-36m
CT thorax/abdomen na	3 tot 6m-12m-24m

Wanneer een recidief wordt gedetecteerd en een salvage behandeling wordt overwogen, verricht dan tevoren eerst een PET-CT.

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Bijlagen bij module 'Nacontrole na definitieve chemoradiatie'

Evidence table systematic review and observational cohort studies

Research question: What are the recurrence rates or time to recurrences in patients with esophageal- or gastro-esophageal cancer after definitive chemoradiotherapy?

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Du, 2017 PS. Study characteristics and results are extracted from the SR (unless stated otherwise)	SR and meta-analysis of RCTs and cohort studies *Literature search up to February 2015* **A**: Cooper, 1999 **B**: Nishimura, 2009 **C**: Yamashita, 2011 **D**: Onozawa, 2009 **E**: Ishikura, 2003 **F**: Kato, 2013 **G**: Poplin, 1996 **H**: Roca, 1996 **I:** Jefford, 2002 **J:** Ishida, 1996 **K:** Liu, 2014 **L:** Morota, 2009 **M:** Ohtsu, 1999 **N:** Kodaira, 2006 **O:** Hironaka, 2003 <u>Study design</u>:	Inclusion criteria SR: - Studies containing original data on definitive chemoradiotherapy with elective node irradiation (ENI) in patients with esophageal carcinoma - Report of outcome failure pattern Exclusion criteria SR: - Neoadjuvant or adjuvant chemoradiotherapy combined with surgery - Palliative chemoradiotherapy - Radiotherapy delivered by Co-60 or by	Describe intervention: <u>Chemotherapy</u> **A**: Cisplatin + 5-Fu **B**: Cisplatin + 5-Fu **C**: Nedaplatin + 5-Fu **D**: Cisplatin + 5-Fu **E**: Cisplatin + 5-Fu **F**: Cisplatin + 5-Fu **G**: Cisplatin + 5-Fu **H**: Cisplatin + 5-Fu + leucovorin + bleomycin + mitomycin C **I:** Carboplatin + 5-Fu **J:** Cisplatin + 5-Fu **K:** PF/TP/TPF **L:** Cisplatin + 5-Fu **M:** Cisplatin + 5-Fu **N:** Nedaplatin + 5-Fu **O:** Cisplatin + 5-Fu <u>Radiation dose (Gy)</u> **A**: 50 **B**: 60 **C**: 50-50.4 **D**: 60 **E**: 60 **F**: 60 **G**: 50 **H**: 60	Describe control: Not applicable	<u>End-point of follow-up</u>: Not reported <u>For how many participants were no complete outcome data available?</u> Not reported	<u>Outcome measure-1</u> Defined as patterns of failure *See table 1 in summary of literature*	<u>Risk of bias (high, some concerns or low):</u> No individual risk of bias assessment by authors of systematic review <u>Authors conclusion</u>: The comparison of failure patterns suffered from bias since they were performed during different time periods or based on different evaluation criteria. These biases might have influenced the pooled results and interpretation of the findings.

	A: RCT + prospective cohort **B**: RCT **C**: Retrospective cohort **D**: Retrospective cohort **E**: Retrospective cohort **F**: Prospective cohort **G**: Prospective cohort **H**: Prospective cohort **I:** Prospective cohort **J:** Prospective cohort **K:** Retrospective cohort **L:** Retrospective cohort **M:** Prospective cohort **N:** Prospective cohort **O:** Retrospective cohort <u>Setting and Country</u>: **A**: USA **B**: Japan **C**: Japan **D**: Japan	unconventional fractions - Not published in full-text - Phase I study - Results mixed with ENI and conventional RT filed - Results not reported exactly - Other sites of cancer - Reviews and meta analyses *22 studies included (regarding the scope and outcome of interest of this review, only data from 15 studies is reported)* <u>Important patient characteristics at baseline</u>: <u>N, % male</u> **A**: 134, not reported **B**: 91, 90% **C**: 126, 88%	**I:** 50 **J:** 60 **K:** 60-68.4 **L:** 60 **M:** 60 **N:** 63 **O:** 60				

	E: Japan **F**: Japan **G**: USA **H**: Argentina **I:** Australia **J:** Japan **K:** China **L:** Japan **M:** Japan **N:** Japan **O:** Japan <u>Source of funding and conflicts of interest:</u> The authors indicated no potential conflicts of interest	**D**: 102, 83% **E**: 139, 87% **F**: 76, 89% **G**: 32, 81% **H**: 55, 69% **I:** 23, 65% **J:** 45, 96% **K:** 169, 76% **L:** 69, 87% **M:** 54, 96% **N:** 25, 88% **O:** 53, 85% <u>TNM/Stage</u> **A**: T1-3N0-1M0 **B**: II-IVa **C**: I-IV **D**: I-IVb **E**: I-IVa **F**: II-III **G**: I-III **H**: I-III **I:** Not reported **J:** T4Nx-1M0-1 **K:** I-IV **L:** I-IVb **M:** T4NxM0-1 **N:** T1b-4N0-1M0-1 **O:** IIa-III Studies are not comparable at baseline					
Sudo, 2018	Type of study: Retrospective cohort study	<u>Inclusion criteria</u>:	Describe intervention <u>Chemotherapy:</u>	Describe control Not applicable	<u>Length of follow-up</u>:	Outcome measures:	<u>Authors conclusion:</u> Intensive surveillance with

	Setting and country: Japan Funding and conflicts of interest: Study was supported by a National Cancer Center Research and Development Fund. Authors have no conflicts of interest to disclose	- Patients who were diagnosed with stage II-III esophageal squamous cell carcinoma; - Between 2000 and 2011 - Patients who received definitive chemoradiotherapy (dCRT) - Patients with complete respons after dCRT <u>Exclusion criteria</u>: - Patients with T4 esophageal squamous cell carcinoma - Patients with double cancer - Received chemoradiotherapy as a salvage treatment for recurrent disease after surgery <u>N total at baseline</u>: 204	5-Fu and cisplatin: N=184 (90%) 5-Fu and nedaplatin: N=9 (4%) S-1 and cisplatin: N=9 (4%) Docetaxel: N=2 (1%) <u>Total radiation dose:</u> 50.4Gy: N=57 (28%) 60.0Gy: N=147 (72%)		Median follow-up time: 75.7 months (IQR 53.1-104.7) <u>Loss-to-follow-up</u>: Not reported <u>Incomplete outcome data</u>: Not reported	*See results and table 2 in summary of literature*	esophagogastroduodenoscopy may be important in the first 3 years after dCRT to detect luminal relapse, and esophagogastroduodenoscopy might be needed to detect new-found cancer beyond 3 years from dCRT.

		Important prognostic factors[2]: *Median age: 65 (range 42-81)* *Sex:* *83% male* *Baseline stage:* *Stage II: N=134 (66%)* *Stage III: N=70 (34%)*					

Table of quality assessment for systematic reviews of RCTs and observational studies

Based on AMSTAR checklist (Shea et al.; 2007, BMC Methodol 7: 10; doi:10.1186/1471-2288-7-10) and PRISMA checklist (Moher et al 2009, PLoS Med 6: e1000097; doi:10.1371/journal.pmed1000097)

Study First author, year	Appropriate and clearly focused question?[1] Yes/no/unclear	Comprehensive and systematic literature search?[2] Yes/no/unclear	Description of included and excluded studies?[3] Yes/no/unclear	Description of relevant characteristics of included studies?[4] Yes/no/unclear	Appropriate adjustment for potential confounders in observational studies?[5] Yes/no/unclear/not applicable	Assessment of scientific quality of included studies?[6] Yes/no/unclear	Enough similarities between studies to make combining them reasonable?[7] Yes/no/unclear	Potential risk of publication bias taken into account?[8] Yes/no/unclear	Potential conflicts of interest reported?[9] Yes/no/unclear
Du, 2017	Yes	No	No, no description of excluded studies	No	No, no multivariate analysis	No	No, RCT's and observational studies were combined	Yes	Yes

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Risk of bias table for observational studies

Author, year	Selection of participants Was selection of exposed and non-exposed cohorts drawn from the same population?	Exposure Can we be confident in the assessment of exposure?	Outcome of interest Can we be confident that the outcome of interest was not present at start of study?	Confounding-assessment Can we be confident in the assessment of confounding factors?	Confounding-analysis Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these confounding variables?	Assessment of outcome Can we be confident in the assessment of outcome?	Follow up Was the follow up of cohorts adequate? In particular, was outcome data complete or imputed?	Co-interventions Were co-interventions similar between groups?	Overall Risk of bias
	Definitely yes, probably yes, probably no, definitely no	Definitely yes, probably yes, probably no, definitely no	Definitely yes, probably yes, probably no, definitely no	Definitely yes, probably yes, probably no, definitely no	Definitely yes, probably yes, probably no, definitely no	Definitely yes, probably yes, probably no, definitely no	Definitely yes, probably yes, probably no, definitely no	Definitely yes, probably yes, probably no, definitely no	Low, Some concerns, High
Sudo, 2018	*Definitely yes* Reason: Participants were selected from a hospital registry	*Unclear* Reason: Therapy response was assessed by CT-scan and esophagogastroduodenoscopy. Possible cases of exposure were missed	*Unclear* Reason: Outcome of interest at start of study was assessed by CT-scan and esophagogastroduodenoscopy	*Probably no* Reason: Limited characteristic and confounding factors were reported	*Definitely no* Reason: No multivariate analysis	*Unclear* Reason: Outcome was assessed by CT-scan and esophagogastroduodenoscopy. Possible cases of exposure were missed	*Probably yes* Reason: Follow-up time was adequate. No reported of imputing missing data	*No information* Reason: Not clear if there were any co-interventions	**High**

Table of excluded studies

Reference	Reason for exclusion
Kumagai K, Mariosa D, Tsai JA, Nilsson M, Ye W, Lundell L, Rouvelas I. Systematic review and meta-analysis on the significance of salvage esophagectomy for persistent or recurrent esophageal squamous cell carcinoma after definitive chemoradiotherapy. Dis Esophagus. 2016 Oct;29(7):734-739. doi: 10.1111/dote.12399. Epub 2015 Aug 28. PMID: 26316181.	Wrong comparison: Salvage surgery versus chemoradiotherapy
Chen M, Liu P, Chen Y, Chen Z, Shen M, Liu X, Li X, Lin Y, Yang R, Ni W, Zhou X, Zhang L, Tian Y, Chen J. Primary tumor regression patterns in esophageal squamous cell cancer treated with definitive chemoradiotherapy and implications for surveillance schemes. Cancer Manag Res. 2019 Apr 17;11:3361-3369. doi: 10.2147/CMAR.S198524. PMID: 31114372; PMCID: PMC6489665.	Wrong comparison: comparison of recurrence patterns
Sudo K, Xiao L, Wadhwa R, Shiozaki H, Elimova E, Taketa T, Blum MA, Lee JH, Bhutani MS, Weston B, Ross WA, Komaki R, Rice DC, Swisher SG, Hofstetter WL, Maru DM, Skinner HD, Ajani JA. Importance of surveillance and success of salvage strategies after definitive chemoradiation in patients with esophageal cancer. J Clin Oncol. 2014 Oct 20;32(30):3400-5. doi: 10.1200/JCO.2014.56.7156. Epub 2014 Sep 15. PMID: 25225435; PMCID: PMC4195852.	Wrong population: Patients who underwent surgery or salvage surgery
Dong D, Zhao D, Li S, Liu W, Du F, Xu X, Xiao S, Zheng B, Sun Y, Wang W. Nomogram to predict overall survival for patients with non-metastatic cervical esophageal cancer: a SEER-based population study. Ann Transl Med. 2020 Dec;8(23):1588. doi: 10.21037/atm-20-2505. PMID: 33437787; PMCID: PMC7791199.	No outcomes of interest reported
Doosti-Irani A, Mansournia MA, Rahimi-Foroushani A, Haddad P, Holakouie-Naieni K. Local recurrence of esophageal squamous cell carcinoma after treatment: Comparison of frequentist and Bayesian network meta-analysis. Clinical Epidemiology and Global Health 2019 7(2), 145-152, doi: https://doi.org/10.1016/j.cegh.2018.02.009.	Wrong comparisons: Surgery + chemotherapie vs. Surgery
Hipp J, Nagavci B, Schmoor C, Meerpohl J, Hoeppner J, Schmucker C. Post-Neoadjuvant Surveillance and Surgery as Needed Compared with Post-Neoadjuvant Surgery on Principle in Multimodal Treatment for Esophageal Cancer: A Scoping Review. Cancers (Basel). 2021 Jan 23;13(3):429. doi: 10.3390/cancers13030429. PMID: 33561090; PMCID: PMC7865772.	Wrong design: Scoping review
Mikhail S, Wei L, Salem ME, Bekaii-Saab T. Outcomes of definitive chemoradiation in patients with esophageal cancer. Dis Esophagus. 2017 Feb 1;30(2):1-7. doi: 10.1111/dote.12506. PMID: 27868290.	Narrative review
Mummudi N, Jiwnani S, Niyogi D, Srinivasan S, Ghosh-Laskar S, Tibdewal A, Rane P, Karimundackal G, Pramesh CS, Agarwal JP. Salvage radiotherapy for postoperative locoregional failure in esophageal cancer: a systematic review and meta-analysis. Dis Esophagus. 2022 Mar 12;35(3):doab020. doi: 10.1093/dote/doab020. PMID: 33912933.	Wrong population: Patients who underwent salvage radiotherapie (after developing locoregional recurrence)
Salcedo J, Suen SC, Bian SX. Cost-effectiveness of chemoradiation followed by esophagectomy versus chemoradiation alone in squamous cell carcinoma of the esophagus. Cancer Med. 2020 Jan;9(2):440-446. doi: 10.1002/cam4.2721. Epub 2019 Nov 20. PMID: 31749330; PMCID: PMC6970052.	Wrong comparison: Chemoradiation and surgery verus chemoradiation alone
van den Boorn HG, Engelhardt EG, van Kleef J, Sprangers MAG, van Oijen MGH, Abu-Hanna A, Zwinderman AH, Coupé VMH, van Laarhoven HWM. Prediction models for patients with esophageal or gastric cancer: A systematic review and meta-analysis. PLoS One. 2018 Feb 8;13(2):e0192310. doi: 10.1371/journal.pone.0192310. PMID: 29420636; PMCID: PMC5805284.	Wrong population: Patients who underwent resection; Wrong outcome: Survival
Chang X, Liu J, Zhao Y, Shi A, Yu H, Yu R, Wang W. Neoadjuvant chemoradiotherapy followed by oesophagectomy may be the optimal treatment option for lower thoracic oesophageal cancer with supraclavicular lymph node metastasis: An inverse probability of treatment-weighted analysis of SEER database. J Med Imaging Radiat Oncol. 2023 Sep;67(6):676-683. doi: 10.1111/1754-9485.13561. Epub 2023 Jul 14. PMID: 37452459.	Wrong population: Patients with locoregional disease, metastasis or distant metastasis

Grou-Boileau F, Tankel J, Nevo Y, Najmeh S, Spicer J, Cools-Lartigue J, Mueller C, Ferri L. Locoregional Recurrence of Esophageal Cancer Treated with Curative Intent Local Salvage Therapy: A Single Center Experience. J Gastrointest Cancer. 2023 Dec;54(4):1292-1299. doi: 10.1007/s12029-023-00929-0. Epub 2023 Mar 29. PMID: 36988820.	Wrong intervention: en bloc esophagectomy
Chen D, Zha X, Ye D, Kang M, Zhu L, Yang M, Chen Y, Zhu K, Xia W, Wang Z, Wang Y. Patterns of care and prognostic evaluation for stage I-III upper esophageal squamous cell carcinoma: a population-based study. Ann Transl Med. 2022 Nov;10(22):1222. doi: 10.21037/atm-22-4577. PMID: 36544690; PMCID: PMC9761128.	Wrong design: Prognostic models for optimal treatment pattern (chemoradiotherapy, chemoradiotherapy and/or surgery)
Yang Y, Chen M, Xie J, Ji Y, Sheng L, Qiu G, Du X, Wei Q. Treatment Patterns and Outcomes of Elderly Patients With Potentially Curable Esophageal Cancer. Front Oncol. 2022 Feb 14;12:778898. doi: 10.3389/fonc.2022.778898. PMID: 35237508; PMCID: PMC8882918.	Wrong intervention: Optimal treatment patterns (resection, chemoradiotherapy, radiotherapy, etc) in elderly patients
Gaber CE, Shaheen NJ, Edwards JK, Sandler RS, Nichols HB, Sanoff HK, Lund JL. Trimodality Therapy vs Definitive Chemoradiation in Older Adults With Locally Advanced Esophageal Cancer. JNCI Cancer Spectr. 2022 Nov 1;6(6):pkac069. doi: 10.1093/jncics/pkac069. PMID: 36205723; PMCID: PMC9623425.	Wrong comparison: Trimodal therapy versus chemoradiation; Wrong outomes: No report of (time to) recurrence
Bakhos CT, Acevedo E Jr, Petrov RV, Abbas AE. Surveillance Following Treatment of Esophageal Cancer. Surg Clin North Am. 2021 Jun;101(3):499-509. doi: 10.1016/j.suc.2021.03.011. PMID: 34048769.	Narrative review
Mori K, Sugawara K, Aikou S, Yamashita H, Yamashita K, Ogura M, Chin K, Watanabe M, Matsubara H, Toh Y, Kakeji Y, Seto Y. Esophageal cancer patients' survival after complete response to definitive chemoradiotherapy: a retrospective analysis. Esophagus. 2021 Jul;18(3):629-637. doi: 10.1007/s10388-021-00817-1. Epub 2021 Feb 24. PMID: 33625649.	Wrong population: Also included patients with neoadjuvant chemotherapy
van der Wilk BJ, Noordman BJ, Neijenhuis LKA, Nieboer D, Nieuwenhuijzen GAP, Sosef MN, van Berge Henegouwen MI, Lagarde SM, Spaander MCW, Valkema R, Biermann K, Wijnhoven BPL, van der Gaast A, van Lanschot JJB, Doukas M, Nikkessen S, Luyer M, Schoon EJ, Roef MJ, van Lijnschoten I, Oostenbrug LE, Riedl RG, Gisbertz SS, Krishnadath KK, Bennink RJ, Meijer SL; Collaborators:. Active Surveillance Versus Immediate Surgery in Clinically Complete Responders After Neoadjuvant Chemoradiotherapy for Esophageal Cancer: A Multicenter Propensity Matched Study. Ann Surg. 2021 Dec 1;274(6):1009-1016. doi: 10.1097/SLA.0000000000003636. PMID: 31592898.	Wrong comparison: Immediate surgery versus active surveillance
Wang J, Qin J, Jing S, Liu Q, Cheng Y, Wang Y, Cao F. Clinical complete response after chemoradiotherapy for carcinoma of thoracic esophagus: Is esophagectomy always necessary? A systematic review and meta-analysis. Thorac Cancer. 2018 Dec;9(12):1638-1647. doi: 10.1111/1759-7714.12874. Epub 2018 Oct 1. PMID: 30277016; PMCID: PMC6275815.	Wrong comparison: Surgical versus non-surgical treatment
Schlottmann F, Strassle PD, Gaber C, Patti MG. Stage III esophageal adenocarcinoma: definitive chemoradiation vs. chemoradiation plus surgery. Updates Surg. 2018 Dec;70(4):423-426. doi: 10.1007/s13304-018-0541-5. Epub 2018 Jun 20. PMID: 29926306.	Wrong comparison: Def. Chemoradiation versus chemoradiation + surgery
Khangura SK, Greenwald BD. Endoscopic management of esophageal cancer after definitive chemoradiotherapy. Dig Dis Sci. 2013 Jun;58(6):1477-85. doi: 10.1007/s10620-012-2554-0. Epub 2013 Jan 17. PMID: 23325163.	Wrong intervention: Salvage endoscopic therapies
Taketa T, Correa AM, Suzuki A, Blum MA, Chien P, Lee JH, Welsh J, Lin SH, Maru DM, Erasmus JJ, Bhutani MS, Weston B, Rice DC, Vaporciyan AA, Hofstetter WL, Swisher SG, Ajani JA. Outcome of trimodality-eligible esophagogastric cancer patients who declined surgery after preoperative chemoradiation. Oncology. 2012;83(5):300-4. doi: 10.1159/000341353. Epub 2012 Sep 4. PMID: 22964903; PMCID: PMC3832345.	Wrong study population: Patients who declined surgery were included
Smith GL, Smith BD, Buchholz TA, Liao Z, Jeter M, Swisher SG, Hofstetter WL, Ajani JA, McAleer MF, Komaki R, Cox JD. Patterns of care and locoregional treatment outcomes in older esophageal cancer patients: The SEER-Medicare Cohort. Int J Radiat Oncol Biol Phys. 2009 Jun 1;74(2):482-9. doi: 10.1016/j.ijrobp.2008.08.046. Epub 2009 Mar 14. PMID: 19289262.	Wrong comparisons: Different treatments (surgery, radiotherapy, chemotherapy, chemotherapy + surgery)

Aurello P, Berardi G, Moschetta G, Cinquepalmi M, Antolino L, Nigri G, D'Angelo F, Valabrega S, Ramacciato G. Recurrence Following Anastomotic Leakage After Surgery for Carcinoma of the Distal Esophagus and Gastroesophageal Junction: A Systematic Review. Anticancer Res. 2019 Apr;39(4):1651-1660. doi: 10.21873/anticanres.13270. PMID: 30952703.	Wrong intervention: Surgery; Wrong outcome: Anastomotic leakage
Li F, Ding N, Zhao Y, Yuan L, Mao Y. The current optimal multimodality treatments for oesophageal squamous-cell carcinoma: A systematic review and meta-analysis. Int J Surg. 2018 Dec;60:88-100. doi: 10.1016/j.ijsu.2018.10.037. Epub 2018 Oct 31. PMID: 30389537.	Wrong comparisons; nCRT + surgery versus dCRT
Mei LX, Mo JX, Chen Y, Dai L, Wang YY, Chen MW. Esophagectomy versus definitive chemoradiotherapy as initial treatment for clinical stage I esophageal cancer: a systematic review and meta-analysis. Dis Esophagus. 2022 Mar 12;35(3):doab049. doi: 10.1093/dote/doab049. PMID: 34318324.	No outcome data for recurrence rates regarding dCRT
Sun Z, Zheng J, Xu X, Zhao X, Ma X, Ye Q. Comparison of clinical outcomes of conservative treatment and surgery for esophageal cancer patients who achieve a clinical complete response following neoadjuvant chemoradiotherapy: a systematic review and meta-analysis. Ann Transl Med. 2022 Dec;10(24):1378. doi: 10.21037/atm-22-6186. PMID: 36660656; PMCID: PMC9843363.	No outcome data for recurrence rates regarding CRT only, data comparing CRT + conservative treatment versus CRT + surgery
Vellayappan BA, Soon YY, Ku GY, Leong CN, Lu JJ, Tey JC. Chemoradiotherapy versus chemoradiotherapy plus surgery for esophageal cancer. Cochrane Database Syst Rev. 2017 Aug 22;8(8):CD010511. doi: 10.1002/14651858.CD010511.pub2. PMID: 28829911; PMCID: PMC6483706.	Wrong outcomes: No recurrence rates
Wang J, Xiao L, Wang S, Pang Q, Wang J. Addition of Induction or Consolidation Chemotherapy in Definitive Concurrent Chemoradiotherapy Versus Concurrent Chemoradiotherapy Alone for Patients With Unresectable Esophageal Cancer: A Systematic Review and Meta-Analysis. Front Oncol. 2021 Sep 13;11:665231. doi: 10.3389/fonc.2021.665231. PMID: 34589418; PMCID: PMC8473880.	Wrong comparison: Induction chemotherapy versus consolidation chemotherapy; Wrong population: Patients with unresectable esophageal cancer
Mitani S, Kato K, Daiko H, Ito Y, Nozaki I, Kojima T, Yano M, Nakagawa S, Ueno M, Watanabe M, Tsunoda S, Abe T, Kadowaki S, Kadota T, Sasaki K, Machida R, Kitagawa Y. Second primary malignancies in patients with clinical T1bN0 esophageal squamous cell carcinoma after definitive therapies: supplementary analysis of the JCOG trial: JCOG0502. J Gastroenterol. 2022 Jul;57(7):455-463. doi: 10.1007/s00535-022-01870-y. Epub 2022 May 11. PMID: 35546373; PMCID: PMC9232445.	Wrong outcome: Combined cumulative incidence for second primary malignancies for different treatment types (surgery, chemoradiation)
van der Bogt RD, van der Wilk BJ, Nikkessen S, Krishnadath KK, Schoon EJ, Oostenbrug LE, Siersema PD, Vleggaar FP, Doukas M, van Lanschot JJB, Spaander MCW. Predictive value of endoscopic esophageal findings for residual esophageal cancer after neoadjuvant chemoradiotherapy. Endoscopy. 2021 Nov;53(11):1098-1104. doi: 10.1055/a-1362-9375. Epub 2021 Mar 2. PMID: 33652496.	Wrong outcome: Predictive value of endoscopy
Eyck BM, Onstenk BD, Noordman BJ, Nieboer D, Spaander MCW, Valkema R, Lagarde SM, Wijnhoven BPL, van Lanschot JJB. Accuracy of Detecting Residual Disease After Neoadjuvant Chemoradiotherapy for Esophageal Cancer: A Systematic Review and Meta-analysis. Ann Surg. 2020 Feb;271(2):245-256. doi: 10.1097/SLA.0000000000003397. PMID: 31188203.	Wrong outcome: Diagnostic accuracy of various modalities for detecting residual disease
Lim JT, Truong PT, Berthelet E, Pai H, Joe H, Wai E, Larsson S, Kader HA, Weinerman B, Wilson K, Olivotto IA. Endoscopic response predicts for survival and organ preservation after primary chemoradiotherapy for esophageal cancer. Int J Radiat Oncol Biol Phys. 2003 Dec 1;57(5):1328-35. doi: 10.1016/s0360-3016(03)00751-x. PMID: 14630270.	Wrong comparisons
Khangura SK, Greenwald BD. Endoscopic management of esophageal cancer after definitive chemoradiotherapy. Dig Dis Sci. 2013 Jun;58(6):1477-85. doi: 10.1007/s10620-012-2554-0. Epub 2013 Jan 17. PMID: 23325163.	FU strategy after chemoradiation
Shridhar R, Imani-Shikhabadi R, Davis B, Streeter OA, Thomas CR Jr. Curative treatment of esophageal cancer; an evidenced based review. J Gastrointest Cancer. 2013 Dec;44(4):375-84. doi: 10.1007/s12029-013-9511-9. PMID: 23824628.	Narrative review

Weidenbaum C, Gibson MK. Approach to Localized Squamous Cell Cancer of the Esophagus. Curr Treat Options Oncol. 2022 Oct;23(10):1370-1387. doi: 10.1007/s11864-022-01003-w. Epub 2022 Aug 31. PMID: 36042147; PMCID: PMC9526684.	Wrong scope: No follow-up or recurrence rates
Wong R, Malthaner R. Esophageal cancer: a systematic review. Curr Probl Cancer. 2000 Nov-Dec;24(6):297-373. doi: 10.1016/s0147-0272(00)80002-1. PMID: 11198836.	Narrative review
Zhu W, Xing L, Yue J, Sun X, Sun X, Zhao H, Yu J. Prognostic significance of SUV on PET/CT in patients with localised oesophagogastric junction cancer receiving neoadjuvant chemotherapy/chemoradiation:a systematic review and meta-analysis. Br J Radiol. 2012 Sep;85(1017):e694-701. doi: 10.1259/bjr/29946900. Epub 2012 Feb 14. PMID: 22337686; PMCID: PMC3487087.	No comparison: Only outcomes regarding FDG-PET
al-Sarraf M, Martz K, Herskovic A, Leichman L, Brindle JS, Vaitkevicius VK, Cooper J, Byhardt R, Davis L, Emami B. Progress report of combined chemoradiotherapy versus radiotherapy alone in patients with esophageal cancer: an intergroup study. J Clin Oncol. 1997 Jan;15(1):277-84. doi: 10.1200/JCO.1997.15.1.277. Erratum in: J Clin Oncol 1997 Feb;15(2):866. PMID: 8996153.	Wrong comparison: Chemoradiotherapy versus radiotherapy
Burmeister BH, Walpole ET, D'Arcy N, Burmeister EA, Cox S, Thomson DB, Harvey JA, Smithers BM. A phase II trial of chemoradiation therapy with weekly oxaliplatin and protracted infusion of 5-fluorouracil for esophageal cancer. Invest New Drugs. 2009 Jun;27(3):275-9. doi: 10.1007/s10637-008-9178-4. Epub 2008 Oct 8. PMID: 18841327.	Wrong comparison
Chang H, Shin SK, Cho BC, Lee CG, Kim CB, Kim DJ, Lee JG, Hur J, Lee CY, Bae MK, Kim HR, Lee SK, Park JC, Lee H, Kim HI, Chung H, Cha J, Lee YC, Kim JH. A prospective phase II trial of S-1 and cisplatin-based chemoradiotherapy for locoregionally advanced esophageal cancer. Cancer Chemother Pharmacol. 2014 Apr;73(4):665-71. doi: 10.1007/s00280-013-2371-y. Epub 2014 Feb 22. PMID: 24562525.	Wrong comparison
Cui J, Zhang D, Gao Y, Duan J, Wang L, Li L, Yuan S. CT-based radiomics combined with hematologic parameters for survival prediction in locally advanced esophageal cancer patients receiving definitive chemoradiotherapy. Insights Imaging. 2024 Mar 25;15(1):87. doi: 10.1186/s13244-024-01647-2. PMID: 38523188; PMCID: PMC10961297.	Wrong scope: Radiomic and genomics model CT
Cui Y, Li Z, Xiang M, Han D, Yin Y, Ma C. Machine learning models predict overall survival and progression free survival of non-surgical esophageal cancer patients with chemoradiotherapy based on CT image radiomics signatures. Radiat Oncol. 2022 Dec 27;17(1):212. doi: 10.1186/s13014-022-02186-0. PMID: 36575480; PMCID: PMC9795769.	Wrong scope: Prediction CT image radiomics model
Glasgow RE, Ilson DH, Hayman JA, Gerdes H, Mulcahy MF, Ajani JA. Modern approaches to localized cancer of the esophagus. J Natl Compr Canc Netw. 2011 Aug 1;9(8):902-11. doi: 10.6004/jnccn.2011.0074. PMID: 21900220.	Narrative review
Teoh AY, Yan Chiu PW, Wong TC, Liu SY, Hung Wong SK, Ng EK. Functional performance and quality of life in patients with squamous esophageal carcinoma receiving surgery or chemoradiation: results from a randomized trial. Ann Surg. 2011 Jan;253(1):1-5. doi: 10.1097/SLA.0b013e3181fcd991. PMID: 21233603.	Wrong comparison

Literature search strategy

Uitgangsvraag 1.1: Wat is de optimale nacontrole voor patiënten met oesofaguscarcinoom na definitieve chemoradiatie?	
Database(s): Medline, Embase	Datum: 14 + 27-5-2023
Periode: >2019	

Zoekverantwoording

Database	Aantallen treffers	Aantallen treffers na ontdubbelen	Database aanvulling	Aantallen treffers	Aantallen treffers na ontdubbelen
Medline 13 mei 2023	820	819	**Medline 27 mei 2023**	383	165

Embase 14 mei 2023	1079	423	**Embase 27 mei 2023**	486	195
Totaal	820	550		869	360

➔ Aantal SRs: 52; aantal RCT's: 144, aantal observationele studies: 936, aantal SR's recurrence rate: 110.

➔ Aanvulling 27 mei: aantal SRs: 29; aantal RCT's: 36, aantal observationele studies: 295.

OVID/Medline 13 mei 2023
Ovid MEDLINE(R) ALL <1946 to May 11, 2023>

1	exp Esophageal Neoplasms/ or ((carcinoma* or neoplas* or adenoma* or adenocarcinoma* or tumor* or tumour* or cancer* or oncolog* or malignan* or carcinogen* or oncogen* or anticarcinogen* or squamous*) adj3 (oesophag* or esophag* or gastroesophag* or gastrooesophag* or oesogastr* or esogastr*)).ti,ab,kf.	**78886**
2	exp Chemoradiotherapy/ or (chemoradio* or radiochemo* or chemo-radio* or radio-chemo* or chemoradiati*).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word]	**51331**
3	Survival Rate/ or exp Survival Analysis/ or Survivors/ or Reoperation/ or ((surviv* adj3 (rate or mean or analys* or disease-free or progression-free or event-free or overall)) or survivor* or (surg* adj3 (revis* or repeat*))).ti,ab,kf.	**955206**
4	Endoscopy/ or exp Laryngoscopy/ or exp Endoscopy, Gastrointestinal/ or (endoscop* or gastroscop* or laryngoscop* or esophagoscop* or oesophagoscop*).ti,ab,kf.	**334931**
5	exp Tomography, X-Ray Computed/ or (computed-tomograph* or ct or cts or cat-scan* or computer-assisted-tomograph* or computerized-tomograph* or computerised-tomograph* or computed-x-ray-tomograph* or computed-xray-tomograph*).ti,ab,kf.	**838842**
6	exp Tomography, Emission-Computed/ or (spect or petscan* or pet-scan* or pet or (emission adj3 tomogra*) or radionuclid*).ti,ab,kf.	**239779**
7	exp Magnetic Resonance Imaging/ or ((magnetic-resonance adj3 imag*) or mri or mris or nmr or mra or mras or zeugmatograph* or mr-tomograph* or proton-spin or ((magneti* or chemical-shift) adj3 imag*) or fmri or fmris).ti,ab,kf.	**930203**
8	4 or 5 or 6 or 7	**2028680**
9	1 and 2 and 3 and 8	**837**
10	9 not ((Adolescent/ or Child/ or Infant/) not Adult/)	**837**
11	10 not ((exp animals/ or exp models, animal/) not humans/)	**837**
12	11 not (comment/ or editorial/ or letter/ or Case Reports/)	**821**
13	(systematic-review.pt. or (meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data extraction" or "data source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.)) not (comment/ or editorial/ or letter/ or ((exp animals/ or exp models, animal/) not humans/))	**633188**
14	12 and 13	**36**
15	exp randomized controlled trial/ or random*.ti,ab,kf. or ((pragmatic or practical) adj clinical trial*).ti,ab,kf. or ((non-inferiority or noninferiority or superiority or equivalence) adj3 trial*).ti,ab,kf.	**1551076**
16	(12 and 15) not 14	**91**
17	exp Epidemiologic Studies/ or (cohort or (case adj5 (control or controll* or comparison or referent)) or risk or causation or causal or odds-ratio or etiol* or aetiol* or natural-history or predict* or prognos* or outcome or course or retrospect* or followup or follow-up).ti,ab,kf.	**8448338**
18	(12 and 17) not (14 or 16)	**640**

19	14 or 16	**127**
20	Recurrence/ or (recurrenc* or recrudescenc* or relaps*).ti,ab,kf.	**697437**
21	1 and 2 and 13 and 20	**66**
22	21 not (14 or 16 or 18)	**53**

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No.	Query	Results
#27	#26 NOT (#15 OR #17 OR #23)	**104**
#26	#1 AND #2 AND #14 AND #25	**125**
#25	'tumor recurrence'/exp OR 'cancer recurrence'/de OR 'recurrent disease'/exp OR recurrenc*:ti,ab,kw OR recrudescenc*:ti,ab,kw OR relaps*:ti,ab,kw	**1152822**
#24	#23 NOT (#15 OR #17)	**778**
#23	#13 AND #22	**915**
#22	'epidemiology'/de OR 'prospective study'/exp OR 'cohort analysis'/exp OR cohort:ti,ab,kw OR ((case NEAR/5 (control OR controll* OR comparison OR referent)):ti,ab,kw) OR risk:ti,ab,kw OR causation:ti,ab,kw OR causal:ti,ab,kw OR 'odds ratio':ti,ab,kw OR etiol*:ti,ab,kw OR aetiol*:ti,ab,kw OR 'natural history':ti,ab,kw OR predict*:ti,ab,kw OR prognos*:ti,ab,kw OR outcome:ti,ab,kw OR course:ti,ab,kw OR retrospect*:ti,ab,kw OR 'case control':ti,ab,kw OR 'multivariate':ti,ab,kw OR followup:ti,ab,kw OR 'follow up':ti,ab,kw	**11119520**
#18	#17 NOT #15	**118**
#17	#13 AND #16	**150**
#16	'randomized controlled trial'/exp OR random*:ti,ab,kw OR (((pragmatic OR practical) NEAR/1 'clinical trial*'):ti,ab,kw) OR ((('non inferiority' OR noninferiority OR superiority OR equivalence) NEAR/3 trial*):ti,ab,kw)	**2045803**
#15	#13 AND #14	**58**
#14	('meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab) NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp) NOT ('conference abstract'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it)	**705870**
#13	#12 NOT ('conference abstract'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'case report'/exp) AND [1999-2023]/py	**1033**
#12	#11 NOT ('conference abstract'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'case report'/exp)	**1052**
#11	#10 NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	**1728**
#10	#9 NOT (('adolescent'/exp OR 'child'/exp) NOT ('adult'/exp OR 'aged'/exp OR 'middle aged'/exp))	**1731**
#9	#1 AND #2 AND #3 AND #8	**1735**
#8	#4 OR #5 OR #6 OR #7	**2935052**
#7	'nuclear magnetic resonance imaging'/exp OR (('magnetic resonance' NEAR/3 imag*):ti,ab,kw) OR mri:ti,ab,kw OR mris:ti,ab,kw OR nmr:ti,ab,kw OR mra:ti,ab,kw OR mras:ti,ab,kw OR zeugmatograph*:ti,ab,kw OR 'mr tomograph*':ti,ab,kw OR 'proton spin':ti,ab,kw OR (((magneti* OR 'chemical shift') NEAR/3 imag*):ti,ab,kw) OR fmri:ti,ab,kw OR fmris:ti,ab,kw	**1519472**
#6	'computer assisted emission tomography'/exp OR 'gated single photon emission computed tomography'/exp OR 'single photon emission computer tomography'/exp OR spect:ti,ab,kw OR petscan*:ti,ab,kw OR 'pet scan*':ti,ab,kw OR ((emission NEAR/3 tomograph*):ti,ab,kw) OR radionuclid*:ti,ab,kw	**373318**

#5	'x-ray tomography'/exp OR 'computed tomograph*':ti,ab,kw OR ct:ti,ab,kw OR cts:ti,ab,kw OR 'cat scan*':ti,ab,kw OR 'computer assisted tomograph*':ti,ab,kw OR 'computerized tomograph*':ti,ab,kw OR 'computerised tomograph*':ti,ab,kw OR 'computed x ray tomograph*':ti,ab,kw OR 'computed xray tomograph*':ti,ab,kw	**1026673**
#4	'endoscopy'/de OR 'digestive tract endoscopy'/de OR 'esophagogastroduodenoscopy'/de OR 'gastrointestinal endoscopy'/de OR 'pharyngoscopy'/de OR 'laryngoscopy'/exp OR endoscop*:ti,ab,kw OR gastroscop*:ti,ab,kw OR laryngoscop*:ti,ab,kw OR esophagoscop*:ti,ab,kw OR oesophagoscop*:ti,ab,kw	**504563**
#3	'survival rate'/exp OR 'survival analysis'/exp OR 'survivor'/de OR 'cancer survivor'/de OR 'reoperation'/de OR ((surviv* NEAR/3 (rate OR mean OR analys* OR 'disease free' OR 'progression free' OR 'event free' OR overall)):ti,ab,kw) OR survivor*:ti,ab,kw OR (surg*:ti,ab,kw AND adj3:ti,ab,kw AND (revis*:ti,ab,kw OR repeat*:ti,ab,kw))	**1148912**
#2	'chemoradiotherapy'/de OR chemoradio*:ti,ab,kw OR radiochemo*:ti,ab,kw OR 'chemo radio*':ti,ab,kw OR 'radio chemo*':ti,ab,kw OR chemoradiati*:ti,ab,kw	**102465**
#1	'esophagus tumor'/exp OR (((oesophag* OR esophag* OR gastroesophag* OR gastrooesophag* OR oesogastr* OR esogastr*) NEAR/3 (carcinoma* OR neoplas* OR tumour* OR adenoma* OR adenocarcinoma* OR tumor* OR cancer* OR oncolog* OR malignan* OR carcinogen* OR oncogen* OR anticarcinogen* OR squamous*)):ti,ab,kw)	**125442**

Aanvulling 27 mei met de uitkomsten 'metastases' en 'kwaliteit van leven'

Ovid/Medline 27 mei 2023

Ovid MEDLINE(R) ALL <1946 to May 25, 2023>

1	exp Esophageal Neoplasms/ or ((carcinoma* or neoplas* or adenoma* or adenocarcinoma* or tumor* or tumour* or cancer* or oncolog* or malignan* or carcinogen* or oncogen* or anticarcinogen* or squamous*) adj3 (oesophag* or esophag* or gastroesophag* or gastrooesophag* or oesogastr* or esogastr*)).ti,ab,kf.	**79060**
2	exp Chemoradiotherapy/ or (chemoradio* or radiochemo* or chemo-radio* or radio-chemo* or chemoradiati*).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word]	**51440**
3	exp Neoplasm Metastasis/ or (metasta* or seeding* or micrometasta*).ti,ab,kf.	**716194**
4	exp "Quality of Life"/ or (quality-of-life or qoli or qol or qolis or hrqol* or hr-qol* or life-qual*).ti,ab,kf.	**434799**
5	3 or 4	**1135104**
6	Endoscopy/ or exp Laryngoscopy/ or exp Endoscopy, Gastrointestinal/ or (endoscop* or gastroscop* or laryngoscop* or esophagoscop* or oesophagoscop*).ti,ab,kf.	**335712**
7	exp Tomography, X-Ray Computed/ or (computed-tomograph* or ct or cts or cat-scan* or computer-assisted-tomograph* or computerized-tomograph* or computerised-tomograph* or computed-x-ray-tomograph* or computed-xray-tomograph*).ti,ab,kf.	**840604**
8	exp Tomography, Emission-Computed/ or (spect or petscan* or pet-scan* or pet or (emission adj3 tomogra*) or radionuclid*).ti,ab,kf.	**240281**
9	exp Magnetic Resonance Imaging/ or ((magnetic-resonance adj3 imag*) or mri or mris or nmr or mra or mras or zeugmatograph* or mr-tomograph* or proton-spin or ((magneti* or chemical-shift) adj3 imag*) or fmri or fmris).ti,ab,kf.	**932004**
10	6 or 7 or 8 or 9	**2032856**
11	1 and 2 and 5 and 10	**688**
12	11 not ((Adolescent/ or Child/ or Infant/) not Adult/)	**688**
13	12 not ((exp animals/ or exp models, animal/) not humans/)	**688**
14	13 not (comment/ or editorial/ or letter/ or Case Reports/)	**507**
15	limit 14 to yr="1999 -Current"	**488**
16	(systematic-review.pt. or (meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data extraction" or "data source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid)	**635721**

	adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.)) not (comment/ or editorial/ or letter/ or ((exp animals/ or exp models, animal/) not humans/))	
17	15 and 16	**23**
18	exp randomized controlled trial/ or random*.ti,ab,kf. or ((pragmatic or practical) adj clinical trial*).ti,ab,kf. or ((non-inferiority or noninferiority or superiority or equivalence) adj3 trial*).ti,ab,kf.	**1554523**
19	(15 and 18) not 17	**44**
20	exp Epidemiologic Studies/ or (cohort or (case adj5 (control or controll* or comparison or referent)) or risk or causation or causal or odds-ratio or etiol* or aetiol* or natural-history or predict* or prognos* or outcome or course or retrospect* or followup or follow-up).ti,ab,kf.	**8469031**
21	(15 and 20) not (17 or 19)	**356**

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No.	Query	Results
#21	#15 AND #20 NOT (#17 OR #19)	**636**
#20	'epidemiology'/de OR 'prospective study'/exp OR 'cohort analysis'/exp OR cohort:ti,ab,kw OR ((case NEAR/5 (control OR controll* OR comparison OR referent)):ti,ab,kw) OR risk:ti,ab,kw OR causation:ti,ab,kw OR causal:ti,ab,kw OR 'odds ratio':ti,ab,kw OR etiol*:ti,ab,kw OR aetiol*:ti,ab,kw OR 'natural history':ti,ab,kw OR predict*:ti,ab,kw OR prognos*:ti,ab,kw OR outcome:ti,ab,kw OR course:ti,ab,kw OR retrospect*:ti,ab,kw OR 'case control':ti,ab,kw OR 'multivariate':ti,ab,kw OR followup:ti,ab,kw OR 'follow up':ti,ab,kw	**11156975**
#19	#15 AND #18 NOT #17	**96**
#18	'randomized controlled trial'/exp OR random*:ti,ab,kw OR (((pragmatic OR practical) NEAR/1 'clinical trial*'):ti,ab,kw) OR ((('non inferiority' OR noninferiority OR superiority OR equivalence) NEAR/3 trial*):ti,ab,kw)	**2051905**
#17	#15 AND #16	**61**
#16	('meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab) NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp) NOT ('conference abstract'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it)	**709516**
#15	#13 NOT ('conference abstract'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'case report'/exp) AND [1999-2023]/py	**931**
#14	#13 NOT ('conference abstract'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'case report'/exp)	**956**
#13	#12 NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	**1960**
#12	#11 NOT (('adolescent'/exp OR 'child'/exp) NOT ('adult'/exp OR 'aged'/exp OR 'middle aged'/exp))	**1966**
#11	#1 AND #2 AND #5 AND #10	**1967**
#10	#6 OR #7 OR #8 OR #9	**2946237**
#9	'nuclear magnetic resonance imaging'/exp OR (('magnetic resonance' NEAR/3 imag*):ti,ab,kw) OR mri:ti,ab,kw OR mris:ti,ab,kw OR nmr:ti,ab,kw OR mra:ti,ab,kw OR mras:ti,ab,kw OR zeugmatograph*:ti,ab,kw OR 'mr tomograph*':ti,ab,kw OR 'proton spin':ti,ab,kw OR (((magneti* OR 'chemical shift') NEAR/3 imag*):ti,ab,kw) OR fmri:ti,ab,kw OR fmris:ti,ab,kw	**1524676**

#8	'computer assisted emission tomography'/exp OR 'gated single photon emission computed tomography'/exp OR 'single photon emission computer tomography'/exp OR spect:ti,ab,kw OR petscan*:ti,ab,kw OR 'pet scan*':ti,ab,kw OR ((emission NEAR/3 tomograph*):ti,ab,kw) OR radionuclid*:ti,ab,kw	**374555**
#7	'x-ray tomography'/exp OR 'computed tomograph*':ti,ab,kw OR ct:ti,ab,kw OR cts:ti,ab,kw OR 'cat scan*':ti,ab,kw OR 'computer assisted tomograph*':ti,ab,kw OR 'computerized tomograph*':ti,ab,kw OR 'computerised tomograph*':ti,ab,kw OR 'computed x ray tomograph*':ti,ab,kw OR 'computed xray tomograph*':ti,ab,kw	**1030961**
#6	'endoscopy'/de OR 'digestive tract endoscopy'/de OR 'esophagogastroduodenoscopy'/de OR 'gastrointestinal endoscopy'/de OR 'pharyngoscopy'/de OR 'laryngoscopy'/exp OR endoscop*:ti,ab,kw OR gastroscop*:ti,ab,kw OR laryngoscop*:ti,ab,kw OR esophagoscop*:ti,ab,kw OR oesophagoscop*:ti,ab,kw	**507790**
#5	#3 OR #4	**1878971**
#4	'quality of life'/exp OR 'quality of life':ti,ab,kw OR qoli:ti,ab,kw OR qol:ti,ab,kw OR qolis:ti,ab,kw OR hrqol*:ti,ab,kw OR 'hr qol*':ti,ab,kw OR 'life qual*':ti,ab,kw	**781281**
#3	'metastasis'/exp OR metasta*:ti,ab,kw OR seeding*:ti,ab,kw OR micrometasta*:ti,ab,kw	**1136733**
#2	'chemoradiotherapy'/de OR chemoradio*:ti,ab,kw OR radiochemo*:ti,ab,kw OR 'chemo radio*':ti,ab,kw OR 'radio chemo*':ti,ab,kw OR chemoradiati*:ti,ab,kw	**102849**
#1	'esophagus tumor'/exp OR (((oesophag* OR esophag* OR gastroesophag* OR gastrooesophag* OR oesogastr* OR esogastr*) NEAR/3 (carcinoma* OR neoplas* OR tumour* OR adenoma* OR adenocarcinoma* OR tumor* OR cancer* OR oncolog* OR malignan* OR carcinogen* OR oncogen* OR anticarcinogen* OR squamous*)):ti,ab,kw)	**125890**

Module 3 Palliatie van dysfagie

Uitgangsvraag
Wat is de optimale behandeling voor palliatie van dysfagie bij het niet curabel oesofaguscarcinoom?

Introduction
Dysphagia is common in esophageal cancer. Managing dysphagia in patients with incurable esophageal carcinoma is crucial to enhance their quality of life and promote well-being. In the Netherlands, various treatments are employed to alleviate dysphagia in cases of incurable esophageal carcinoma, namely brachytherapy, stent placement, and external beam radiotherapy.

Search and select
A systematic review of the literature was performed to answer the following question:

P: patients with palliation of dysphagia in incurable esophageal cancer;
I: Brachytherapy;
C: external beam radiotherapy;
O: improvement of dysphagia (validated scale), quality of life (validated scale), complications/adverse events.

Relevant outcome measures
The guideline development group considered improvement of dysphagia, quality of life, complications/adverse events as a critical outcome measures for decision making.

A priori, the working group did not define the outcome measures listed above but used the definitions used in the studies.

The working group defined a difference on 10 points on the Quality of Life scale and a difference of 1 point on the Mellow & Inkas scale as a minimal clinically (patient) important difference.

Search and select (Methods)
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until May 22nd, 2023. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 102 hits. Studies were selected based on the following criteria: following the right PICO, methodology of SR or RCT. Twelve studies were initially selected based on title and abstract screening. After reading the full text, eight studies were excluded (see the table with reasons for exclusion under the tab Methods), and four studies were included (of which one Cochrane review).

Results
Three randomised studies were included in the analysis of the literature. Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables.

Summary of literature

Description of studies

Three studies were found that compared the two treatment modalities in combination in a randomized setting; two studies compared brachytherapy monotherapy with brachytherapy plus external beam radiotherapy (sur, 2004 and Rosenblatt, 2010), and one study compared external beam radiotherapy (EBRT) with or without brachytherapy (Yadav 2007). No randomized studies were found that compared the two modalities directly. One Cochrane review was included where one comparison was relevant for the current topic (Yang, 2014). In the relevant comparison of this review, no other studies were included then two of the three described original studies (Sur, 2004 and Rosenblatt, 2010).

Sur (2004)

In the study executed by Sur in 2004, in the Johannesburg Hospital in South-Africa, two methods of palliation of dysphagia are compared in combination: high-dose-rate intraluminal brachytherapy (2x8 Gy HDR) alone versus high-dose-rate intraluminal brachytherapy with external beam therapy (10x3 Gy EBRT). A total of 60 non-metastatic squamous cell carcinoma patients were randomized to one of these two arms. The participants were followed for a year, and dyspgahia-free survival, and overall survival were measured, as well as adverse effects.

Rosenblatt (2010)

In the study executed by Rosenblatt in 2010, 219 squamous cell carcinoma patients were randomized in a multi-center study in six countries (Brazil, Croatia, China, India. South-Africa and Sudan) to either high-dose-rate intraluminal brachytherapy alone (2x8 Gy HDR), or high-dose-rate intraluminal brachytherapy with external beam therapy (10x3 Gy EBRT). The median follow-up rate was 197 days, and primary outcome was dysphagia relief experience. Other outcomes were performance status, weight and adverse events.

Yadav (2007)

In the study executed by Yadav in 2007, 116 squamous cell carcinoma patients were randomized to either external beam radiotherapy (EBRT) with two sessions of brachytherapy (ILBT), or EBRT alone in two different doses (high and low). The study took place in the Chandigarh Postgraduate Institute of Medical Education and Research, India. The median follow-up was 9 months, and the included outcomes were Improvement in Mean Dysphagia Grade, barium/endoscopy response and toxicity score.

Results

Improvement of dysphagia

In the study by Sur (2004), dysphagia was measured with a scoring system that defined dysphagia as 1: no dysphagia, 2: dysphagia to solids, 3: dysphagia to semisolids, 4: dysphagia to liquids and 5: total dysphagia. These scores were not analyzed, only dysphagia free survival was used as an outcome. This did not differ between the two groups after 12 months.

In the study by Rosenblatt (2010), dysphagia was defined as Dysphagia-relief experience (DRE) and measured similarly as in the study by Sur (2004). A log-rank test was performed on the proportion of participants without a dysphagia event between the study arms, and the estimated differences in absolute percent chance of not having experienced a dysphagia-event when high-dose-rate intraluminal brachytherapy was added were +16.0% after 100 days, +17.8% after 200 days and +19.0% after 300 days. Cox regression analyses were conducted hierarchically. For the addition of EBRT the p-value was 0.022, ignoring other

variables. Then, during stepwise addition of covariates, p-values were always <0.02, and the final p-value was 0.014 in favor of a combined therapy, stratified by country. No other variable was significantly associated with DRE once the addition of EBRT was taken into account.

In the study by Yadav (2007), dysphagia relief was measured according to the WHO grading. The study reports that the study arm of EBRT plus ILBT had a maximum improvement of 36.7%, followed by the study arm of EBRT alone in high dose with a maximum improvement of 28.6% in dysphagia. After 1 month there was no further improvement in dysphagia in all the three arms. At 6 months, improvement in mean dysphagia grade in the EBRT plus ILBT arm was 21%, in the EBRT in high dose arm it was 15.6%; while in the EBRT in low dose arm it was only 14.2%.

Quality of life
No included study used quality of life as an outcome in their trials.

Complications/adverse events
In the Cochrane review done by Yang (2014), the outcome of adverse events was evaluated (among other outcomes and comparisons). The studies of Sur (2004) and Rosenblatt (2010) were included in this systematic review on the outcome of adverse events. The meta-analysis is summarized in Figure 1. The number of adverse events did not differ significantly between the groups of brachytherapy versus brachytherapy plus radiotherapy.

In the study by Yadav (2007), radiation toxicity was reported, but not analyzed.

Analysis 9.1. Comparison 9: Brachytherapy versus brachytherapy plus radiotherapy, Outcome 1: Adverse effects

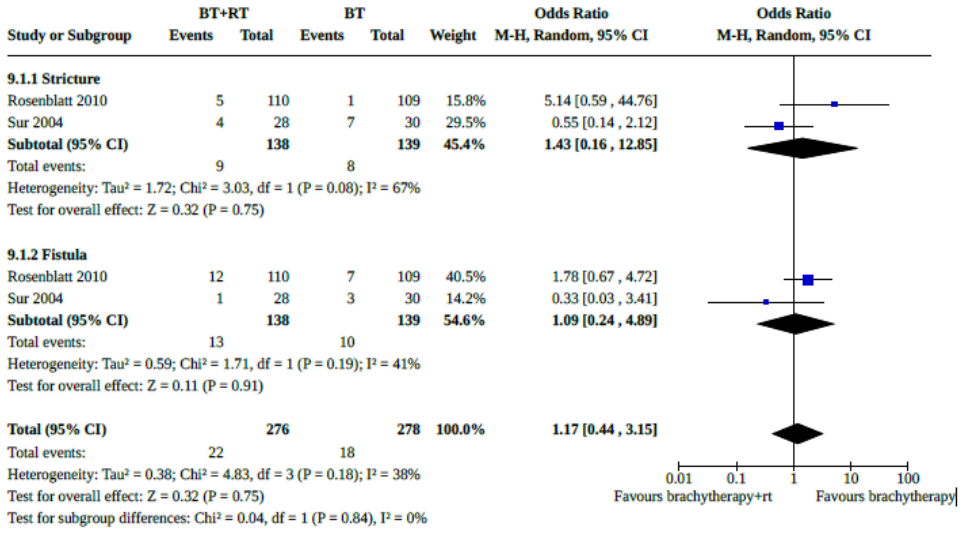

Figure 1. Meta-analysis of adverse events within brachytherapy versus brachytherapy plus radiotherapy (Yang 2014)

Level of evidence of the literature
The level of evidence regarding the outcome measure **Improvement of Dysphagia** was downgraded by three levels: one level because of study limitations (risk of bias) due to the unblinded study design of the included studies; one level because of applicability since the compared arms in the study were not similar to those defined in the PICO (bias due to indirectness); and one level because of the limited number of included patients (imprecision).

The level of evidence regarding the outcome measure **Adverse events** was downgraded by three levels: one level because of study limitations (risk of bias) due to the unblinded study design of the included studies; one level because of applicability since the compared arms in the study were not similar to those defined in the PICO (bias due to indirectness); and one level because of the limited number of included patients (imprecision).

Conclusions

Improvement of Dysphagia

Very low GRADE	The evidence is very uncertain on the effect of brachytherapy versus external beam radiotherapy on reducing dysphagia in patients with palliation of dysphagia in incurable esophageal cancer. *Source: Sur, 2004; Rosenblatt, 2010; Yadav, 2007*

Quality of Life

- GRADE	No evidence from randomized studies was found regarding the effect of brachytherapy and/or external beam radiotherapy on quality of life for patients with palliation of dysphagia in incurable esophageal cancer. *Source: -*

Adverse events

Very low GRADE	The evidence is very uncertain on the number of adverse events occurring in patients treated with brachytherapy versus external beam radiotherapy in patients with palliation of dysphagia in incurable esophageal cancer. *Source: Sur, 2004; Rosenblatt, 2010*

Overwegingen – van bewijs naar aanbeveling

<u>Voor- en nadelen van de interventie en de kwaliteit van het bewijs</u>

Wanneer gekeken wordt naar de geïncludeerde studies, komt geen duidelijk beeld naar voren van een voorkeur voor external beam radiotherapie of brachytherapie voor de behandeling van patiënten met palliatie van dysfagie bij een niet curabel oesofaguscarcinoom. In de geïncludeerde studies is er geen directe vergelijking gemaakt tussen brachytherapie en external beam radiotherapie. Er is in de studies ook niet gekeken naar kwaliteit van leven. Wel lijkt er een voorkeur te zijn voor een combinatie van beide therapieën vergeleken met monotherapie wanneer wordt gekeken naar verbetering van dysfagieklachten; in de systematic review werd geen verschil gevonden in aantal complicaties. De twee therapievormen zijn wel directer met elkaar vergeleken in een onderzoek met een prospectief observationeel design, namelijk de POLDER-studie (Jeene, 2020). Uit deze studie blijkt dat kortdurende external beam radiotherapie (5 fracties van 4Gy) minstens zo effectief is als brachytherapie op het verminderen van dysfagieklachten en dat dysfagieklachten sneller minder werden bij external beam radiotherapie dan bij brachytherapie. Ook is er in dezelfde POLDER-studie gekeken naar patient reported outcomes zoals kwaliteit van leven, waarbij er een voorkeur bleek voor EBRT op basis van scores op misselijkheid, overgeven, pijn en eetlustvermindering (van Rossum, 2021).

In het onderzoek uitgevoerd door Vermeulen in 2020 werden 292 patiënten retrospectief geanalyseerd, waarbij een vergelijking werd gemaakt tussen lage dosis externe radiotherapie (5x4 Gy) en hoge dosis radiotherapie (10x3 Gy EBRT gevolgd door 1x12 Gy brachytherapie). Het onderzoek vond plaats in Nederland, bij het Radboud Universitair

Medisch Centrum Nijmegen en Radiotherapiegroep. Het primaire resultaat was verbetering van dysfagie zes weken na het begin van de stralingstherapie. Bijkomende resultaten waren aanhoudende en terugkerende dysfagie gedurende het resterende leven van de patiënten, ernstige bijwerkingen en overleving. Uit deze studie bleek dat een hogere dosis EBRT gevolgd door een brachyboost na 6 weken termijn vergelijkbare verbetering gaf van dysfagie als een lage dosis EBRT. Wel trad er na een hogere dosis radiotherapie minder vaak terugkeer op van dysfagieklachten. Dit werd bevestigd in de studie van Walterbos in 2019, echter waren dit kleine en heterogene groepen. Er was geen verschil in toxiciteit.

Overige behandelopties bij dysfagie
In twee gerandomiseerde onderzoeken (Adam, 1997 en Dallal, 2001) werden laserbehandeling en stentplaatsing met elkaar vergeleken. In het onderzoek van Adam et al. werd alleen wat betreft het aantal behandelingen voor hernieuwde passageklachten een verschil gevonden, namelijk 12% voor laser en 33% voor stentplaatsing (27). Patiënten die met de laser werden behandeld, ondergingen echter elke vier weken een vervolgbehandeling, zodat laserbehandelde patiënten waarschijnlijk toch vaker een behandeling ondergingen. In het onderzoek van Dallal et al. was het enige verschil dat laserbehandelde patiënten, die met intervallen van vier tot zes weken werden behandeld, significant langer leefden dan patiënten die een stent kregen (28). Dit verschil is echter, gezien het biologisch gedrag van een inoperabel oesofaguscarcinoom, moeilijk te begrijpen. Verder werd in dit onderzoek gevonden dat de kwaliteit van leven sneller achteruitging in de stentgroep, wat wellicht uit het verschil in overleving te verklaren valt, terwijl de behandelingskosten van laser hoger waren. Concluderend lijken stentplaatsing en laserbehandeling even effectief wat betreft de verbetering van passageklachten op korte termijn, maar heeft laserbehandeling het nadeel dat patiënten elke vier tot zes weken dienen terug te komen voor een vervolgbehandeling.

In de SIREC-trial werden patiënten gerandomiseerd tussen brachytherapie en stentplaatsing. Beide interventies gaven goede verlichting van dysfagie, waarbij het effect van een stent sneller optrad maar het effect van brachytherapie langer aanhield. De auteurs concludeerden dat een stent de eerste keus heeft bij patiënten met een prognose van minder dan 3 maanden en dat bij een betere prognose brachytherapie de voorkeur heeft.

Voor wat betreft de radiotherapie-dosis lijkt een dosis van 5x4 Gy voor kortdurende palliatie bij patiënten met gemetastaseerde ziekte vergelijkbaar met brachytherapie. Er zijn aanwijzingen dat een hogere bestralingsdosis een langduriger effect heeft op de dysfagie. Of een hogere dosis te prefereren is boven een eventuele herbestraling is onbekend.

Het valt te overwegen om bij patiënten met beperkte dysfagie die gaan starten met systemische therapie eerst het effect van systeemtherapie af te wachten.

<u>Kosten, aanvaardbaarheid, haalbaarheid en implementatie</u>
EBRT is beter beschikbaar, minder invasief en heeft lagere kosten en een eenvoudiger logistiek. Daarmee gaat de voorkeur uit naar EBRT.

Aanbeveling
<u>Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies</u>
Plaats een stent indien de levensverwachting korter is dan drie maanden, gezien het snelle effect op de verbetering van passageklachten.

Bij een geschatte levensverwachting van meer dan drie maanden gaat de voorkeur uit naar radiotherapie gezien het langer aanhoudende effect. Aangezien er geen voordeel lijkt te zijn voor brachytherapie ten opzichte van EBRT spelen andere argumenten een rol in de keuze tussen EBRT en brachytherapie. Gelet op de betere beschikbaarheid van EBRT, het non-invasieve karakter, de lagere kosten en de eenvoudigere logistiek rondom EBRT gaat de voorkeur uit naar EBRT.

Geef kortdurend External Beam Radio Therapy (EBRT) (5x4 Gy) bij patiënten met dysfagie veroorzaakt door een incurabel oesofaguscarcinoom en een beperkte levensverwachting. Overweeg bij patiënten met een langere levensverwachting een hogere dosis.

Plaats een stent indien de levensverwachting korter is dan drie maanden, gezien het snelle effect op de verbetering van passageklachten.

Literatuur

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Jeene PM, Vermeulen BD, Rozema T, Braam PM, Lips I, Muller K, van Kampen D, Homs MYV, Oppedijk V, Berbée M, van Rossum PSN, El Sharouni S, Siersema PD, Hulshof MCCM; POLDER Study Group. Short-Course External Beam Radiotherapy Versus Brachytherapy for Palliation of Dysphagia in Esophageal Cancer: A Matched Comparison of Two Prospective Trials. J Thorac Oncol. 2020 Aug;15(8):1361-1368. Doi: 10.1016/j.jtho.2020.04.032. Epub 2020 May 11. PMID: 32407795.

Rosenblatt E, Jones G, Sur RK, Donde B, Salvajoli JV, Ghosh-Laskar S, Frobe A, Suleiman A, Xiao Z, Nag S. Adding external beam to intra-luminal brachytherapy improves palliation in obstructive squamous cell oesophageal cancer: a prospective multi-centre randomized trial of the International Atomic Energy Agency. Radiother Oncol. 2010 Dec;97(3):488-94. Doi: 10.1016/j.radonc.2010.09.001. Epub 2010 Oct 13. PMID: 20950882.

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Van Rossum PSN, Jeene PM, Rozema T, Braam PM, Lips IM, Muller K, van Kampen D, Vermeulen BD, Homs MYV, Oppedijk V, Berbée M, Hulshof MCCM, Siersema PD, El Sharouni SY. Patient-reported outcomes after external beam radiotherapy versus brachytherapy for palliation of dysphagia in esophageal cancer: A matched comparison of two prospective trials. Radiother Oncol. 2021 Feb;155:73-79. Doi: 10.1016/j.radonc.2020.10.009. Epub 2020 Oct 14. PMID: 33065190.

Vermeulen BD, Jeene PM, Sijben J, Krol R, Rütten H, Bogers JA, Braam PM, Siersema PD. Low-Dose Versus High-Dose Radiation Therapy for the Palliation of Dysphagia From Esophageal Cancer: A Multicenter Retrospective Cohort Study. Pract Radiat Oncol. 2020 Jul-Aug;10(4):e255-e263. Doi: 10.1016/j.prro.2019.10.010. Epub 2019 Oct 24. PMID: 31669401.

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Yang C, Li J, Fu W, Xu W, Yang S. Interventions for dysphagia in oesophageal cancer. Cochrane Database of Systematic Reviews 2014, Issue 10. Art. No.: CD005048. DOI: 10.1002/14651858.CD005048.pub4. Accessed 10 October 2023.

Bijlagen bij hoofdstuk 'Palliatie van dysfagie'

Evidence tables

Study reference	Study characteristics	Patient characteristics [2]	Intervention (I)	Comparison / control I [3]	Follow-up	Outcome measures and effect size [4]	Comments
Sur, 2004	Type of study: One-centred randomized controlled trial Setting and country: Johannesburg Hospital, University of Witwatersrand, Johannesburg, South-Africa Funding and conflicts of interest: The study was supported by technical contract no. 302-E3-SAF-10800 of the International Atomic Energy Agency, Vienna, Austria. There is no conflicts of interest statement.	Inclusion criteria: lesion in the thoracic esophagus; Inoperable advanced disease; histologically proven squamous cell carcinoma; and an ECOG performance score of 0–2 Exclusion criteria: evidence of distant metastasis; involvement of tncogenheo-bronchial tree on bronchoscopy and/or barium swallow N total at baseline: Intervention: 30 Control: 30	Describe intervention (treatment/procedure/test): Treatment with high-dose-rate intraluminal brachytherapy (HDRILBT) with a Microselectron HDR unit followed by external beam radiotherapy (named Group B in the study)	Describe control (treatment/procedure/test): Treatment with high-dose-rate intraluminal brachytherapy (HDRILBT) with a Microselectron HDR unit alone (named Group A in the study)	Length of follow-up: 1 year Loss-to-follow-up: Intervention: N=2 (7%) Reasons: these two participants refused treatment with EBRT because they had no dysphagia at the time of randomization. These participants were excluded from the analysis and subsequently lost to follow-up Control: No loss to follow-up Incomplete outcome data: No incomplete outcome data	Outcome measures and effect size (include 95%CI and p-value if available): There was no statistically significant difference (p>0.05) in DFS between the two groups at the end of 12 months. The overall survival of the two groups was also similar (p>0.05). The median survival for Group A was 7.2 months, whereas for Group B it was 7.5 months. The addition of EBRT did not appear to improve DFS or OS in this analysis. In terms of adverse effects potentially attributable to radiotherapy, 11 patients developed strictures (7 patients in Group A and 4 in Group B, p>0.05). Furthermore, 4 patients had	Pilot study, therefore underpowered

		Important prognostic factors[2]: *age ± SD:* *I: 52.8 (38-69)* *C: 54.0 (33-70)* *Sex:* *I: 63% M* *C: 70% M* Groups comparable at baseline? Yes				progressive luminal disease that progressed to fistula (3 in Group A and 1 in Group B, p>0.05).	
Rosenblatt, 2010	Type of study: Multi-centred, international randomized controlled trial Setting and country: The study was executed in Brazil, Croatia, China, India. South-Africa and Sudan Funding and conflicts of interest: sponsorship of this trial has been the International Atomic Energy Agency (IAEA) under Coordinated	Inclusion criteria: dysphagia prior to treatment; performance status Eastern Cooperative Oncology Group (ECOG) 1 to 2 (19); squamous cell carcinoma of the oesophagus; Successful completion of one HDRBT insertion; and signed informed consent	Describe intervention (treatment/procedure/test): HDRBT plus EBRT	Describe control (treatment/procedure/test): HDRBT alone	Length of follow-up: Median: 197 days Loss-to-follow-up: Intervention: None reported Control: None reported Incomplete outcome data: None reported	Outcome measures and effect size (include 95%CI and p-value if available): Overall survival: There was no effect of the intervention on overall survival: 'Overall survival was significantly influenced by both age and ECOG on a univariate log-rank analysis. Step-wise regression led to a model with only older age (p = 0.002) and lower ECOG (p = 0.038) as significant predictors of	

	Research Project E3.30.21. Authors declare no conflicts of interest.	Exclusion criteria: fistulae at baseline; perforation during the first HDRBT; prior therapy (e.g. chemotherapy, laser, surgery, stent) except one prior dilatation; disease beyond the mediastinum, or being eligible and agreeing to potentially curative therapies N total at baseline: Intervention: 110 Control: 109 Important prognostic factors[2]: *age:* *I: 60.7* *C: 61.9* *Sex:* *I: 64% M* *C: 54 % M*				better survival. Thus, randomization to EBRT was clearly not associated with improved overall survival.' Important clinical events See table 1 Dysphagia-relief experience (DRE) At 100 days, the DRE was 66.7% with HDRBT alone, but it was 82.7% with combined therapy. At 200 days, the respective values were 51.8 and 69.6%; at 300 days these were 36.9 and 55.9%, indicating a continued benefit. Therefore the estimated differences in absolute percent chance of not having experienced a dysphagia-event, and in favor of the addition of EBRT to HDRBT were +16.0%, +17.8% and +19.0%, respectively. Cox regression analyses were conducted hierarchically. For the addition of EBRT the p-	

		Groups comparable at baseline? Yes, no significant differences between the two groups				value was 0.022, ignoring other variables.	
Yadav, 2007	Type of study: RCT Setting and country: Department of radiotherapy and gastroenterology, PGIMER, Chandigarh, India Funding and conflicts of interest: None disclosed in the article, funding also not disclosed	<u>Inclusion criteria</u>: biopsy proven squamous cell carcinoma, tumor more than or equal to 5 cm in length on endoscopy and/or barium swallow, surgically inoperable disease, age; 17 to 70 years, Karnofsky performance score > 50 and no prior malignancy in the past 5 years. <u>N total at baseline</u>: Intervention: 38 Control: Arm B 40, arm C 38	Describe intervention (treatment/procedure/test): Arm A: external beam radiation (EBRT) to a dose of 30Gy/10 #/2 weeks along with two sessions of intraluminal brachytherapy (ILBT), 600cGy each, one week apart, after a gap of two weeks from EBRT	Describe control (treatment/procedure/test): Arm B: only EBRT to a dose of 30Gy/10 #/2 weeks Arm C: EBRT to a dose of 20Gy/5#/1week without brachytherapy	<u>Length of follow-up</u>: Median 9 months (range 3-34 months) <u>Loss-to-follow-up</u>: Intervention: N= 2(6%) Reasons (describe) Reasons not described Control: Arm B: N=2 (5.7%) Arm C: N=5 (14%) Reasons not described <u>Incomplete outcome data</u>: None reported	Outcome measures and effect size (include 95%CI and p-value if available): <u>Improvement in Mean Dysphagia Grade</u> Arm-A had maximum improvement of 36.7%, followed by Arm-B 28.6%. After 1 month there was no further improvement in dysphagia in all the three arms. At 6 months, improvement in mean dysphagia grade in Arm-A was 21%, in Arm-B it was 15.6%; while in Arm-C it was only 14.2%. <u>Barium/endoscopy Response</u> On barium swallow / endoscopic assessment; at 3	No conflicts of interest disclosed

		Important prognostic factors[2]: *No analyses done.* Groups comparable at baseline? Endoscopic status may differ significantly between groups.				months of interval in Arm-A 68.8% of patients had shown improvement while 32.2% had stable disease. In Arm-B 61.2% had improvement and 39.8% were with stable disease. In Arm-C, only 45.6% patients had improvement. At six months, 53.8% of patients in Arm-A had improvement and 26.6% had stable disease. In Arm-B results were 33.6%and 24.6% respectively. In Arm-C only 22.6% of patients had improvement, while 16.9% had stable disease. Toxicity score See table 2	

Risk of bias table

Study reference (first author, publication year)	**Was the allocation sequence adequately generated?**	**Was the allocation adequately concealed?**	**Blinding: Was knowledge of the allocated interventions adequately prevented?** **Were patients blinded?**	**Was loss to follow-up (missing outcome data) infrequent?**	**Are reports of the study free of selective outcome reporting?**	**Was the study apparently free of other problems that could put it at a risk of bias?**	**Overall risk of bias** **If applicable/necessary, per outcome measure**

	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	**Were healthcare providers blinded?** **Were data collectors blinded?** **Were outcome assessors blinded?** **Were data analysts blinded?** Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	**LOW** **Some concerns** **HIGH**
Sur, 2004	Definitely yes Reason: A random number table was used	No information	Definitely no Reason: Patients and health care providers were not blinded, no information on blinding of data collectors and analysts	Probably yes Reason: Loss to follow-up was infrequent in intervention and control group.	Definitely yes; Reason: All relevant outcomes were reported	Probably no Reason: Pilot study and therefore underpowered	HIGH Unblinded and underpowered study
Rosenblatt, 2010	Definitely yes; Reason: Central randomization by Data Management Centre, stratified by centres with 1-to-1 allocation	No information	Definitely no Reason: Patients and health care providers were not blinded, no information on blinding of data collectors and analysts	Probably yes Reason: Loss to follow-up was infrequent in intervention and control group.	Definitely yes; Reason: All relevant outcomes were reported	Definitely yes; Reason: No other problems noted	Some concerns
Yadav, 2007	Definitely yes Reason: Tippet's random number table was used	No information	Definitely no Reason: Patients and health care providers were not blinded, no	Probably yes Reason: Loss to follow-up was infrequent in	Definitely yes; Reason: All relevant	Definitely yes; Reason: No other problems noted	Some concerns

			information on blinding of data collectors and analysts	intervention and control group.	outcomes were reported		

Table of excluded studies

Reference	Reason for exclusion
Chakarova A, Karanov S, Petkova E, Bakardjiev S, Bogdanov G. Brachytherapy after laser recanalization versus external beam radiotherapy after laser recanalization versus laser alone in inoperable oesophagocardial cancer: a controlled pilot study. J BUON. 2005 Oct-Dec;10(4):511-6. PMID: 17357209.	Not the pre-defined treatment modalities of interest
Eldeeb H, Reza S, Shmueli U, Logsdail G, Hinks P, Mukherjee S. External beam radiotherapy versus brachytherapy in the management of malignant oesophageal dysphagia: a retrospective study. J BUON. 2012 Jul-Sep;17(3):508-11. PMID: 23033290.	Observational study
Hanna WC, Sudarshan M, Roberge D, David M, Waschke KA, Mayrand S, Alcindor T, Ferri LE. What is the optimal management of dysphagia in metastatic esophageal cancer? Curr Oncol. 2012 Apr;19(2):e60-6. doi: 10.3747/co.19.892. PMID: 22514498; PMCID: PMC3320233.	Observational study
Jeene PM, Vermeulen BD, Rozema T, Braam PM, Lips I, Muller K, van Kampen D, Homs MYV, Oppedijk V, Berbée M, van Rossum PSN, El Sharouni S, Siersema PD, Hulshof MCCM; POLDER Study Group. Short-Course External Beam Radiotherapy Versus Brachytherapy for Palliation of Dysphagia in Esophageal Cancer: A Matched Comparison of Two Prospective Trials. J Thorac Oncol. 2020 Aug;15(8):1361-1368. doi: 10.1016/j.jtho.2020.04.032. Epub 2020 May 11. PMID: 32407795.	Observational study
Lancellotta V, Cellini F, Fionda B, De Sanctis V, Vidali C, Fusco V, Barbera F, Gambacorta MA, Corvò R, Magrini SM, Tagliaferri L. The role of palliative interventional radiotherapy (brachytherapy) in esophageal cancer: An AIRO (Italian Association of Radiotherapy and Clinical Oncology) systematic review focused on dysphagia-free survival. Brachytherapy. 2020 Jan-Feb;19(1):104-110. doi: 10.1016/j.brachy.2019.09.005. Epub 2019 Oct 18. PMID: 31636025.	Not the pre-defined treatment modalities of interest
Opstelten JL, de Wijkerslooth LR, Leenders M, Bac DJ, Brink MA, Loffeld BC, Meijnen-Bult MJ, Minderhoud IM, Verhagen MA, van Oijen MG, Siersema PD. Variation in palliative care of esophageal cancer in clinical practice: factors associated with treatment decisions. Dis Esophagus. 2017 Feb 1;30(2):1-7. doi: 10.1111/dote.12478. PMID: 26919349.	Observational study
Pichel RC, Araújo A, Domingues VDS, Santos JN, Freire E, Mendes AS, Romão R, Araújo A. Best Supportive Care of the Patient with Oesophageal Cancer. Cancers (Basel). 2022 Dec 19;14(24):6268. doi: 10.3390/cancers14246268. PMID: 36551753; PMCID: PMC9776873.	Narrative review (although systematic search is in place)
van Rossum PSN, Jeene PM, Rozema T, Braam PM, Lips IM, Muller K, van Kampen D, Vermeulen BD, Homs MYV, Oppedijk V, Berbée M, Hulshof MCCM, Siersema PD, El Sharouni SY. Patient-reported outcomes after external beam radiotherapy versus brachytherapy for palliation of dysphagia in esophageal cancer: A matched comparison of two prospective trials. Radiother Oncol. 2021 Feb;155:73-79. doi: 10.1016/j.radonc.2020.10.009. Epub 2020 Oct 14. PMID: 33065190.	Observational study

Literature search strategy

Aantallen treffers en ontdubbeling

22 mei 2023	Aantal treffers	Aantal treffers na ontdubbelen
Medline	52	51
Embase	99	51
Totaal	151	102

Ovid/Medline 22 mei 2023 (52)
Ovid MEDLINE(R) ALL <1946 to May 18, 2023>

1	exp Esophageal Neoplasms/ or ((carcinoma* or neoplas* or adenoma* or adenocarcinoma* or tumor* or tumour* or cancer* or oncolog* or malignan* or carcinogen* or oncogen* or anticarcinogen* or squamous*) adj3 (oesophag* or esophag* or gastroesophag* or gastrooesophag* or oesogastr* or esogastr*)).ti,ab,kf.	**78972**
2	Deglutition Disorders/ or Esophageal Motility Disorders/ or (((deglutiti* or swallow*) adj3 (disorder* or disease* or problem*)) or dysphagi* or ((esophag* or oesophag*) adj3 motil*	**47552**

	adj3 (disorder or disease or problem)) or ((esophag* or oesophag*) adj3 dysmotil*) or (nutcrack* adj3 (esophag* or oesophag*))).ti,ab,kf.	
3	exp Brachytherapy/ or (brachytherap* or brachy-therap* or curietherap* or curie-therap* or (plaque* adj3 (therap* or treatment*)) or ((surfac* or intracavit* or interstitial* or implant*) adj3 (radiation* or radiotherap* or radio-therap*))).ti,ab,kf.	**33580**
4	(Radiotherapy/ and external*.ti,ab,kf.) or (external* adj3 (radiation* or radiotherap* or radio-therap*)).ti,ab,kf.	**18852**
5	1 and 2 and 3 and 4	**81**
6	"32407795".ui.	**1**
7	5 and 6	**1**
8	5	**81**
9	limit 8 to yr="2000 -Current"	**56**
10	9 not ((Adolescent/ or Child/ or Infant/) not Adult/)	**56**
11	10 not ((exp animals/ or exp models, animal/) not humans/)	**56**
12	11 not (comment/ or editorial/ or letter/ or Case Reports/)	**52**

Embase.com 22 mei 2023

No.	Query	Results
#9	#8 NOT ('conference abstract'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'case report'/exp)	**99**
#8	#7 NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	**147**
#7	#6 NOT (('adolescent'/exp OR 'child'/exp) NOT ('adult'/exp OR 'aged'/exp OR 'middle aged'/exp))	**148**
#6	#1 AND #2 AND #3 AND #4 AND [2000-2023]/py	**148**
#5	#1 AND #2 AND #3 AND #4	**173**
#4	'external beam radiotherapy'/exp OR ('radiotherapy'/de AND external*:ti,ab,kw) OR ((external* NEAR/3 (radiation* OR radiotherap* OR 'radio therap*')):ti,ab,kw)	**119207**
#3	'brachytherapy'/de OR 'interstitial radiation'/de OR brachytherap*:ti,ab,kw OR 'brachy therap*':ti,ab,kw OR curietherap*:ti,ab,kw OR 'curie therap*':ti,ab,kw OR ((plaque* NEAR/3 (therap* OR treatment*)):ti,ab,kw) OR (((surfac* OR intracavit* OR interstitial* OR implant*) NEAR/3 (radiation* OR radiotherap* OR 'radio therap*')):ti,ab,kw)	**57369**
#2	'dysphagia'/de OR 'esophagus function disorder'/de OR (((deglutiti* OR swallow*) NEAR/3 (disorder* OR disease* OR problem*)):ti,ab,kw) OR dysphagi*:ti,ab,kw OR (((esophag* OR oesophag*) NEAR/3 motil* NEAR/3 (disorder OR disease OR problem)):ti,ab,kw) OR (((esophag* OR oesophag*) NEAR/3 dysmotil*):ti,ab,kw) OR ((nutcrack* NEAR/3 (esophag* OR oesophag*)):ti,ab,kw)	**106945**
#1	'esophagus tumor'/exp OR (((oesophag* OR esophag* OR gastroesophag* OR gastrooesophag* OR oesogastr* OR esogastr*) NEAR/3 (carcinoma* OR neoplas* OR tumour* OR adenoma* OR adenocarcinoma* OR tumor* OR cancer* OR oncolog* OR malignan* OR carcinogen* OR oncogen* OR anticarcinogen* OR squamous*)):ti,ab,kw)	**125789**

Module 4 Palliatieve immuuntherapie

Uitgangsvraag
Wat is de rol van eerstelijns immunotherapie in de palliatieve fase bij een carcinoom van de maag, gastro-oesofageale overgang of oesofagus?

Introduction
Esophageal and gastric cancers have limited treatment options in the locally advanced and metastatic setting, with chemotherapy resistance limiting efficacy beyond the first- or second-line setting. With the exception of trastuzumab and ramucirumab, results of clinical trials utilizing targeted agents have been disappointing. The last years a lot of research has been focusing on the use of immunotherapy. Immunotherapy can have an anti-tumor effect by activating the innate immune systems through blocking of PD-1, PD-L1 or CTLA-4, among others, all checkpoint molecules involved in immune activation. These so-called checkpoint have been incorporated in the treatment paradigm of various solid cancer types, as monotherapy or in combination or following chemotherapy, in a biomarker-unselected population or only in patients with certain molecular features or upregulation of checkpoint proteins. PD-L1 upregulation occurs in approximately 40% of gastroesophageal cancers.

Here we discuss the role of first-line immunotherapy in the palliative setting in patients with gastric carcinoma, gastro-oesophageal junction, or oesophageal carcinoma.

Search and select
A systematic review of the literature was performed to answer the following question:
What is the effect of immunotherapy (with or without chemotherapy) compared to standard of care or best supportive care on overall survival, progression-free survival, adverse events and quality of life as first line therapy for patients with unresectable or metastatic gastric, gastro-oesophageal junction, or oesophageal carcinoma?

P: patients with unresectable or metastatic gastric, gastro-oesophageal junction, or oesophageal adenocarcinoma or squamous cell carcinoma;
I: first-line immunotherapy +/- chemotherapy;
C: standard of care (chemotherapy) or best supportive care;
O: overall survival, progression-free survival, adverse events, quality of life.

Relevant outcome measures
The guideline development group considered overall survival as a critical outcome measure for decision making, and progression-free survival, adverse events and quality of life as important outcome measures for decision making.

The working group defined the outcome measures as follows:
- Overall survival: Time to death from any cause
- Progression-free survival: Time from randomization or initiation of treatment to the occurrence of disease progression or death from any cause
- Adverse events: Grade 3 or higher adverse events of any cause
- Quality of life: Quality of life measured by a validated instrument

The working group defined the following differences as a minimal clinically (patient) important difference:
If median overall survival in control group ≤12 months:
- Overall survival: >12 weeks **and** hazard ratio (HR)<0.7

If median overall survival in control group >12 months:

- Overall survival: >16 weeks **and** hazard ratio (HR)<0.7
- Progression-free survival: >16 weeks **and** hazard ratio (HR)<0.7

- Adverse events: absolute difference >5% for lethal complications, or >25% for serious complications
- Quality of life: validated questionnaire, e.g. Functional Assessment of Cancer Therapy-Gastric (FACT-Ga): 15.1 points or Functional Assessment of Cancer Therapy-Esophagus (FACT-E): 9.5 points

Search and select (Methods)

The databases Medline (via OVID) and Embase (via Embase.com) were searched from 2015 until 29-05-2023. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 807 hits. Studies were selected based on the following criteria:

- Systematic reviews or randomized controlled trials (RCTs)
- Full-text English language publication
- Complying with the PICO criteria

We initially selected 176 studies based on title and abstract screening, from which one recent systematic review (Duan, 2023) was used as the basis for this literature summary. This systematic review included phase III RCTs with patients with unresectable locally advanced or metastatic gastric oesophageal cancer, and compared immunotherapy-based regimens with chemotherapy alone. The outcomes that were reported were OS, PFS, ORR, DCR and/or AEs. Duan searched PubMed, Embase and Cochrane Library electronic databases with relevant search terms until June 2022. Detailed search strategies were published in supplemental tables (Duan, 2023).

After reading the full text of the RCTs published after the search date from the systematic review by Duan, seventeen RCTs were excluded (see the table with reasons for exclusion under the tab Methods), and 2 additional RCTs were included (Song, 2023; Xu, 2023).

Results

The selected systematic review included nine RCTs. With the two additional RCTs, this resulted in eleven studies that were included in the analysis of the literature. One publication of the KEYNOTE-811 study (Janjigian, 2023) was added, as the first interim analysis (Janjigian, 2021) did not report the selected outcomes. Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables.

GRADE

GRADE was applied to assess the certainty of the evidence for the main comparisons, subgroups and critical outcome measures. The credibility of subgroup effects was assessed using the following criteria:

1. Is the subgroup variable a characteristic specified at baseline or after randomization? (subgroup hypotheses should be developed a priori)
2. Is the subgroup difference suggested by comparisons within rather than between studies?
3. Does statistical analysis suggest that chance is an unlikely explanation for the subgroup difference?

4. Did the hypothesis precede rather than follow the analysis and include a hypothesized direction that was subsequently confirmed?
5. Was the subgroup hypothesis one of a smaller number tested?
6. Is the subgroup difference consistent across studies and across important outcomes?
7. Does external evidence (biological or sociological rationale) support the hypothesized subgroup difference?

When subgroup analyses were considered convincing and showed an interaction between the **PD-L1 status** and the magnitude of effect, we only graded the evidence for the subgroups and only presented conclusions for the subgroups.

Summary of literature

Description of studies

Song (2023) - ASTRUM-007 describes a randomized, double-blind, phase 3 trial, which was conducted in 70 institutes in China with a median follow-up length of 15.0 months. The researchers evaluated the efficacy and safety of first-line serplulimab plus chemotherapy versus placebo plus chemotherapy in patients with previously untreated, PD-L1-positive advanced oesophageal squamous cell carcinoma. A total of 551 patients was randomized to receive serplulimab (n=368) (3 mg/kg) on day 1 once every 2 weeks for up to 2 years plus cisplatin (50 mg/m^2) on day 1 for up to 8 cycles and continuous infusion of 5-fluorouracil (1,200 mg/m^2) on days 1 and 2, for up to 12 cycles, both administered every 2 weeks, or placebo (n=183) plus the same chemotherapy regimen. The median age (range) was 64 (57-68) in the serplulimab group and 64 (57-68) in the placebo group. In the serplulimab group 86% of the participants was male, compared with 84% in the placebo group. The following relevant outcomes were reported: overall survival (OS), progression-free survival (PFS), and adverse events (AEs).

Xu (2023) - RATIONALE-306 describes a randomized, double-blind, phase 3 trial, which was conducted in 162 institutes across Asia, Europe, Oceania, and North America. The researchers evaluated the efficacy and safety of first-line tislelizumab plus chemotherapy versus placebo plus chemotherapy in patients with advanced or metastatic oesophageal squamous cell carcinoma. The median follow-up length was 16.4 months in the intervention group and 9.8 months in the control group. A total of 649 patients was randomized to receive tislelizumab (n=326) (200 mg) every 3 weeks on day 1 of 21-day cycles plus an investigator-chosen chemotherapy doublet, or matching placebo (n=323) plus an investigator-chosen chemotherapy doublet. The median age (range) was 64 (59-68) in the tislelizumab group and 65 (58-70) in the placebo group. In both the tislelizumab and the placebo group 87% of the participants was male. The following relevant outcomes were reported: OS, PFS, and AEs.

Doki (2022) - CHECKMATE-648 describes a randomized, open-label, three-arm phase 3 trial, which was conducted in 182 institutions in 26 countries with a minimum follow-up length of 13 months. The researchers evaluated the efficacy and safety of first-line nivolumab plus ipilimumab versus nivolumab plus chemotherapy versus chemotherapy alone in patients with previously untreated, unresectable advanced, recurrent, or metastatic oesophageal squamous cell carcinoma. A total of 970 patients was randomized to receive nivolumab (3 mg/kg every 2 weeks) plus ipilimumab (1 mg/kg every 6 weeks) (n=325), nivolumab (240 mg every 2 weeks) plus chemotherapy (4-week cycle of intravenous fluorouracil and cisplatin) (n=321), or chemotherapy alone (n=324). The median age (range) was 63 (28-81) in the nivolumab plus ipilimumab group, 64 (40-90) in the nivolumab plus chemotherapy group and 64 (26-81) in the chemotherapy alone group. The percentage of male participants was

83%, 79% and 85% for the three groups, respectively. The following relevant outcomes were reported: OS, pFS, AEs, and quality of life (QoL) (measured with FACT-E).

Kang (2022) - ATTRACTION-4 describes a randomized, double-blind, phase 3 trial, which was conducted in 130 institutions across Japan, South Korea and Taiwan with a median follow-up of 26.6 months. The researchers evaluated the efficacy and safety of first-line nivolumab plus chemotherapy versus placebo plus chemotherapy in patients with HER2-negative, untreated, unresectable advanced or recurrent gastric or gastro-oesophageal junction cancer. A total of 724 patients was randomized to receive nivolumab (360 mg every 3 weeks) plus chemotherapy (oxaliplatin 130 mg/m^2 plus either oral S-1 40 mg/m^2 or oral capecitabine) (n=362), or matching placebo plus the same chemotherapy regimen (n=362). The median age (range) was 64 (25-86) in the nivolumab plus chemotherapy group and 65 (27-89) in the placebo plus chemotherapy group. In the nivolumab group 70% of the participants was male, compared with 75% in the placebo group. The following relevant outcomes were reported: OS, pFS, AEs, and QoL (measured with EQ-5D-3L and FACT-Ga).

Lu (2022) - ORIENT-15 describes a randomized, double-blind, phase 3 trial, which was conducted in 79 institutions in 5 countries (China, France, Spain, United States and Australia). The researchers evaluated the efficacy and safety of first-line sintilimab plus chemotherapy versus placebo plus chemotherapy in patients with locally advanced or metastatic oesophageal squamous cell carcinoma. The median follow-up length was 16.0 months in the intervention group and 16.9 months in the control group. A total of 658 patients was randomized to receive sintilimab (3 mg/kg in patients weighing <60 kg or 200 mg in patients weighing ≥60 kg on day 1 of each cycle) plus chemotherapy (regimen chosen by the investigator) (n=327) or matching placebo plus chemotherapy (n=332). The median age (range) was 63 (57-67) in the sintilimab plus chemotherapy group and 63 (56-67) in the placebo plus chemotherapy group. In the sintilimab group 85% of the participants was male, compared with 87% in the placebo group. The following relevant outcomes were reported: OS, pFS, AEs, and QoL (measured with QLQ-C30, QLQ-OES18 and EQ-5D-5L).

Wang (2022) - JUPITER-06 describes a randomized, double-blind, phase 3 trial, which was conducted in 72 institutions across China with a median follow-up of 7.1 months. The researchers evaluated the efficacy and safety of first-line toripalimab plus chemotherapy versus placebo plus chemotherapy in patients with treatment-naïve advanced oesophageal squamous cell carcinoma. A total of 514 patients was randomized to receive toripalimab (240 mg) plus chemotherapy (paclitaxel 175 mg/m^2 and cisplatin 75 mg/m^2) (n=257) or matching placebo plus the same chemotherapy regimen (n=257). The median age (range) was 63 (20-75) in the toripalimab group and 62 (40-74) in the placebo group. In the toripalimab group 84% of the participants was male, compared with 86% in the placebo group. The following relevant outcomes were reported: OS, PFS, and AEs.

Janjigian (2021) - CHECKMATE-649 describes a randomized, open-label, phase 3 trial, which was conducted in 175 institutions in 29 countries across Asia, Australia, Europe, North America and South America with a median follow-up of 13.1 months. The researchers evaluated the efficacy and safety of first-line nivolumab plus chemotherapy versus chemotherapy alone in patients with advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma. A total of 1581 patients was randomized to receive nivolumab (360 mg every 3 weeks or 240 mg every 2 weeks) plus chemotherapy (investigator's choice) (n=789) or chemotherapy alone (n=792). The median age (range) was 62 (53-68) in the nivolumab group and 61 (53-68) in the chemotherapy group. In the nivolumab group 68% of the participants was male, compared with 71% in the

chemotherapy group. The following relevant outcomes were reported: OS, pFS, AEs, and QoL (measured with FACT-Ga).

Janjigian (2021), Janjigian (2023) - KEYNOTE-811 describes a randomized, double-blind, phase 3 trial, which was conducted in 186 institutions in 20 countries with a median follow-up of 38.4 (intervention) and 38.6 (control) months. The researchers evaluated the efficacy and safety of first-line pembrolizumab plus trastuzumab (targeted therapy) plus chemotherapy versus placebo plus trastuzumab plus chemotherapy in patients with previously untreated unresectable or metastatic, HER2-positive gastric or gastro-oesophageal junction adenocarcinoma. A total of 698 patients was randomized to receive pembrolizumab (200 mg every 3 weeks) plus trastuzumab (6 mg/kg every 3 weeks) plus chemotherapy (investigator's choice) (n=350) or matching placebo plus the same trastuzumab and chemotherapy regimen (n=348). The median age (range) was 62 (54-69) in the pembrolizumab plus trastuzumab plus chemotherapy group and 63 (55-70) in the trastuzumab plus chemotherapy group. The percentage of male participants was 81% and 80% for the two groups, respectively. The following relevant outcomes were reported: OS, PFS, and AEs.

Luo (2021) - ESCORT-1ST describes a randomized, double-blind, phase 3 trial, which was conducted in 60 institutions in China with a median follow-up of 10.8 months. The researchers evaluated the efficacy and safety of first-line camrelizumab plus chemotherapy versus placebo plus chemotherapy in patients with advanced or metastatic oesophageal squamous cell carcinoma. A total of 596 patients was randomized to receive camrelizumab (200 mg) plus chemotherapy (up to 6 cycles of paclitaxel and cisplatin) every 3 weeks (n=298) or matching placebo plus the same chemotherapy regimen (n=298). The median age (range) was 62 (56-66) in the camrelizumab group and 62 (56-67) in the placebo group. In the camrelizumab group 87% of the participants was male, compared with 88% males in the placebo group. The following relevant outcomes were reported: OS, pFS, AEs, and QoL (measured with QLQ-C30 and QLQ-OES18).

Sun (2021) - KEYNOTE-590 describes a randomized, double-blind, phase 3 trial, which was conducted in 168 institutions in 26 countries with a median follow-up of 22.6 months. The researchers evaluated the efficacy and safety of first-line pembrolizumab plus chemotherapy versus placebo plus chemotherapy in patients with advanced oesophageal cancer and Siewert type 1 gastro-oesophageal junction cancer (both adenocarcinoma and squamous cell carcinoma). A total of 749 patients was randomized to receive pembrolizumab (200 mg) plus chemotherapy (5-fluorouracil and cisplatin) every 3 weeks (n=373) or matching placebo plus the same chemotherapy regimen (n=376). The median age (range) was 64 (28-94) in the pembrolizumab group and 62 (27-89) in the placebo group. In the pembrolizumab group 82% of the participants was male, compared with 85% males in the placebo group. The following relevant outcomes were reported: OS, PFS and AEs.

Shitara (2020) - KEYNOTE-062 describes a randomized, partially blinded, three-arm phase 3 trial, which was conducted in 200 institutions in 29 countries with a median follow-up of 29.4 months. The researchers evaluated efficacy and safety of first-line pembrolizumab versus pembrolizumab plus chemotherapy versus placebo plus chemotherapy in patients with untreated, advanced gastric or gastro-oesophageal junction cancer with programmed cell death ligand 1 (PD-L1) combined positive score (CPS) of 1 or greater. A total of 763 patients was randomized to receive pembrolizumab (200 mg) (n=256), pembrolizumab plus chemotherapy (cisplatin plus fluorouracil) (n=257) or matching placebo plus chemotherapy (n=250). The median age (range) was 61 (20-83) in the pembrolizumab group, 62 (22-83) in

the pembrolizumab plus chemotherapy group and 63 (23-87) in the placebo plus chemotherapy group. The percentage of male participants was 70%, 76% and 72% for the three groups, respectively. The following relevant outcomes were reported: OS, PFS and AEs.

Results

Currently, pembrolizumab, nivolumab, and ipilimumab are the only available immunotherapy regimens in the Netherlands within the palliative setting for patients with unresectable or metastatic gastric, gastro-oesophageal junction, or oesophageal carcinoma. Therefore, the analysis of outcomes below is restricted to these regimens.
The studies with immunotherapy regimens containing pembrolizumab, nivolumab, and/or ipilimumab are presented in table 1.

Table 1. Study characteristics of the analysed studies

Study (author, year)	Study design	Intervention	Control	Type	PD-L1 subgroups	Reported outcomes
HER2-negative adenocarcinoma						
KEYNOTE-062 (a) (Shitara, 2020)	RCT (3 arms*)	Pembrolizumab n= 256	Placebo + CT n= 250	GC/GEJC	CPS 1 or more, CPS 10 or more	OS PFS AE
KEYNOTE-062 (b) (Shitara, 2020)	RCT (3 arms*)	Pembrolizumab + CT n= 257	Placebo + CT n= 250	GC/GEJC	CPS 1 or more, CPS 10 or more	OS PFS AE
CHECKMATE-649 (Janjigian, 2021)	RCT	Nivolumab + CT n= 789	CT n= 792	GC/GEJC/EC	CPS 1 or more, CPS 5 or more	OS PFS AE QoL (FACT-Ga)
ATTRACTION-4 (Kang, 2022)	RCT	Nivolumab + CT n= 362	Placebo + CT n= 362	GC/GEJC	TPS 1% or more	OS PFS AE QoL (FACT-Ga)
KEYNOTE-590 (Sun, 2021)	RCT	Pembrolizumab + CT n= 373 *(AC: n=99)*	Placebo + CT n= 376 *(AC: n=102)*	EC/GEJC[a]	CPS 10 or more	OS PFS AE
HER2-positive adenocarcinoma						
KEYNOTE-811 (Janjigian, 2021; Janjigian, 2023)	RCT	Pembrolizumab + trastuzumab + CT n= 350	Placebo + trastuzumab + CT n= 348	GC/GEJC	CPS 1 or more	OS PFS AE
Squamous cell carcinoma						
CHECKMATE-648 (a) (Doki, 2022)	RCT (3 arms*)	Nivolumab + ipilimumab n= 325	CT n= 324	EC	TPS 1% or more	OS PFS AE QoL (FACT-E)
CHECKMATE-648 (b) (Doki, 2022)	RCT (3 arms*)	Nivolumab + CT n= 321	CT n= 324	EC	TPS 1% or more	OS PFS AE QoL (FACT-E)
KEYNOTE-590 (Sun, 2021)	RCT	Pembrolizumab + CT n= 373 *(SCC: n=274)*	Placebo + CT n= 376 *(SCC: n=274)*	EC/GEJC[a]	CPS 10 or more	OS PFS AE

*** three-arm RCT: two comparisons**

AC = adenocarcinoma, AE = adverse events, CPS = combined positive score, CT = chemotherapy EC = esophageal cancer, GC = gastric cancer, GEJC = gastro-oesophageal junction cancer, NR = not reported , OS = overall survival, PFS = progression-free survival, TPS = tumor proportion score, QoL = quality of life, SCC = squamous cell carcinoma

[a] Siewert type 1 (GEJC not defined in the other included studies)

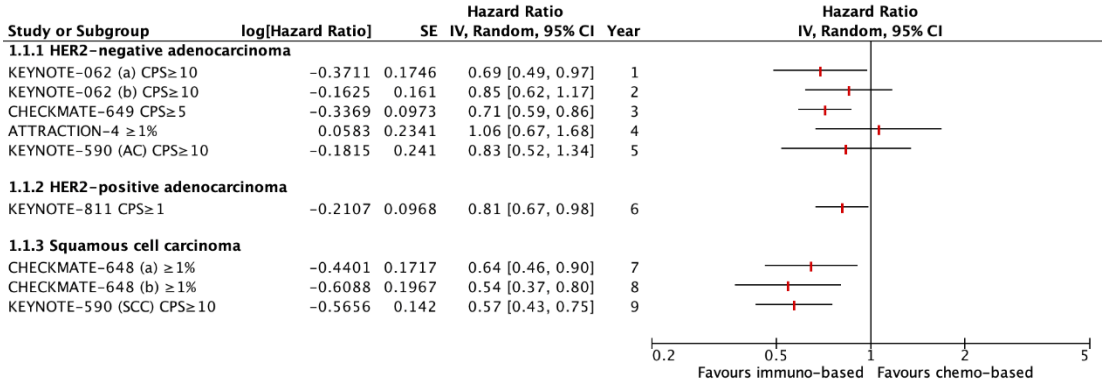

Figure 1. Outcome Overall survival with immunotherapy based regimen versus chemotherapy based regimen alone in PD-L1 subgroups

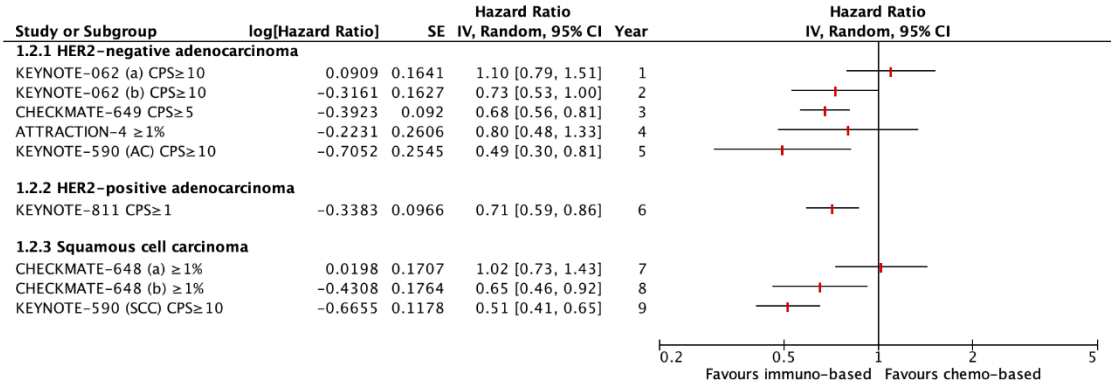

Figure 2. Outcome Progression-free survival with immunotherapy based regimen versus chemotherapy based regimen alone in PD-L1 subgroups

HER2-negative adenocarcinoma

Four studies reported outcomes for patients with a HER2-negative adenocarcinoma: KEYNOTE-062 (Shitara, 2020), CheckMate 649 (Janjigian, 2021), ATTRACTION-4 (Kang, 2022) and KEYNOTE-590 (Sun, 2021). The KEYNOTE-590 trial also included patients with a squamous cell carcinoma.

Overall survival (critical)

The median OS in the three-armed KEYNOTE-062 study was 10.6 months (95% CI: 7.7 to 13.8) in the pembrolizumab group versus 11.1 months (95% CI: 9.2 to 12.8) in the CT group (all randomized patients, PD-L1 CPS≥1). The HR was 0.91 (95% CI: 0.74 to 1.10).
The median OS was 12.5 months (95% CI: 10.8 to 13.9) in the pembrolizumab plus CT group versus 11.1 months (95% CI: 9.2 to 12.8) in the CT group (all randomized patients, PD-L1 CPS≥1). The HR was 0.85 (95% CI: 0.70 to 1.03). Nor pembrolizumab plus chemotherapy nor pembrolizumab monotherapy was superior to chemotherapy for OS in this population. Pembrolizumab was found to be non-inferior to chemotherapy for OS (all randomized patients, PD-L1 CPS≥1).

The median OS in the CheckMate 649 study was 13.8 months (95% CI: 12.6 to 14.6) in the nivolumab plus CT group versus 11.6 months (95% CI: 10.9 to 12.5) in the CT group. The HR was 0.80 (99.3% CI: 0.68 to 0.94) favoring nivolumab plus CT (Janjigian, 2021). This difference was not considered clinically relevant.

The median OS in the ATTRACTION-4 study was 17.5 months (95% CI: 15.7 to 20.8) in the nivolumab plus CT group versus 17.2 months (95% CI: 15.2 to 19.7) in the placebo plus CT

group. The HR was 0.90 (95% CI: 0.75 to 1.08) favoring nivolumab plus CT (Kang, 2022). This difference was not considered clinically relevant.

The median OS in the KEYNOTE-590 study was 12.4 months (95% CI: 10.5 to 14.0) in the pembrolizumab plus CT group versus 9.8 months (95% CI: 8.8 to 10.8) in the placebo plus CT group (all randomized patients). The hazard ratio (HR) was 0.73 (95% CI: 0.62 to 0.86) favoring pembrolizumab plus CT. In patients with adenocarcinoma (n=201), the HR for OS was 0.74 (95% CI: 0.54 to 1.02) (Sun, 2021). This difference was not considered clinically relevant.

Overall survival – PD-L1 subgroups (critical)
In the three-armed KEYNOTE-062 study, an OS subgroup analysis was done for patients with a PD-L1 CPS of 10 or more. The median OS in this subgroup was 17.4 months (95% CI: 9.1 to 23.1) in the pembrolizumab group (n=92) versus 10.8 months (95% CI: 8.5 to 13.8) in the CT group (n=90). The HR for this comparison was 0.69 (95% CI: 0.49 to 0.97) favoring pembrolizumab. This difference was considered clinically relevant.

The median OS in this subgroup was 12.3 months (95% CI: 9.5 to 14.8) in the pembolizumab plus CT group (n=99) versus 10.8 months (95% CI: 8.5 to 13.8) in the CT group (n=90). The HR for this comparison was 0.85 (95% CI: 0.62 to 1.17) (Shitara, 2020) favoring pembrolizumab plus CT. This difference was not considered clinically relevant.

In the CheckMate 649 study, an OS subgroup analysis was done for patients with a PD-L1 CPS of 5 or more. The median OS in this subgroup was 14.4 months (95% CI: 13.1 to 16.2) in the nivolumab plus CT group (n=473) versus 11.1 months (95% CI: 10.0 to 12.1) in the CT group (n=482). The HR was 0.71 (98.4% CI: 0.59 to 0.86) favoring nivolumab plus CT (Janjigian, 2021). This difference was not considered clinically relevant.

In the ATTRACTION-4 study, an OS subgroup analysis was done for patients with a PD-L1 TPS of 1% or more. The median OS in this subgroup was 16.6 months (95% CI: 10.5 to 22.7) in the nivolumab plus CT group (n=58) versus 16.6 months (95% CI: 10.1 to 23.5) in the placebo plus CT group (n=56). The HR was 1.06 (95% CI: 0.67 to 1.68) favoring placebo plus CT (Kang, 2022). This difference was not considered clinically relevant

In the KEYNOTE-590 study, an OS subgroup analysis was done for patients with a PD-L1 CPS of 10 or more. The median OS in this subgroup was 13.5 months (95% CI: 11.1 to 15.6) in the pembrolizumab plus CT group (n=186) versus 9.4 months (95% CI: 8.0 to 10.7) in the placebo plus CT group (n=197). The HR was 0.62 (95% CI: 0.49 to 0.78) (Sun, 2021) favoring pembrolizumab plus CT. This difference was considered clinically relevant.

In patients in this subgroup with adenocarcinoma (n=97), the HR was 0.83 (95% CI: 0.52 to 1.34) favoring pembrolizumab plus CT. This difference was not considered clinically relevant.

Progression-free survival
The median PFS in the three-armed KEYNOTE-062 study was 2.0 months (95% CI: 1.5 to 2.8) in the pembrolizumab group versus 6.4 months (95% CI: 5.7 to 7.0) in the CT group (all randomized patients, PD-L1 CPS≥1). The HR was 1.66 (95% CI: 1.37 to 2.01).

The median PFS was 6.9 months (95% CI: 5.7 TO 7.3) in the pembrolizumab plus CT group versus 6.4 months (95% CI: 5.7 to 7.0) in the CT group (all randomized patients, PD-L1

CPS≥1). The HR was 0.84 (95% CI: 0.70 to 1.02). Pembrolizumab plus chemotherapy was not superior to chemotherapy for PFS in this population.

The median PFS in the CheckMate 649 study was 7.7 months (95% CI: 7.1 to 8.5) in the nivolumab plus CT group versus 6.9 months (95% CI: 6.6 to 7.1) in the CT group. The HR was 0.77 (95% CI: 0.68 to 0.87) favoring nivolumab plus CT (Janjigian, 2021). As the median overall survival in the control group was <12 months, the clinical relevance of PFS was not considered.

The median PFS in the ATTRACTION-4 study was 10.5 months (95% CI: 8.4 to 14.8) in the nivolumab plus CT group versus 8.3 months (95% CI: 7.0 to 9.4) in the placebo plus CT group. The HR was 0.68 (98.5% CI: 0.51 to 0.90) favoring nivolumab plus CT (Kang, 2022). This difference was not considered clinically relevant.

The median PFS in the KEYNOTE-590 study was 6.3 months (95% CI: 6.2 to 6.9) in the pembrolizumab plus CT group versus 5.8 months (95% CI: 0.55 to 0.76) in the placebo plus CT group (all randomized patients). The HR was 0.65 (95% CI: 0.55 to 0.76) favoring pembrolizumab plus CT. In patients with adenocarcinoma (n=201), the HR for PFS was 0.63 (95% CI: 0.46 to 0.87) (Sun, 2021). As the median overall survival in the control group was <12 months, the clinical relevance of PFS was not considered.

Progression-free survival – PD-L1 subgroups
In the three-armed KEYNOTE-062 study, a PFS subgroup analysis was done for patients with a PD-L1 CPS of 10 or more. The median PFS in this subgroup was 2.9 months (95% CI: 1.6 to 5.4) in the pembrolizumab group (n=92) versus 6.1 months (95% CI: 5.3 to 6.9) in the CT group (n=90). The HR for this comparison was 1.10 (95% CI: 0.79 to 1.51) favoring CT.

The HR for the comparison pembrolizumab plus CT (n=99) versus CT (n=90) was 0.73 (95% CI: 0.53 to 1.00) favoring pembrolizumab plus CT, but the median PFS in months was not given (Shitara, 2020). As the median overall survival in the control group was <12 months, the clinical relevance of PFS was not considered.

In the CheckMate 649 study, a PFS subgroup analysis was done for patients with a PD-L1 CPS of 5 or more. The median PFS in this subgroup was 7.7 months (95% CI: 7.0 to 9.2) in the nivolumab plus CT group (n=473) versus 6.0 months (95% CI: 5.6 to 6.9) in the CT group (n=482). The HR was 0.68 (98% CI: 0.56 to 0.81) favoring nivolumab plus CT (Janjigian, 2021). As the median overall survival in the control group was <12 months, the clinical relevance of PFS was not considered.

In the ATTRACTION-4 study, a PFS subgroup analysis was done for patients with a PD-L1 TPS of 1% or more. The median PFS in this subgroup was 8.3 months (95% CI: 4.3 to 12.5) in the nivolumab plus CT group (n=58) versus 4.4 months (95% CI: 3.6 to 11.1) in the placebo plus CT group (n=56). The HR was 0.80 (95% CI: 0.48 to 1.33) favoring nivolumab plus CT (Kang, 2022). This difference was not considered clinically relevant.

In the KEYNOTE-590 study, a PFS subgroup analysis was done for patients with a PD-L1 CPS of 10 or more. The median PFS in this subgroup was 7.5 months (95% CI: 6.2 to 8.2) in the pembrolizumab plus CT group (n=186) versus 5.5 months (95% CI: 4.3 to 6.0) in the placebo plus CT group (n=197). The HR was 0.51 (95% CI: 0.41 to 0.65) (Sun, 2021) favoring pembrolizumab plus CT. As the median overall survival in the control group was <12 months, the clinical relevance of PFS was not considered.

In patients in this subgroup with adenocarcinoma (n=97), the HR was 0.49 (95% CI: 0.30 to 0.81) favoring pembrolizumab plus CT.

Adverse events
In the three-armed KEYNOTE-062 study, treatment-related adverse events of grade 3 or higher occurred in 43/254 patients (17%) in the pembrolizumab group, versus 183/250 patients (73%) in the pembrolizumab plus CT group, versus 169/244 (69%) in the CT group (Shitara, 2020).

The RR for the comparison pembrolizumab versus CT was 0.24 (95% CI: 0.18 to 0.33) favoring pembrolizumab. This difference was considered clinically relevant.

The RR for the comparison pembrolizumab plus CT versus CT was 1.06 (95% CI: 0.94 to 1.18) favoring CT. This difference was not considered clinically relevant.

In the CheckMate 649 study, adverse events of grade 3 or higher occurred in 466/782 patients (60%) in the nivolumab plus CT group versus 341/767 patients (44%) in the CT group. The most common adverse events were nausea, diarrhea and peripheral neuropathy (Janjigian, 2021). The RR for this comparison was 1.34 (95% CI: 1.22 to 1.48) favoring CT. This difference was not considered clinically relevant.

In the ATTRACTION-4 study, adverse events of grade 3 or higher occurred in 71/359 patients (20%) in the nivolumab plus CT group versus 57/358 patients (16%) in the placebo plus CT group. The most common adverse events were neutrophil count decreased, platelet count decreased and decreased appetite (Kang, 2022). The RR for this comparison was 1.24 (95% CI: 0.91 to 1.70) favoring placebo plus CT. This difference was not considered clinically relevant.

In the KEYNOTE-590 study, adverse events of grade 3 or higher occurred in 370/370 patients (100%) in the pembrolizumab plus CT group versus 318/370 patients (86%) in the placebo plus CT group. The most common adverse events were decreased neutrophil count, anaemia and neutropenia (Sun, 2021). The risk ratio (RR) for this comparison was 1.03 (95% CI: 0.97 to 1.10) favoring placebo plus CT. This difference was not considered clinically relevant.

Adverse events were not reported for histology subgroups.

Quality of life
Quality of life was assessed with the Functional Assessment of Cancer Therapy-Gastric (FACT-Ga) or Functional Assessment of Cancer Therapy-Esophagus (FACT-E) questionnaires.

Quality of life was a pre-specified end point in the KEYNOTE-062 study, but no results were reported yet (Shitara, 2020).

In the CheckMate 649 study, baseline mean FACT-Ga scores were similar between the nivolumab plus CT group (126.6 [28.3]) and the CT group (126.8 [26.8]). The least squares mean difference between the two groups favored nivolumab plus CT, but the result did not exceed the minimally important difference of 15.1 points (Janjigian, 2021).

In the ATTRACTION-4 study, baseline FACT-Ga total scores were similar between the nivolumab plus CT group and the placebo plus CT group. The HR for time to symptom deterioration was 0.86 (95% CI: 0.70 to 1.06) (Kang, 2022).

Quality of life was a pre-specified end point in the KEYNOTE-590 study, but no results were reported yet (Sun, 2021).

HER2-positive adenocarcinoma
One study reported outcomes for patients with a HER2-positive adenocarcinoma: KEYNOTE-811 (Janjigian, 2021; Janjigian, 2023).

Overall survival (critical)
OS was not reported in the results of the protocol-specified first interim analysis of the KEYNOTE-811 study (Janjigian, 2021).

At the third interim analysis (Janjigian, 2023), the median OS was 20.0 months (95% CI: 17.8-22.1) in the pembrolizumab plus trastuzumab plus CT group versus 16.8 months (95% CI: 15.0-18.7) in the placebo plus trastuzumab plus CT group. The HR was 0.84 (95% CI: 0.70 to 1.01) favoring pembrolizumab plus trastuzumab plus CT (Janjigian, 2023). This difference was not considered clinically relevant.

Overall survival – PD-L1 subgroup (CPS≥1) (critical)
In the KEYNOTE-811 study, an OS subgroup analysis was done for patients with a PD-L1 CPS of 1 or more. The median OS in this subgroup was 20.0 months (95% CI: 17.9 to 22.7) in the pembrolizumab plus trastuzumab plus CT group versus 15.7 months (95% CI: 13.5 to 18.5) in the placebo plus trastuzumab plus CT group. The HR was 0.81 (95% CI: 0.67 to 0.98) favoring pembrolizumab plus trastuzumab plus CT (Janjigian, 2023). This difference was not considered clinically relevant.

Progression-free survival
PFS was not reported in the results of the protocol-specified first interim analysis of the KEYNOTE-811 study (Janjigian, 2021).

At the third interim analysis (Janjigian, 2023), the median PFS was 10.0 months (95% CI: 8.6 to 12.2) in the pembrolizumab plus trastuzumab plus CT group versus 8.1 months (95% CI: 7.1 to 8.6) in the placebo plus trastuzumab plus CT group. The HR was 0.73 (95% CI: 0.61 to 0.87) favoring pembrolizumab plus trastuzumab plus CT (Janjigian, 2023). This difference was not considered clinically relevant.

Progression-free survival – PD-L1 subgroup (CPS≥1)
In the KEYNOTE-811 study, a PFS subgroup analysis was done for patients with a PD-L1 CPS of 1 or more. The median PFS in this subgroup was 10.9 months (95% CI: 8.5 to 12.5) in the pembrolizumab plus trastuzumab plus CT group versus 7.3 months (95% CI: 6.8 to 8.5) in the placebo plus trastuzumab plus CT group. The HR was 0.71 (95% CI: 0.59 to 0.86) favoring pembrolizumab plus trastuzumab plus CT (Janjigian, 2023). This difference was not considered clinically relevant.

Adverse events
In the KEYNOTE-811 study, adverse events of grade 3 or higher occurred in 248/350 patients (71%) in the pembrolizumab plus trastuzumab plus CT group versus 225/348 patients (65%) in the placebo plus trastuzumab plus CT group. The most common adverse events were diarrhea and anaemia (Janjigian, 2023). This difference was not considered clinically relevant.

Quality of life
Quality of life was not an endpoint of the KEYNOTE-811 study (Janjigian, 2021; Janjigian, 2023).

Squamous cell carcinoma
Two studies reported outcomes for patients with a squamous cell carcinoma: CheckMate 648 (Doki, 2022) and KEYNOTE-590 (Sun, 2021). The KEYNOTE-590 trial also included patients with a HER2-negative adenocarcinoma.

Overall survival (critical)
The median OS in the three-armed CheckMate 648 study was 13.2 months (95% CI: 11.1 to 15.7) in the nivolumab plus CT group versus 10.7 months (95% CI: 9.4 to 11.9) in the CT group. The HR was 0.74 (99.1% CI: 0.58 to 0.96) favoring nivolumab plus CT (Doki, 2022). This difference was not considered clinically relevant.

The median OS was 12.7 months (95% CI: 11.3 to 15.5) in the nivolumab plus ipilimumab group versus 10.7 months (95% CI: 9.4 to 11.9) in the CT group. The HR was 0.78 (98.2% CI: 0.62 to 0.98) favoring nivolumab plus ipilimumab (Doki, 2022). This difference was not considered clinically relevant.

The median OS in the KEYNOTE-590 study was 12.4 months (95% CI: 10.5 to 14.0) in the pembrolizumab plus CT group versus 9.8 months (95% CI: 8.8 to 10.8) in the placebo plus CT group (all randomized patients). The hazard ratio (HR) was 0.73 (95% CI: 0.62 to 0.86) favoring pembrolizumab plus CT. In patients with squamous cell carcinoma (n=548), the HR for OS was 0.72 (95% CI: 0.60 to 0.88) (Sun, 2021). This difference was not considered clinically relevant.

Overall survival – PD-L1 subgroups (critical)
In the three-armed CheckMate 648 study, an OS subgroup analysis was done for patients with a PD-L1 TPS of 1% or more. The median OS in this subgroup was 15.4 months (95% CI: 11.9 to 19.5) in the nivolumab plus CT group (n=158) versus 9.1 months (95% CI: 7.7 to 10.0) in the CT group (n=157). The HR was 0.54 (99.5% CI: 0.37 to 0.80) favoring nivolumab plus CT (Doki, 2022). This difference was considered clinically relevant.

The median OS in this subgroup was 13.7 months (95% CI: 11.2 to 17.0) in the nivolumab plus ipilimumab group (n=158) versus 9.1 months (95% CI: 7.7 to 10.0) in the CT group (n=157). The HR was 0.64 (98.6% CI: 0.46 to 0.90) favoring nivolumab plus ipilimumab (Doki, 2022). This difference was considered clinically relevant.

In the KEYNOTE-590 study, a OS subgroup analysis was done for patients with a PD-L1 CPS of 10 or more. The median OS in this subgroup was 13.5 months (95% CI: 11.1 to 15.6) in the pembrolizumab plus CT group (n=186) versus 9.4 months (95% CI: 8.0 to 10.7) in the placebo plus CT group (n=197). The HR was 0.62 (95% CI: 0.49 to 0.78) (Sun, 2021) favoring pembrolizumab plus CT. This difference was considered clinically relevant.

In patients in this subgroup with squamous cell carcinoma (n=286), the HR was 0.57 (95% CI: 0.43 to 0.75) favoring pembrolizumab plus CT. This difference was considered clinically relevant.

Progression-free survival
The median PFS in the three-armed CheckMate 648 study was 5.8 months (95% CI: 5.6 to 7.0) in the nivolumab plus CT group versus 5.6 months (95% CI: 4.3 to 5.9) in the CT group. The HR was 0.81 (98.5% CI: 0.64 to 1.04) favoring nivolumab plus CT (Doki, 2022). As the median overall survival in the control group was <12 months, the clinical relevance of PFS was not considered.

The median PFS was 2.9 months (95% CI: 2.7 to 4.2) in the nivolumab plus ipilimumab group versus 5.6 months (95% CI: 4.3 to 5.9) in the CT group. The HR was 1.26 (95% CI: 1.04 to 1.52) favoring CT (Doki, 2022). As the median overall survival in the control group was <12 months, the clinical relevance of PFS was not considered.

The median PFS in the KEYNOTE-590 study was 6.3 months (95% CI: 6.2 to 6.9) in the pembrolizumab plus CT group versus 5.8 months (95% CI: 0.55 to 0.76) in the placebo plus CT group (all randomized patients). The HR was 0.65 (95% CI: 0.55 to 0.76) favoring pembrolizumab plus CT. In patients with squamous cell carcinoma (n=548), the HR for PFS was 0.65 (95% CI: 0.54 to 0.78) (Sun, 2021). As the median overall survival in the control group was <12 months, the clinical relevance of PFS was not considered.

Progression-free survival – PD-L1 subgroups
In the three-armed CheckMate 648 study, a PFS subgroup analysis was done for patients with a PD-L1 TPS of 1% or more. The median PFS in this subgroup was 6.9 months (95% CI: 5.7 to 8.3) in the nivolumab plus CT group (n=158) versus 4.4 months (95% CI: 2.9 to 5.8) in the CT group (n=157). The HR was 0.65 (98.5% CI: 0.46 to 0.92) favoring nivolumab plus CT (Doki, 2022). As the median overall survival in the control group was <12 months, the clinical relevance of PFS was not considered.

The median PFS in this subgroup was 4.0 months (95% CI: 2.4 to 4.9) in the nivolumab plus ipilimumab group (n=158) versus 4.4 months (95% CI: 2.9 to 5.8) in the CT group (n=157). The HR was 1.02 (98.5% CI: 0.73 to 1.43) favoring CT (Doki, 2022). As the median overall survival in the control group was <12 months, the clinical relevance of PFS was not considered.

In the KEYNOTE-590 study, a PFS subgroup analysis was done for patients with a PD-L1 CPS of 10 or more. The median PFS in this subgroup was 7.5 months (95% CI: 6.2 to 8.2) in the pembrolizumab plus CT group (n=186) versus 5.5 months (95% CI: 4.3 to 6.0) in the placebo plus CT group (n=197). The HR was 0.51 (95% CI: 0.41 to 0.65) (Sun, 2021) favoring pembrolizumab plus CT. As the median overall survival in the control group was <12 months, the clinical relevance of PFS was not considered.

In patients in this subgroup with squamous cell carcinoma (n=286), the HR was 0.53 (95% CI: 0.40 to 0.69) favoring pembrolizumab plus CT. This difference was considered clinically relevant.

Adverse events
In the three-armed CheckMate 648 study, adverse events of grade 3 or higher occurred in 147/310 patients (47%) in the nivolumab plus CT group versus 108/304 patients (36%) in the CT group. The most common adverse events were nausea, decreased appetite and stomatitis (Doki, 2022). The RR for this comparison was 1.33 (95% CI: 1.10 to 1.62) favoring CT. This difference was not considered clinically relevant.

Adverse events of grade 3 or higher occurred in 102/322 patients (32%) in the nivolumab plus ipilimumab group versus 108/304 patients (36%) in the CT group. The most common adverse events were nausea, decreased appetite and stomatitis (Doki, 2022). The RR for this comparison was 0.89 (95% CI: 0.72 to 1.11) favoring nivolumab plus ipilimumab. This difference was not considered clinically relevant.

In the KEYNOTE-590 study, adverse events of grade 3 or higher occurred in 370/370 patients (100%) in the pembrolizumab plus CT group versus 318/370 patients (86%) in the placebo plus CT group. The most common adverse events were decreased neutrophil count, anaemia and neutropenia (Sun, 2021). The risk ratio (RR) for this comparison was 1.03 (95% CI: 0.97 to 1.10) favoring placebo plus CT. This difference was not considered clinically relevant.

Adverse events were not reported for histology subgroups.

Quality of life
Quality of life was assessed with the Functional Assessment of Cancer Therapy-Gastric (FACT-Ga) or Functional Assessment of Cancer Therapy-Esophagus (FACT-E) questionnaires.

In the three-armed CheckMate 648 study, the least squares mean FACT-E change from baseline was 4.98 points (95% CI: 2.68 to 7.27) in the nivolumab plus CT group and 1.54 points (95% CI: -1.26 to 4.33) in the CT group. This result did not exceed the minimally important difference of 9.5 points (Doki, 2022).

The least squares mean FACT-E change from baseline was 3.45 points (95% CI: 0.96 to 5.94) in the nivolumab plus ipilimumab group and 1.54 points (95% CI: -1.26 to 4.33) in the CT group. This result did not exceed the minimally important difference of 9.5 points (Doki, 2022).

Quality of life was a pre-specified end point in the KEYNOTE-590 study, but no results were reported yet (Sun, 2021).

Level of evidence of the literature
The evidence for the outcomes overall survival (total population), progression-free survival (total population), adverse events and quality of life started at 'high'.

The evidence for the outcomes overall survival (PD-L1 subpopulations) and progression-free survival (PD-L1 subpopulations) was derived from observational data from subgroups of an RCT. Therefore the level of evidence started at 'low'.

HER2-negative adenocarcinoma
The level of evidence regarding the outcome measure **overall survival - PD-L1 subgroups** was downgraded by three levels because of study limitations (risk of bias), inconsistency (unexplained heterogeneity) and indirectness (differences in interventions). Therefore, the level of evidence was graded as very low.

The level of evidence regarding the outcome measure **progression-free survival - PD-L1 subgroups** was downgraded by two levels because of study limitations (risk of bias) and indirectness (differences in interventions). Therefore, the level of evidence was graded as very low.

The level of evidence regarding the outcome measure **adverse events** was downgraded by three levels because of study limitations (risk of bias), inconsistency (unexplained heterogeneity) and indirectness (differences in populations (histology) and interventions). Therefore, the level of evidence was graded as very low.

The level of evidence regarding the outcome measure **quality of life** was downgraded by two levels because of study limitations (risk of bias) and imprecision (number of included patients). Therefore, the level of evidence was graded as low.

HER2-positive adenocarcinoma
The level of evidence regarding the outcome measure **overall survival – PD-L1 subgroup** was downgraded by two levels because of study limitations (risk of bias) and number of included patients (imprecision). Therefore, the level of evidence was graded as very low.

The level of evidence regarding the outcome measure **progression-free survival – PD-L1 subgroup** was downgraded by two levels because of study limitations (risk of bias) and number of included patients (imprecision). Therefore, the level of evidence was graded as very low.

The level of evidence regarding the outcome measure **adverse events** was downgraded by two levels because of study limitations (risk of bias) and number of included patients (imprecision). Therefore, the level of evidence was graded as low.

The level of evidence regarding the outcome measure **quality of life** was not graded for the comparison pembrolizumab plus trastuzumab plus CT versus placebo plus trastuzumab plus CT, because none of the included studies reported this outcome.

Squamous cell carcinoma
The level of evidence regarding the outcome measure **overall survival - PD-L1 subgroups** was downgraded by two levels because of study limitations (risk of bias) and indirectness (differences in interventions). Therefore, the level of evidence was graded as very low.

The level of evidence regarding the outcome measure **progression-free survival - PD-L1 subgroups** was downgraded by two levels because of study limitations (risk of bias) and indirectness (differences in interventions). Therefore, the level of evidence was graded as very low.

The level of evidence regarding the outcome measure **adverse events** was downgraded by two levels because of study limitations (risk of bias) and indirectness (differences in populations (histology) and interventions). Therefore, the level of evidence was graded as low.

The level of evidence regarding the outcome measure **quality of life** was downgraded by three levels because of study limitations (risk of bias), indirectness (differences in interventions) and imprecision (number of included patients). Therefore, the level of evidence was graded as very low.

Conclusions

HER2-negative adenocarcinoma

Overall survival - PD-L1 subgroups

Very low GRADE	Immunotherapy (plus chemotherapy) may have a positive effect on overall survival compared to (placebo plus) chemotherapy in patients with a HER2-negative adenocarcinoma of the oesophagus, gastro-oesophageal junction or stomach with a PD-L1 CPS ≥5 or PD-L1 CPS≥10, but the evidence is very uncertain. *Source: Shitara, 2020; Janjigian, 2021; Kang, 2022; Sun, 2021*

Progression-free survival - PD-L1 subgroups

Very low GRADE	The evidence is very uncertain about the effect of immunotherapy (plus chemotherapy) on progression-free survival when compared with (placebo plus) chemotherapy in patients with a HER2-negative adenocarcinoma of the oesophagus, gastro-oesophageal junction or stomach with a PD-L1 CPS ≥5, PD-L1 CPS≥10 or PD-L1 TPS≥1%. *Source: Shitara, 2020; Janjigian, 2021; Kang, 2022; Sun, 2021*

Adverse events (≥grade 3)

Very low GRADE	The evidence is very uncertain about the effect of immunotherapy plus chemotherapy on adverse events when compared with (placebo plus) chemotherapy in patients with a HER2-negative adenocarcinoma of the oesophagus, gastro-oesophageal junction or stomach. Immunotherapy alone might result in less adverse events than chemotherapy, but this evidence is also very uncertain. *Source: Shitara, 2020; Janjigian, 2021; Kang, 2022; Sun, 2021*

Quality of life

Low GRADE	The evidence suggests that immunotherapy plus chemotherapy results in little to no difference in quality of life when compared with (placebo plus) chemotherapy in patients with a HER2-negative adenocarcinoma of the oesophagus, gastro-oesophageal junction or stomach. *Source: Janjigian, 2021; Kang, 2022*

HER2-positive adenocarcinoma

Overall survival - PD-L1 subgroup

Very low GRADE	The evidence is very uncertain about the effect of immunotherapy plus trastuzumab plus chemotherapy on overall survival when compared with placebo plus trastuzumab plus chemotherapy in patients with a HER2-positive adenocarcinoma of the gastro-oesophageal junction or stomach with a PD-L1 CPS≥1. *Source: Janjigian, 2021; Janjigian, 2023*

Progression-free survival - PD-L1 subgroup

Very low GRADE	The evidence is very uncertain about the effect of immunotherapy plus trastuzumab plus chemotherapy on progression-free survival when

	compared with placebo plus trastuzumab plus chemotherapy in patients with a HER2-positive adenocarcinoma of the gastro-oesophageal junction or stomach with a PD-L1 CPS≥1. *Source: Janjigian, 2021; Janjigian, 2023*

Adverse events (≥grade 3)

Low GRADE	The evidence suggests that immunotherapy plus trastuzumab plus chemotherapy results in little to no difference in adverse events when compared with placebo plus trastuzumab plus chemotherapy in patients with a HER2-positive adenocarcinoma of the gastro-oesophageal junction or stomach. *Source: Janjigian, 2021; Janjigian, 2023*

Quality of life

- GRADE	There is no evidence on the effect of immunotherapy plus trastuzumab plus chemotherapy on quality of life when compared with placebo plus trastuzumab plus chemotherapy in patients with a HER2-positive adenocarcinoma of the gastro-oesophageal junction or stomach. *Source: -*

<u>Squamous cell carcinoma</u>

Overall survival - PD-L1 subgroups

Very low GRADE	Double immunotherapy may have a positive effect on overall survival compared to chemotherapy in patients with a squamous cell carcinoma of the oesophagus with a PD-L1 TPS≥1%, but the evidence is very uncertain. Immunotherapy plus chemotherapy may have a positive effect on overall survival compared to (placebo plus) chemotherapy in patients with a squamous cell carcinoma of the oesophagus with a PD-L1 CPS≥10 or PD-L1 TPS≥1%, but the evidence is very uncertain. *Source: Doki, 2022; Sun, 2021*

Progression-free survival - PD-L1 subgroups

Very low GRADE	The evidence is very uncertain about the effect of double immunotherapy on progression-free survival when compared with chemotherapy in patients with with a squamous cell carcinoma of the oesophagus with a PD-L1 TPS≥1%. Immunotherapy plus chemotherapy may have a positive effect on progression-free survival compared to (placebo plus) chemotherapy in patients with a squamous cell carcinoma of the oesophagus with a PD-L1 CPS≥10 or PD-L1 TPS≥1%, but the evidence is very uncertain. *Source: Doki, 2022; Sun, 2021*

Adverse events (≥grade 3)

Low GRADE	The evidence suggests that (double) immunotherapy (plus chemotherapy) results in little to no difference in adverse events when compared with (placebo plus) chemotherapy in patients with a squamous cell carcinoma of the oesophagus. *Source: Doki, 2022; Sun, 2021*

Quality of life

Very low GRADE	The evidence is very uncertain about the effect of (double) immunotherapy (plus chemotherapy) on quality of life when compared with chemotherapy in patients with a squamous cell carcinoma of the oesophagus. *Source: Doki, 2022*

Overwegingen – van bewijs naar aanbeveling

Voor- en nadelen van de interventie en de kwaliteit van het bewijs

In de eerste lijn bestaat de palliatieve behandeling van een carcinoom van de maag, gastro-oesofageale overgang of oesofagus vaak uit chemotherapie. Afhankelijk van de plaats van origine, histologie, HER2 expressie en PD-L1-expressie kan immuuntherapie, meestal in combinatie met chemotherapie, een alternatief zijn.

De beschikbare gerandomiseerde trials vertonen op verschillende vlakken tekortkomingen, zoals in de literatuursamenvatting vermeld. Er is een aanzienlijk risico op bias en de GRADE-scores voor bewijskracht voor de studies zijn daarom naar beneden bijgesteld.

Echter, de studieresultaten wijzen wel op een mogelijk voordeel in totale overleving en progressievrije overleving voor verschillende immuuntherapie behandelingen op basis van pembrolizumab, ipilimumab of nivolumab. Voor specifieke PD-L1 subgroepen zijn positieve commissie BOM adviezen uitgebracht (NVMO-commissie ter Beoordeling van Oncologische Middelen (BOM), 2022), op basis van de toen geldende PASKWIL-criteria. De richtlijnwerkgroep heeft de beschikbare data beoordeeld op klinische relevantie naar aanleiding van de nieuwe (2023) PASKWIL-criteria.

De individuele onderzochte studies gebruikten verschillende anti-PD-1 antilichamen. Directe onderlinge vergelijking naar de effectiviteit van de verschillende antilichamen is er niet, en een simpele vergelijking van twee verschillende studies is onmogelijk gezien de bekende vormen van bias. Op basis van het werkingsmechanisme valt echter geen verschil in effectiviteit te verwachten.

De individuele onderzochte studies zijn bij subgroepen en in uiterst geselecteerde patiënten verricht. Het is aan te raden een zekere mate van voorzichtigheid bij de interpretatie van de resultaten te betrachten.

De chemotherapie-backbone verschilde tussen de studies, zowel voor adeno- als plaveiselcelcarcinoom. In de CheckMate 649 werd oxaliplatin gecombineerd met capecitabine dan wel 5FU. In de KEYNOTE-590 werd cisplatin gecombineerd met 5FU, maar in een voor Nederland ongebruikelijk schema. Vanuit meta-analyses is er qua effectiviteit in de gemetastaseerd setting een voorkeur voor oxaliplatin boven cisplatine, al zijn die data gebaseerd op studies die met name patiënten met een adenocarcinoom includeerden. Gerandomiseerde studies in de gemetastaseerde setting die eerstelijns

chemotherapeutische behandelingen vergeleken voor enkel het plaveiselcelcarcinoom van de oesofagus zijn helaas niet beschikbaar. De EMA-registratie voor zowel nivolumab als pembrolizumab laat een combinatie met elke platinum- en fluoropyrimidinebevattende chemotherapie toe, hetgeen ruimte biedt voor keuzes passend bij de individuele patiënt.

Adenocarcinoom
Doordat patiënten met een adenocarcinoom slechts een subgroep vormden in de KEYNOTE-590 studie, en patiënten alleen konden worden geïncludeerd bij een tumor die volledig in de oesofagus was gelegen (t/m Siewert 1), is het de vraag hoe de resultaten voor de gepoolde groep van patiënten met deze twee zeer verschillende tumortypes uit KEYNOTE-590 naar de klinische praktijk vertaald kunnen worden.

De CheckMate 649 studie includeerde alleen patiënten met een adenocarcinoom, ongeacht de lokalisatie in slokdarm, gastro-oesofageale overgang of maag. De ATTRACTION-4 en de KEYNOTE-062 studies includeerden ook alleen patiënten met een adenocarcinoom, gelegen in de maag of de gastro-oesofageale overgang, waarbij onduidelijk is of ook Siewert 1 tumoren werden geïncludeerd. Hoewel het adenocarcinoom van de oesofagus op moleculair niveau sterkt lijkt op het chromosomaal instabiele subtype van het maagcarcinoom, zijn er dus strikt genomen beperkte data beschikbaar over de effectiviteit van immuuntherapie voor het adenocarcinoom van de oesofagus.

De resultaten van de CheckMate 649 in de subgroep met een CPS≥5 tumor hebben in 2022 geleid tot een positief commissie BOM advies voor deze populatie, en daarna tevens tot vergoeding in Nederland. Dit advies is gegeven op basis van de oude PASKWIL criteria: op basis van de 2023 PASKWIL criteria voldoet de HR van 0.71 net niet. Echter, aangezien de beroepsgroep heeft besloten eerder uitgebrachte positieve adviezen niet opnieuw te beoordelen en aangezien er (voorzichtig) positieve resultaten in de meeste studies in HER2 negatief adenocarcinoom worden gezien, acht de richtlijnwerkgroep het gezamenlijk bewijs voldoende om niet af te wijken van het eerdere positieve commissie BOM advies. De ATTRACTION-4 studie laat geen effect op overleving zien. De redenen daarvoor blijven speculatief maar zouden te wijten kunnen zijn aan het gebruik van een andere selectie biomarker (TPS in plaats van CPS), en de kleine populatie met PD-L1 expressie (114 patiënten) waardoor er mogelijk onvoldoende statistische power was om een effect te zien.

In de KEYNOTE-062 studie werd naast de superioriteit van de toevoeging van immuuntherapie aan chemotherapie, ook de waarde van alleen immuuntherapie vergeleken met chemotherapie in een non-inferioriteit opzet. Statistisch gezien waren de beide regimes non-inferior en werden er geen significante verschillen gezien in toxiciteit. Er zijn geen bevestigende studies voor enkel immuuntherapie. In de klinische praktijk zal slechts bij een zeer klein deel van de patiënten immuuntherapie in plaats van chemotherapie met immuuntherapie worden overwogen, bijvoorbeeld bij patiënten met een specifieke contra-indicatie voor chemotherapie.

Voor de CPS-positieve subgroep (CPS≥1) met een HER2 positief adenocarcinoom zou er mogelijk voordeel kunnen zijn voor de toevoeging van pembrolizumab aan trastuzumab en chemotherapie op totale overleving (Janjigian, 2023). Echter is de evidence beperkt, waardoor er geen aanbeveling geformuleerd is voor deze groep.

Plaveiselcelcarcinoom
Voor het plaveiselcelcarcinoom lieten zowel de CheckMate 648 als de KEYNOTE-590 een meerwaarde zien van het toevoegen van immuuntherapie aan chemotherapie in de

respectievelijke biomarker-positieve populatie. In de CheckMate 648 werd ook de combinatie van ipilimumab met nivolumab vergeleken met chemotherapie alleen, maar niet met chemotherapie met immuuntherapie. Gezien het toxiciteitsprofiel van dubbele immuuntherapie en het gebrek aan bevestigende studies voor deze behandeling, lijkt er vooralsnog geen duidelijke plek voor dubbele immuuntherapie voor het oesofaguscarcinoom.

Waarden en voorkeuren van patiënten (en evt. hun verzorgers)
Het doel van het toedienen (wanneer dit geïndiceerd is) van palliatieve immunotherapie in combinatie met chemotherapie is het bewerkstelligen van levensverlenging en verbetering van de kwaliteit van leven. Er is geen onderzoek gedaan naar de waarden en voorkeuren van patiënten. Het is goed om te realiseren dat in de studies selectie heeft plaatsgevonden, bijvoorbeeld op basis van leeftijd en de aan- of afwezigheid van ernstige comorbiditeit. Met de patiënt moet duidelijk gecommuniceerd worden wat met de huidige behandelopties bereikt kan worden, en tegen welke prijs. Op basis hiervan en in combinatie met de eigen doelen van de patiënt kan een gewogen beslissing worden genomen.

Kosten (middelenbeslag)
De werkgroep heeft geen informatie gevonden over de kosteneffectiviteit. De werkgroep heeft dit aspect daarom niet meegewogen bij het formuleren van de aanbeveling. De werkgroep is zich bewust van de relevante impact op de zorgkosten.

Aanvaardbaarheid, haalbaarheid en implementatie
De werkgroep is van mening dat de aanbevelingen aanvaardbaar zijn voor zowel zorgverleners als patiënten. De werkgroep verwacht dat het uitvoeren van de aanbeveling haalbaar en implementeerbaar is. De aanbeveling sluit aan bij de huidige werkwijze in de praktijk.

Aanbevelingen
Aanbevelingen adenocarcinoom
Rationale van de aanbeveling: weging van de argumenten voor en tegen de interventies
Hoewel de toegevoegde waarde van immuuntherapie bovenop chemotherapie bij adenocarcinomen een beperkte winst in overleving laat zien, lijkt dit in de meeste studies het geval. De bijwerkingen als gevolg van de toevoeging van immuuntherapie zijn in de meeste gevallen hanteerbaar.

Overweeg eerstelijnsbehandeling met pembrolizumab plus chemotherapie bij fitte patiënten met een lokaal gevorderd irresectabel of gemetastaseerd HER2-negatief adenocarcinoom van de gastro-oesofageale overgang (Siewert 1) en een **CPS van 10 of hoger.**

Overweeg eerstelijnsbehandeling met nivolumab en chemotherapie bij patiënten met een lokaal gevorderd irresectabel of gemetastaseerd HER2-negatief adenocarcinoom van maag, gastro-oesofageale overgang of oesofagus met een **CPS van 5 of hoger.**

Indien de patiënt aan beide indicaties voldoet, is er geen voorkeur voor pembrolizumab of nivolumab.

Aanbevelingen plaveiselcelcarcinoom
Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies

Hoewel de toegevoegde waarde van immuuntherapie bovenop chemotherapie bij plaveiselcelcarcinomen een beperkte winst in overleving laat zien, lijkt dit in alle studies het geval. De bijwerkingen als gevolg van de toevoeging van immuuntherapie zijn in de meeste gevallen hanteerbaar.
De plek van dubbele immuuntherapie blijft vooralsnog onduidelijk.

Overweeg eerstelijnsbehandeling met nivolumab en chemotherapie bij fitte patiënten met een irresectabel, gerecidiveerd of gemetastaseerd plaveiselcelcarcinoom van de oesofagus en een TPS van tenminste 1%.

Overweeg eerstelijnsbehandeling met pembrolizumab en chemotherapie bij patiënten met een irresectabel, gerecidiveerd of gemetastaseerd plaveiselcelcarcinoom van de oesofagus en een CPS van 10 of hoger.

Indien de patiënt aan beide indicaties voldoet, is er geen voorkeur voor nivolumab of pembrolizumab.

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Bijlagen bij hoofdstuk Palliatieve immuuntherapie

Evidence table for systematic review of RCTs and observational studies (intervention studies)

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Duan, 2023 [individual study characteristics deduced from Duan, 2023]	SR and meta-analysis of 9 phase III RCTs *Literature search up to June 2022* **A**: Luo, 2021 *ESCORT-1st* **B**: Sun, 2021 *KEYNOTE-590* **C**: Janjigian, 2021 and Janjigian, 2023 *KEYNOTE-811* **D**: Shitara, 2020 *KEYNOTE-062* **E**: Janjigian, 2021 *CHECKMATE-649* **F**: Doki, 2022 *CHECKMATE-648* **G**: Kang, 2022 *ATTRACTION-4* **H**: Lu, 2022 *ORIENT-15* **I**: Wang, 2022	**Inclusion criteria SR:** - RCTs published in English - inoperable locally advanced stage or metastatic gastric esophageal cancer patients of any race, nationality, gender and age - patients in the experimental group were treated with immunotherapy - based regimens (including nivolumab + ipilimumab, nivolumab + FP/SOX, toripalimab + TP, etc.), while	Describe intervention: **A**: Camrelizumab + CT **B**: Pembrolizumab + CT **C**: Pembrolizumab + Trastuzumab + CT **D(1)**: Pembrolizumab **D(2):** Pembrolizumab + CT **E**: Nivolumab + CT **F(1)**: Nivolumab + Ipilimumab **F(2):** Nivolumab + CT **G**: Nivolumab + CT **H**: Sintilimab + CT **I:** Toripalimab + CT Chemotherapy: **A:** 6 cycles of paclitaxel (175mg/m2) and cisplatin (75mg/m2) **B**: 5-fluorouracil 800 mg/m² on days 1–5 plus cisplatin 80 mg/m² on day 1 once every 3 weeks for up to 35 cycles **C:** 5-flurouacil (800 mg per m2 of body-surface area administered	Describe control: **A**: Placebo + CT **B**: Placebo + CT **C**: Placebo + Trastuzumab + CT **D**: Placebo + CT **E**: CT **F**: CT **G**: Placebo + CT **H**: Placebo + CT **I**: Placebo + CT	<u>Follow-up (median):</u> **A**: 10.8 months **B**: 22.6 months **C**: 38.4 months (I) and 38.6 months (C) **D**: 29.4 months **E**: 13.1 months **F**: min. 13 months **G**: 26.6 months **H**: 16.0 months (I) and 16.9 months (C) **I**: 7.1 months <u>Discontinuation treatment</u> (intervention/control) **A:** I: 220 (74%), C: 270 (91%) **B**: I: 328 (89%), C: 359 (97%) **C**: I: 286 (82%), C: 304 (88%) **D**: I(1): 233 (91%), I(2): 226 (88%), C: 237 (95%) **E**: I: 698 (88%), C: 728 (92%) **F**: I(1): 285 (89%), I(2): 301 (93%), C: 300 (93%)	*I vs C* **<u>Overall survival</u>** Effect measure: HR [95% CI]: **A**: 0.70 [0.56, 0.88] **B**: 0.73 [0.62, 0.86] **C:** 0.84 [0.70-1.01] **D(1):** 0.91 [0.74, 1.10] **D(2):** 0.85 (0.70, 1.03) **E:** 0.80 [0.68, 0.94] **F(1):** 0.78 [0.62, 0.98] **F(2):** 0.74 [0.58, 0.96] **G**: 0.90 [0.75, 1.08] **H**: 0.63 [0.51, 0.78] **I**: 0.58 [0.43, 0.78] Pooled effect (fixed effects model): 0.74* [95% CI 0.69 to 0.80] favoring the intervention. Heterogeneity (I^2): 26%, P<0.01 *(KEYNOTE-811 and KEYNOTE-062 were not included in the analysis by Duan)*	<u>Risk of bias:</u> Tool used by authors: *risk of bias assessment tools recommended in the Cochrane Manual for Systematic Reviewers 5.1.0* **A**: Some concerns **B**: Low **C**: Low **D**: Some concerns **E**: Some concerns **F**: Low **G**: Low **H**: Some concerns **I**: Low Author's conclusion: *"Immunotherapy-based regimens are superior to standard chemotherapy in the first-line treatment of advanced gastric oesophageal cancer, with significantly improved OS, PFS, DCR, and ORR. Furthermore, patients*

	JUPITER-06 <u>Source of funding:</u> **A:** Jiangsu Hengrui Pharmaceuticals Co, Ltd. **B:** Merck Sharp & Dohme **C:** Merck Sharp & Dohme **D:** Merck Sharp & Dohme **E:** Bristol Myers Squibb and Ono Pharmaceutical **F:** Bristol Myers Squibb and Ono Pharmaceutical **G:** Bristol Myers Squibb and Ono Pharmaceutical **H:** Innovent Biologics **I:** Shanghai Junshi Biosciences	patients in the control group were treated with chemotherapy alone (including SOX, FP, CAPOX, TP or DP) - outcome indicators included OS and PFS in the total population, PD-L1 CPS ≥10 and PD-L1 <10, ORR, DCR, AEs and adverse event grade ≥3. **Exclusion criteria SR:** - Duplicate literature, case reports, editorials or review literature, etc - non-first-line therapy literature for patients with inoperable locally advanced stage or metastatic gastric	intravenously on days 1–5 of each 3-week cycle) and cisplatin (80 mg per m2 administered intravenously once every 3 weeks) or capecitabine (1,000 mg per m2 administered orally twice daily on days 1–14 of each 3-week cycle) and oxaliplatin (130 mg per m2 administered intravenously once every 3 weeks) for up to 35 cycles **D:** cisplatin 80mg/m2/d on day 1 plus fluorouracil 800mg/m2/d on days 1 to 5 or capecitabine 1000mg/m2 twice daily), **E:** XELOX [capecitabine 1000 mg/m² twice a day, days 1–14 and oxaliplatin 130 mg/m², day 1, every 3 weeks] or FOLFOX [leucovorin 400 mg/m², day 1, fluorouracil 400 mg/m², day 1 and 1200 mg/m², days 1–2, and oxaliplatin 85 mg/m², day 1, every 2 weeks]		**G**: I: 314 (87%), C: 334 (92%) **H**: I: 254 (78%), C: 296 (89%) **I**: I: 166 (65%), C: 188 (73%)	<u>Overall survival – subgroup PD-L1 – CPS ≥1*</u> D(1): 0.91 [0.69-1.18] *(99.2% CI)* D(2): 0.85 [0.70-1.03] E: 0.77 [0.64, 0.92] *(99.3% CI)* <u>Overall survival – subgroup PD-L1 – CPS ≥5*</u> E: 0.71 [0.59, 0.86] *(98.4% CI)* <u>Overall survival – subgroup PD-L1 – CPS ≥10*</u> B: 0.62 [0.49, 0.78] D(1): 0.69 [0.49, 0.97] D(2): 0.85 [0.62, 1.17] <u>Overall survival – subgroup PD-L1 CPS≥1%*</u> F(1): 0.64 [0.46, 0.90] *(98.6% CI)* F(2): 0.54 [0.37, 0.80] *(99.5% CI)* G: 1.06 [0.67, 1.68] **<u>Progression-free survival</u>** Effect measure: HR [95% CI]: **A**: 0.56 [0.45, 0.68] **B**: 0.65 [0.55, 0.76] **C**: 0.73 [0.61-0.87]	*in the PDL1 CPS ≥10 subgroup appeared to benefit more significantly than the total population. The incidence of adverse reactions in the immunotherapy-based group was not higher than that in the chemotherapy-based group."*

		esophageal cancer - literature with missing primary data - non-English articles *9 studies included* *<u>Population – histology</u>* **A:** EC - SCC **B:** EC/GEJC - AC/SCC **C:** GC/GEJC - AC **D:** GC/GEJC - AC **E:** GC/GEJC/EC - AC **F:** EC - SCC **G:** GC/GEJC - AC **H:** EC - SCC **I:** EC – SCC *<u>Ethnicity</u>* **A**: Asian **B**: Asian/non-Asian **C**: Asian/non-Asian **D**: Asian/non-Asian **E**: Asian/non-Asian **F**: Asian/non-Asian	**F:** 4-week cycle of intravenous fluorouracil at a dose of 800 mg per square meter of body-surface area on days 1 through 5 and intravenous cisplatin at a dose of 80 mg per square meter on day 1 **G:** intravenous oxaliplatin 130 mg/m2 on day 1 plus either oral S-1 40 mg/m2 [SOX] or oral capecitabine 1000 mg/m2 [CAPOX], twice daily on days 1-14 **H:** cisplatin 75 mg/m2 plus paclitaxel 175 mg/m2 every three weeks or cisplatin plus 5-fluorouracil (800 mg/m2 continuous infusion on days 1-5) **I:** paclitaxel (175 mg/m2) and cisplatin (75 mg/m2) on Day 1 of each 3-week cycle			**D(1)**: 1.66 [1.37, 2.01] **D(2):** 0.84 [0.70, 1.02] **E**: 0.77 [0.68, 0.87] **F(1):** 1.26 [1.04, 1.52] **F(2):** 0.81 [0.64, 1.03] **G**: 0.68 [0.51, 0.90] **H**: 0.56 [0.46, 0.68] **I**: 0.58 [0.46, 0.74] Pooled effect (fixed effects model): 0.71* [95% CI 0.59 to 0.86] favoring the intervention. Heterogeneity (I^2): 87%, P<0.01 *(KEYNOTE-811 and KEYNOTE-062 were not included in the analysis by Duan)* <u>Progression-free survival – subgroup PD-L1 – CPS ≥1*</u> D(1): 1.66 [1.37, 2.01] D(2): 0.84 [0.70, 1.02] E: 0.74 [0.65, 0.85] <u>Progression-free survival – subgroup PD-L1 – CPS ≥5*</u> E: 0.68 [0.56, 0.81] *(98% CI)* <u>Progression-free survival – subgroup PD-L1 – CPS ≥10*</u>	

		G: Asian **H**: Asian/non-Asian **I**: Asian <u>Important patient characteristics at baseline</u>: <u>N, median age</u> **A**: 596 patients, 62 yrs **B**: 749 patients, 62 yrs **C**: 698 patients, 62 yrs **D**: 763 patients, 62 yrs **E**:1581 patients, 62 yrs **F**: 970 patients, 64 yrs **G**: 724 patients, 65 yrs **H**: 659 patients, 63 yrs **I**: 514 patients, 63 yrs <u>*Sex (% Male)*</u>*:* **A**: 87.8% **B**: 83.4% **C**: 81% **D**: 72.6% **E**: 69.6% **F**: 82.2%				B: 0.51 [0.41, 0.65] D(1): 1.10 [0.79, 1.51] D(2): 0.73 [0.53, 1.00] <u>Progression-free – subgroup PD-L1 CPS≥1%*</u> F(1): 1.02 [0.73, 1.43] *(98.5% CI)* F(2): 0.65 [0.46, 0.92] *(98.5% CI)* G: 0.80 [0.48, 1.33] **<u>Adverse events (≥Grade 3)</u>** Effect measure: RR [95% CI]: **A**: 0.94 [0.83, 1.05] **B**: 1.03 [0.97, 1.10] **C**: 1.00 [0.85, 1.17] **D(1):** 0.24 [0.18, 0.33] **D(2):** 1.06 [0.94, 1.18] **E:** 1.34 [1.22, 1.48] **F(1):** 0.89 [0.72, 1.11] **F(2):** 1.33 [1.10, 1.62] **G:** 1.24 [0.91, 1.70] **H:** 1.00 [0.85, 1.17] **I:** 1.04 [0.94, 1.16] Pooled effect (random effects model): 0.97 [95% CI 0.84 to 1.12] slightly favoring the intervention. Heterogeneity (I^2): 93%, P=0.69	

		G: 72.2% **H**: 86.0% **I**: 85.0% *PD-L1 expression* **A:** subgroups in article **B:** 51% CPS ≥10, 46% CPS<10, 3% unknown **C:** 85% CPS ≥1, 15% CPS<1 **D:** 37% CPS ≥10 **E:** 16% TPS≥1%, 84% <1% **F:** 49% TPS≥1%, 51% <1% or indeterminate **G:** 16% TPS≥1%, 84% <1% **H:** subgroups in article **I:** subgroups in article				**Quality of life*** FACT-Ga (week 60, *read from graph*) E: 6.9 [3.9, 9.9] versus 2.5 [-1.6, 6.6] HR for time to symptom deterioration G: 0.86 [0.70, 1.06] FACT-E Least square mean change (week 49) F(1): 3.45 [0.96, 5.94] versus 1.54 [-1.26, 4.33] F(2): 4.98 [2.68, 7.27] versus 1.54 [-1.26, 4.33]	

*deduced from original full-text study article: this was only done for studies with immunotherapy regimens that were available in the Netherlands when this module was written (nivolumab/pembrolizumab/ipilimumab).
AC = adenocarcinoma; CPS = combined positive score; CT = chemotherapy; EC = esophageal cancer; FACT-E = Functional Assessment of Cancer Therapy-Esophagus; FACT-Ga = Functional Assessment of Cancer Therapy-Gastric; GC = gastric cancer; GEJC = gastro-oesophageal junction cancer; HR = hazard ratio; NR = not reported; RR = risk ratio; SCC = squamous cell carcinoma

Evidence table for intervention studies

Study reference	Study characteristics	Patient characteristics [2]	Intervention (I)	Comparison / control (C) [3]	Follow-up	Outcome measures and effect size [4]	Comments
Song, 2023 *ASTRUM-007*	Type of study: Randomized, double-blind phase 3 trial Setting and country: Multicenter (70 hospitals), China Funding and conflicts of interest: Shanghai Henlius Biotech, Inc. supported in study execution, study design, data acquisition, statistical analyses and manuscript revisions.	Inclusion criteria: - aged 18–75 years - previously untreated, histologically confirmed, inoperable locally advanced or metastatic, PD-L1-positive (CPS ≥ 1) ESCC, with at least one measurable lesion based on central imaging in accordance with RECIST v1.1 - adequate organ function - ECOG performance status 0–1 *(Full eligibility criteria in the article appendix)* Exclusion criteria: - previously received PD-1 or PD-L1 inhibitors - central nervous system metastases - active infection - active autoimmune diseases *(Full eligibility criteria in the article appendix)* N total at baseline: Intervention: 368	**Serplulimab + CF** Serplulimab (3 mg kg^{-1}) on day 1 once every 2 weeks for up to 2 years Cisplatin (50 mg m^{-2}) on day 1 for up to 8 cycles and 5-FU (1,200 mg m^{-2}) continuous administration daily on days 1 and 2 of each cycle for up to 12 cycles, both administered intravenously every 2 weeks. Treatment was continued until disease progression, intolerable toxicities, investigator decision, patient withdrawal of consent, completion of 2 years of therapy or death, whichever occurred first.	**Placebo + CF** Placebo (3 mg kg^{-1}) on day 1 once every 2 weeks for up to 2 years Cisplatin (50 mg m^{-2}) on day 1 for up to 8 cycles and 5-FU (1,200 mg m^{-2}) continuous administration daily on days 1 and 2 of each cycle for up to 12 cycles, both administered intravenously every 2 weeks. Treatment was continued until disease progression, intolerable toxicities, investigator decision, patient withdrawal of consent, completion of 2 years of therapy or death, whichever occurred first.	Length of follow-up, median (IQR): I: 14.9 (8.8-19.7) months C: 15.0 (9.4-19.9) months Loss-to-follow-up: Intervention: 278 (76%) discontinued treatment: *184 disease progression* *31 patient decision* *20 adverse event* *18 died* *6 physician decision* *19 other reasons* Control: 165 (90%) discontinued treatment:	Overall survival I: 15.3 months (95% CI: 14.0 to 18.6) C: 11.8 months (95% CI: 9.7 to 14.0 months) HR = 0.68 (95% CI: 0.53 to 0.87), P<0.01 Progression-free survival I: 5.8 months (95% CI: 5.7 to 6.9) C: 5.3 months (95% CI: 4.3 to 5.6) HR = 0.60 (95% CI: 0.48 to 0.75), P<0.01 Adverse events	Author's conclusion: *"In conclusion, first-line serplulimab in combination with chemotherapy significantly improved PFS and OS in patients with previously untreated, PD-L1-positive, locally advanced or metastatic ESCC, compared with chemotherapy alone, with a manageable safety profile."* N.B.: fifteen patients in the placebo plus chemotherapy group received serplulimab owing to an error in drug distribution.

		Control: 183 <u>Population – histology:</u> EC - SCC <u>Ethnicity:</u> Asian **<u>Important prognostic factors</u>[2]:** <u>Median age (IQR):</u> I: 64 (57-68) C: 64 (57-68) <u>Sex:</u> I: 86% M C: 84% M <u>PD-L1 expression:</u> I: 56% 1≤CPS<10, 44% CPS≥ 10 C: 57% 1≤CPS<10, 43% CPS≥ 10 Groups comparable at baseline? Yes			*118 disease progression* *17 patient decision* *10 adverse event* *10 died* *4 physician decision* *6 other reasons*	I: 201 patients (53%) C: 81 patients (48%) *specified in article (table 2)* <u>Quality of life</u> No results reported.	
Xu, 2023 *RATIONALE-306*	Type of study: Randomized, double-blind phase 3 trial Setting and country: 162 medical centres across	<u>Inclusion criteria</u>: - aged 18 years or older - histologically confirmed, unresectable, locally advanced, recurrent or metastatic oesophageal squamous cell carcinoma	**Tislelizumab+chemotherapy** Tislelizumab 200 mg intravenously every 3 weeks on day 1 of 21-day cycles, together with an investigator-chosen chemotherapy doublet.	**Placebo+chemotherapy** Matching placebo intravenously every 3 weeks on day 1 of 21-day cycles, together with an investigator-chosen chemotherapy doublet.	<u>Length of follow-up, median (IQR)</u>: I: 16.4 (8.6-21.8) C: 9.8 (5.8-19.0)	<u>Overall survival</u> I: 17.2 months (95% CI: 15.8-20.1) C: 10.6 months (95% CI: 9.3-12.1)	Author's conclusion: *"First-line treatment of advanced or metastatic oesophageal squamous cell carcinoma with tislelizumab plus chemotherapy*

	Asia, Europe, Oceania, and North America Funding and conflicts of interest: BeiGene had a role in study design, data collection, data analysis, data interpretation, and writing of the clinical study report. Medical writing support was provided by the funder. Detailed declarations of interests are provided in the article.	- not treated with previous systemic therapy for advanced disease - not amenable to definitive therapies (including surgery or radiation) per local investigator - ECOG performance status of 0 or 1 - measurable or evaluable disease per Response Evaluation Criteria in Solid Tumours (RECIST; version 1.1) *(Full eligibility criteria in the article appendix)* <u>Exclusion criteria</u>: - brain or leptomeningeal metastases that were symptomatic or required treatment - evidence of complete oesophageal obstruction not amenable to treatment - evidence of fistula - active autoimmune diseases - medical conditions requiring systemic corticosteroids or immunosuppressants	Chemotherapy options: - a platinum agent (cisplatin 60–80 mg/m² intravenously on day 1 or oxaliplatin 130 mg/m² intravenously on day 1) combined with a fluoropyrimidine (fluorouracil [750–800 mg/m² intravenously on days 1–5] - capecitabine [1000 mg/m² orally twice daily on days 1–14]) - paclitaxel (175 mg/m² intravenously on day 1). Treatment was continued until investigator-assessed disease progression per RECIST version 1.1, unacceptable toxicity, death, or withdrawal of consent.	Chemotherapy options: - a platinum agent (cisplatin 60–80 mg/m² intravenously on day 1 or oxaliplatin 130 mg/m² intravenously on day 1) combined with a fluoropyrimidine (fluorouracil [750–800 mg/m² intravenously on days 1–5] - capecitabine [1000 mg/m² orally twice daily on days 1–14]) - paclitaxel (175 mg/m² intravenously on day 1). Treatment was continued until investigator-assessed disease progression per RECIST version 1.1, unacceptable toxicity, death, or withdrawal of consent.	<u>Loss-to-follow-up</u>: Intervention: 286 (88%) discontinued treatment: *177 progressive disease* *41 withdrew* *39 adverse event* *5 treatment interruption* *4 doctor's decision* *20 other (eg, death)* Control: 306 (95%) discontinued treatment: *223 progressive disease* *35 withdrew* *20 adverse event* *1 treatment interruption* *7 doctor's decision* *1 non-compliance with study drug*	HR = 0.66 (95% CI: 0.54 to 0.80), P<0.01 <u>Progression-free survival</u> I: 7.3 months (95% CI: 6.9-8.3) C: 5.6 months (95% CI: 4.9-6.0) HR = 0.62 (95% CI: 0.52 to 0.75), P<0.01 <u>Adverse events</u> I: 216 patients (67%) C: 207 patients (64%) <u>Quality of life</u> No results reported, will be published in a separate publication.	*resulted in significant and clinically meaningfully overall survival benefit versus placebo plus chemotherapy. The safety profile of tislelizumab in combination with chemotherapy was manageable, with no new safety signals identified."*

		- previous therapies targeting PD-1, PD-L1, or PD-L2 *(Full eligibility criteria in the article appendix)* <u>N total at baseline</u>: Intervention: 326 Control: 323 <u>Population – histology:</u> EC - SCC <u>Ethnicity:</u> I: 75% Asian, 24% non-Asian C: 75% Asian, 24% non-Asian **<u>Important prognostic factors</u>[2]:** <u>Median age (IQR):</u> I: 64.0 (59.0-68.0) C: 65.0 (58.0-70.0) <u>Sex:</u> I: 87% C: 87% <u>PD-L1 expression:</u> I: 36% TAP score ≥10%, 46% TAP score <10%, 18% unknown C: 33% TAP score ≥10%, 52% TAP score <10%, 15% unknown			*19 other (eg, death)*		

		Groups comparable at baseline? Yes					
AC = adenocarcinoma; CF = cisplatin and 5-fluorouracil; EC = esophageal cancer; ECOG = Eastern Cooperative Oncology Group; GC = gastric cancer; GEJC = gastro-oesophageal junction cancer; NR = not reported; SCC = squamous cell carcinoma							

Risk of bias table for intervention studies (randomized controlled trials; based on Cochrane risk of bias tool and suggestions by the CLARITY Group at McMaster University)

Study reference (first author, publication year)	**Was the allocation sequence adequately generated?**	**Was the allocation adequately concealed?**	**Blinding: Was knowledge of the allocated interventions adequately prevented?** **Were patients blinded?** **Were healthcare providers blinded?** **Were data collectors blinded?** **Were outcome assessors blinded?** **Were data analysts blinded?**	**Was loss to follow-up (missing outcome data) infrequent?**	**Are reports of the study free of selective outcome reporting?**	**Was the study apparently free of other problems that could put it at a risk of bias?**	**Overall risk of bias**
Luo, 2021 *ESCORT-1st*	Definitely yes; Reason: Randomization with a centralized interactive web-response system	Probably yes; Reason: The randomization was centralized.	Definitely yes; Reason: Double-blind trial. Patients, investigators, and the sponsor's study team were masked to treatment assignment.	Probably no; Reason: Discontinuation treatment percentages were higher in the control group than in the intervention group.	Definitely yes; Reason: All relevant outcomes from the trial registry were reported.	**Definitely no**; Reason: The funder was involved in data collection, analysis, interpretation, and guaranteed the accuracy, completeness of the data, writing of the	**Some concerns**

						report, and the decision to submit the manuscript for publication. Some authors received personal fees from the funder or were employees of the funding company.	
Sun, 2021 *KEYNOTE-590*	Definitely yes; Reason: An interactive voice response system (IVRS) or integrated web response system was used for randomization.	Probably yes; Reason: The randomized allocation schedule was generated by the sponsor and implemented in the IVRS.	Definitely yes; Reason: Double-blind trial. Patients, investigators, and site staff were masked to group assignment.	Probably no; Reason: Discontinuation treatment percentages were higher in the control group than in the intervention group.	Probably yes; Reason: All relevant outcomes from the trial registry were reported, except for quality of life (secondary outcome).	**Definitely no**; Reason: The funder participated in study design, data interpretation, and the writing of the report, and maintained the study database. Many authors have interests linked to the funding company.	**Some concerns**
Janjigian, 2021; Janjigian, 2023 *KEYNOTE-811*	Definitely yes; Reason: Randomization by means of an integrated interactive voice-response and Web-response system.	Probably yes; Reason: Randomization was central (protocol).	Probably yes; Reason: Double-blind study. Outcomes were assessed by blinded, independent central review.	Probably no; Reason: Discontinuation treatment percentages were higher in the control group than in the intervention group.	Probably yes; Reason: The dual primary endpoints were reported. However, quality of life (exploratory endpoint) was not reported in the articles.	**Definitely no**; Reason: The study was designed by academic advisors and employees of the study sponsor. Many authors have interests linked to the funding company. The funder participated in the study design, data collection, data analysis, data interpretation, report	**Some concerns**

						writing and study database maintenance.	
Shitara, 2020 *KEYNOTE-062*	Definitely yes; Reason: The sponsor generated the allocation schedule using a computerized random list generator (IVRS/IWRS).	No information.	Probably no; Reason: Partially blinded. Patients and site and sponsor personnel were blinded to pembrolizumab or placebo in the combination and chemotherapy groups. Investigators and patients were unblinded to pembrolizumab monotherapy. Imaging data were centrally reviewed and the central reviewer was blinded to subject treatment assignment; and allocation schedule was blinded in the database preventing aggregate analysis.	Probably no; Reason: Discontinuation treatment percentages were higher in the control group than in the intervention group.	Probably yes; Reason: All relevant outcomes from the trial registry were reported, except for quality of life (secondary outcome).	**Definitely no**; Reason: The funder was involved in the design and conduct of the study, in collection, management, analysis, and interpretation of the data. Several authors were employees of the sponsor and were involved in the review, or approval of the manuscript, and decision to submit the manuscript for publication.	**HIGH**
Janjigian, 2021 *CHECKMATE-649*	Definitely yes; Reason: Randomization with interactive web response technology.	Probably yes; Reason: A treatment allocation list was generated by the sponsor. The web registration system was implemented by a third party, which ensured that the assignment sequence was concealed until the treatment allocation was completed.	**Definitely no**; Reason: Open label study. Outcomes were assessed by blinded independent central review.	Probably yes; Reason: Discontinuation treatment percentages were similar in the control group and intervention group.	Definitely yes; Reason: All relevant outcomes from the trial registry were reported.	**Definitely no**; Reason: The funder of the study was involved in study design, data collection, data analysis, data interpretation, and writing of the clinical study report. Many authors have interests linked to the funding company.	**HIGH**
Doki, 2022 *CHECKMATE-648*	Definitely yes;	Probably yes;	**Definitely no**;	Probably yes;	Definitely yes;	**Definitely no**;	**HIGH**

	Reason: Randomization was performed using web-based interactive response technology.	Reason: A treatment allocation list was generated by the sponsor. The web registration system was implemented by a third party, which ensured that the assignment sequence was concealed until the treatment allocation was completed.	Reason: Open label study. Outcomes were assessed by blinded independent central review.	Reason: Discontinuation treatment percentages were similar in the control group and two intervention groups.	Reason: All relevant outcomes from the trial registry were reported.	Reason: the sponsor funded the trial, provided the trial drugs, and collaborated with the academic authors on the trial design and on the collection, analysis, and interpretation of the data.	
Kang, 2022 *ATTRACTION-4*	Definitely yes; Reason: Randomization was performed using an interactive web response system.	Probably yes; Reason: The allocation sequence was generated by the interactive web response system and the sponsor was masked to the allocation sequence.	Definitely yes; Reason: Double-blind trial. Patients, investigators, and the study sponsor were masked to the study treatment. Masking was ensured by keeping nivolumab and placebo identical in appearance, which were checked by a person responsible for investigational product allocation.	Probably yes; Reason: Discontinuation treatment percentages were similar in the control group and intervention group.	Definitely yes; Reason: All relevant outcomes from the trial registry were reported (in the article or in the appendix).	**Definitely no**; Reason: The funders of the study had a role in study design, data collection, data analysis, data interpretation, and writing of the report. Many authors have interests linked to the funding company.	**Some concerns**
Lu, 2022 *ORIENT-15*	Definitely yes; Reason: Randomization was performed using an interactive web response system.	No information.	Probably yes; Reason: Double-blind trial. Patients, investigators, and the sponsor's study team were blinded to the allocation of treatment. The results of the interim analysis were reviewed by an unblinded external statistics team.	Probably no; Reason: Discontinuation treatment percentages were higher in the control group than in the intervention group.	Definitely yes; Reason: All relevant outcomes from the trial registry were reported.	**Definitely no**; Reason: The funder was involved in data analysis and interpretation, verification of data accuracy and completeness, writing of the clinical report, and the decision to submit the manuscript for publication. Several	**Some concerns**

						authors have interests linked to the funding company.	
Wang, 2022 *JUPITER-06*	Definitely yes; Reason: The patient randomization and the dispense of investigational drugs were implemented via an Interactive Web Response System (IWRS).	Probably yes; Reason: The random allocation sequences for patients and investigational drugs were generated and maintained by an independent unblinded statistician from a third-party vendor.	Definitely yes; Reason: Double-blind study. the study personnel, the investigator, study center staff, patient, sponsor, clinical contract research organization and the independent review committee were blinded.	Probably yes; Reason: Discontinuation treatment percentages were slightly higher in the control group than in the intervention group.	Probably yes; Reason: All relevant outcomes from the trial registry were reported, except for time to response and quality of life (secondary outcomes).	Probably no; Reason: Role of the funder is not clear. Some authors were employees of the funding company.	**LOW**
Song, 2023 *ASTRUM-007*	Definitely yes; Reason: Randomization was performed using an integrated web response system.	No information.	Probably yes; Reason: Double-blind study. Patients, investigators and the sponsor's study team were masked to group assignment. The results of the final analyses were conducted by an unblinded external statistician.	Probably no; Reason: Discontinuation treatment percentages were higher in the control group than in the intervention group.	Definitely yes; Reason: All relevant outcomes from the trial registry were reported.	**Definitely no**; Reason: The funder supported in study execution, study design, data acquisition, statistical analyses and manuscript revisions. Some authors were employees of the funding company.	**Some concerns**
Xu, 2023 *RATIONALE-306*	Definitely yes; Reason: Randomization was performed using an interactive response technology system.	No information.	Probably no; Reason: Double-blind trial. Investigators, patients, and sponsor staff or its designees were masked to group assignment. After achieving the primary objective, the study was to be unblinded.	Probably yes; Reason: Discontinuation treatment percentages were slightly higher in the control group than in the intervention group.	Definitely yes; Reason: All relevant outcomes from the trial registry were reported (in the article or in the appendix). Quality of life will be	**Definitely no**; Reason: The funder had a role in study design, data collection, data analysis, data interpretation, and writing of the clinical study report.	**Some concerns**

					reported in a separate publication.		

Table of excluded studies

Reference	Reason for exclusion
Kato K, Doki Y, Ogata T, Motoyama S, Kawakami H, Ueno M, Kojima T, Shirakawa Y, Okada M, Ishihara R, Kubota Y, Amaya-Chanaga C, Chen T, Matsumura Y, Kitagawa Y. First-line nivolumab plus ipilimumab or chemotherapy versus chemotherapy alone in advanced esophageal squamous cell carcinoma: a Japanese subgroup analysis of open-label, phase 3 trial (CheckMate 648/ONO-4538-50). Esophagus. 2023 Apr;20(2):291-301. doi: 10.1007/s10388-022-00970-1. Epub 2022 Nov 19. PMID: 36401133; PMCID: PMC10024660.	CheckMate 648 is included in the selected systematic review (Duan, 2023)
Liu T, Bai Y, Lin X, Li W, Wang J, Zhang X, Pan H, Bai C, Bai L, Cheng Y, Zhang J, Zhong H, Ba Y, Hu W, Xu R, Guo W, Qin S, Yang N, Lu J, Shitara K, Lei M, Li M, Bao N, Chen T, Shen L. First-line nivolumab plus chemotherapy vs chemotherapy in patients with advanced gastric, gastroesophageal junction and esophageal adenocarcinoma: CheckMate 649 Chinese subgroup analysis. Int J Cancer. 2023 Feb 15;152(4):749-760. doi: 10.1002/ijc.34296. Epub 2022 Oct 31. PMID: 36121651; PMCID: PMC10092493.	CheckMate 649 is included in the selected systematic review (Duan, 2023)
Satake H, Lee KW, Chung HC, Lee J, Yamaguchi K, Chen JS, Yoshikawa T, Amagai K, Yeh KH, Goto M, Chao Y, Lam KO, Han SR, Shiratori S, Shah S, Shitara K. Pembrolizumab or pembrolizumab plus chemotherapy versus standard of care chemotherapy in patients with advanced gastric or gastroesophageal junction adenocarcinoma: Asian subgroup analysis of KEYNOTE-062. Jpn J Clin Oncol. 2023 Mar 7;53(3):221-229. doi: 10.1093/jjco/hyac188. PMID: 36533429; PMCID: PMC9991501.	KEYNOTE-062 is included in the selected systematic review (Duan, 2023)
Cao Y, Qin S, Luo S, Li Z, Cheng Y, Fan Y, Sun Y, Yin X, Yuan X, Li W, Liu T, Hsu CH, Lin X, Kim SB, Kojima T, Zhang J, Lee SH, Bai Y, Muro K, Doi T, Bai C, Gu K, Pan HM, Bai L, Yang JW, Cui Y, Lu W, Chen J. Pembrolizumab versus chemotherapy for patients with esophageal squamous cell carcinoma enrolled in the randomized KEYNOTE-181 trial in Asia. ESMO Open. 2022 Feb;7(1):100341. doi: 10.1016/j.esmoop.2021.100341. Epub 2021 Dec 29. PMID: 34973513; PMCID: PMC8764510.	Second-line treatment (KEYNOTE-181)
Chung HC, Kang YK, Chen Z, Bai Y, Wan Ishak WZ, Shim BY, Park YL, Koo DH, Lu J, Xu J, Chon HJ, Bai LY, Zeng S, Yuan Y, Chen YY, Gu K, Zhong WY, Kuang S, Shih CS, Qin SK. Pembrolizumab versus paclitaxel for previously treated advanced gastric or gastroesophageal junction cancer (KEYNOTE-063): A randomized, open-label, phase 3 trial in Asian patients. Cancer. 2022 Mar 1;128(5):995-1003. doi: 10.1002/cncr.34019. Epub 2021 Dec 8. PMID: 34878659; PMCID: PMC9299889.	Second-line treatment (KEYNOTE-063)
Doki Y, Ajani JA, Kato K, Xu J, Wyrwicz L, Motoyama S, Ogata T, Kawakami H, Hsu CH, Adenis A, El Hajbi F, Di Bartolomeo M, Braghiroli MI, Holtved E, Ostoich SA, Kim HR, Ueno M, Mansoor W, Yang WC, Liu T, Bridgewater J, Makino T, Xynos I, Liu X, Lei M, Kondo K, Patel A, Gricar J, Chau I, Kitagawa Y; CheckMate 648 Trial Investigators. Nivolumab Combination Therapy in Advanced Esophageal Squamous-Cell Carcinoma. N Engl J Med. 2022 Feb 3;386(5):449-462. doi: 10.1056/NEJMoa2111380. PMID: 35108470.	CheckMate 648 is included in the selected systematic review (Duan, 2023)
Fuchs CS, Özgüroğlu M, Bang YJ, Di Bartolomeo M, Mandala M, Ryu MH, Fornaro L, Olesinski T, Caglevic C, Chung HC, Muro K, Van Cutsem E, Elme A, Thuss-Patience P, Chau I, Ohtsu A, Bhagia P, Wang A, Shih CS, Shitara K. 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. 2022 Jan;25(1):197-206. doi: 10.1007/s10120-021-01227-z. Epub 2021 Sep 1. PMID: 34468869; PMCID: PMC8732941.	Second-line treatment (KEYNOTE-061)
Janjigian YY, Van Cutsem E, Muro K, Wainberg Z, Al-Batran SE, Hyung WJ, Molena D, Marcovitz M, Ruscica D, Robbins SH, Negro A, Tabernero J. MATTERHORN: phase III study of durvalumab plus FLOT chemotherapy in resectable gastric/gastroesophageal junction cancer. Future Oncol. 2022 Jun;18(20):2465-2473. doi: 10.2217/fon-2022-0093. Epub 2022 May 10. PMID: 35535555.	Study protocol (MATTERHORN)
Kang YK, Chen LT, Ryu MH, Oh DY, Oh SC, Chung HC, Lee KW, Omori T, Shitara K, Sakuramoto S, Chung IJ, Yamaguchi K, Kato K, Sym SJ, Kadowaki S, Tsuji K, Chen JS, Bai LY, Oh SY, Choda Y, Yasui H, Takeuchi K, Hirashima Y, Hagihara S,	ATTRACTION-4 is included in the selected systematic review (Duan, 2023)

Boku N. Nivolumab plus chemotherapy versus placebo plus chemotherapy in patients with HER2-negative, untreated, unresectable advanced or recurrent gastric or gastro-oesophageal junction cancer (ATTRACTION-4): a randomised, multicentre, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2022 Feb;23(2):234-247. doi: 10.1016/S1470-2045(21)00692-6. Epub 2022 Jan 11. PMID: 35030335.	
Kojima T, Hara H, Tsuji A, Yasui H, Muro K, Satoh T, Ogata T, Ishihara R, Goto M, Baba H, Nishina T, Han S, Sakata T, Yatsuzuka N, Doi T, Kato K. First-line pembrolizumab + chemotherapy in Japanese patients with advanced/metastatic esophageal cancer from KEYNOTE-590. Esophagus. 2022 Oct;19(4):683-692. doi: 10.1007/s10388-022-00920-x. Epub 2022 Jun 7. PMID: 35668304; PMCID: PMC9436840.	KEYNOTE-590 is included in the selected systematic review (Duan, 2023)
Lu Z, Wang J, Shu Y, Liu L, Kong L, Yang L, Wang B, Sun G, Ji Y, Cao G, Liu H, Cui T, Li N, Qiu W, Li G, Hou X, Luo H, Xue L, Zhang Y, Yue W, Liu Z, Wang X, Gao S, Pan Y, Galais MP, Zaanan A, Ma Z, Li H, Wang Y, Shen L; ORIENT-15 study group. Sintilimab versus placebo in combination with chemotherapy as first line treatment for locally advanced or metastatic oesophageal squamous cell carcinoma (ORIENT-15): multicentre, randomised, double blind, phase 3 trial. BMJ. 2022 Apr 19;377:e068714. doi: 10.1136/bmj-2021-068714. PMID: 35440464; PMCID: PMC9016493.	ORIENT-15 is included in the selected systematic review (Duan, 2023)
Okada M, Kato K, Cho BC, Takahashi M, Lin CY, Chin K, Kadowaki S, Ahn MJ, Hamamoto Y, Doki Y, Yen CC, Kubota Y, Kim SB, Hsu CH, Holtved E, Xynos I, Matsumura Y, Takazawa A, Kitagawa Y. Three-Year Follow-Up and Response-Survival Relationship of Nivolumab in Previously Treated Patients with Advanced Esophageal Squamous Cell Carcinoma (ATTRACTION-3). Clin Cancer Res. 2022 Aug 2;28(15):3277-3286. doi: 10.1158/1078-0432.CCR-21-0985. PMID: 35294546; PMCID: PMC9662935.	Second-line treatment (ATTRACTION-3)
Shen L, Kato K, Kim SB, Ajani JA, Zhao K, He Z, Yu X, Shu Y, Luo Q, Wang J, Chen Z, Niu Z, Zhang L, Yi T, Sun JM, Chen J, Yu G, Lin CY, Hara H, Bi Q, Satoh T, Pazo-Cid R, Arkenau HT, Borg C, Lordick F, Li L, Ding N, Tao A, Shi J, Van Cutsem E; RATIONALE-302 Investigators. Tislelizumab Versus Chemotherapy as Second-Line Treatment for Advanced or Metastatic Esophageal Squamous Cell Carcinoma (RATIONALE-302): A Randomized Phase III Study. J Clin Oncol. 2022 Sep 10;40(26):3065-3076. doi: 10.1200/JCO.21.01926. Epub 2022 Apr 20. PMID: 35442766; PMCID: PMC9462531.	Second-line treatment (RATIONALE-302)
Stein A, Paschold L, Tintelnot J, Goekkurt E, Henkes SS, Simnica D, Schultheiss C, Willscher E, Bauer M, Wickenhauser C, Thuss-Patience P, Lorenzen S, Ettrich T, Riera-Knorrenschild J, Jacobasch L, Kretzschmar A, Kubicka S, Al-Batran SE, Reinacher-Schick A, Pink D, Sinn M, Lindig U, Hiegl W, Hinke A, Hegewisch-Becker S, Binder M. Efficacy of Ipilimumab vs FOLFOX in Combination With Nivolumab and Trastuzumab in Patients With Previously Untreated ERBB2-Positive Esophagogastric Adenocarcinoma: The AIO INTEGA Randomized Clinical Trial. JAMA Oncol. 2022 Aug 1;8(8):1150-1158. doi: 10.1001/jamaoncol.2022.2228. PMID: 35737383; PMCID: PMC9227706.	Wrong comparison (Ipilimumab + Nivolumab + Trastuzumab versus FOLFOX + Nivolumab + Trastuzumab) (INTEGA)
Tabernero J, Shen L, Elimova E, Ku G, Liu T, Shitara K, Lin X, Boyken L, Li H, Grim J, Ajani J. HERIZON-GEA-01: Zanidatamab + chemo ± tislelizumab for 1L treatment of HER2-positive gastroesophageal adenocarcinoma. Future Oncol. 2022 Sep;18(29):3255-3266. doi: 10.2217/fon-2022-0595. Epub 2022 Aug 24. PMID: 36000541.	Design paper (HERIZON-GEA-01)
Wang ZX, Cui C, Yao J, Zhang Y, Li M, Feng J, Yang S, Fan Y, Shi J, Zhang X, Shen L, Shu Y, Wang C, Dai T, Mao T, Chen L, Guo Z, Liu B, Pan H, Cang S, Jiang Y, Wang J, Ye M, Chen Z, Jiang D, Lin Q, Ren W, Wang J, Wu L, Xu Y, Miao Z, Sun M, Xie C, Liu Y, Wang Q, Zhao L, Li Q, Huang C, Jiang K, Yang K, Li D, Liu Y, Zhu Z, Chen R, Jia L, Li W, Liao W, Liu HX, Ma D, Ma J, Qin Y, Shi Z, Wei Q, Xiao K, Zhang Y, Zhang Y, Chen X, Dai G, He J, Li J, Li G, Liu Y, Liu Z, Yuan X, Zhang J, Fu Z, He Y, Ju F, Liu Z, Tang P, Wang T, Wang W, Zhang J, Luo X, Tang X, May R, Feng H, Yao S, Keegan P, Xu RH, Wang F. Toripalimab plus chemotherapy in treatment-naïve, advanced esophageal squamous cell carcinoma (JUPITER-06): A multi-center phase 3 trial. Cancer Cell. 2022 Mar 14;40(3):277-288.e3. doi: 10.1016/j.ccell.2022.02.007. Epub 2022 Mar 3. PMID: 35245446.	JUPITER-06 is included in the selected systematic review (Duan, 2023)
Xu J, Li Y, Fan Q, Shu Y, Yang L, Cui T, Gu K, Tao M, Wang X, Cui C, Xu N, Xiao J, Gao Q, Liu Y, Zhang T, Bai Y, Li W, Zhang Y, Dai G, Ma D, Zhang J, Bai C, Huang Y, Liao W, Wu L, Chen X, Yang Y, Wang J, Ji S, Zhou H, Wang Y, Ma Z, Wang Y,	Second-line treatment, phase II trial (ORIENT-2)

Peng B, Sun J, Mancao C. Clinical and biomarker analyses of sintilimab versus chemotherapy as second-line therapy for advanced or metastatic esophageal squamous cell carcinoma: a randomized, open-label phase 2 study (ORIENT-2). Nat Commun. 2022 Feb 14;13(1):857. doi: 10.1038/s41467-022-28408-3. PMID: 35165274; PMCID: PMC8844279.	

Literature search strategy

Uitgangsvraag 6+7: Palliatieve immunotherapie: Rol in palliatieve (gemetastaseerd/niet-resectabel) fase van adenocarcinoom + Palliatieve immunotherapie: Rol in palliatieve (gemetastaseerd/niet-resectabel) fase van plaveiselcelcarcinoom	
Database(s): Medline, Embase	Datum: 29-5-2023
Periode: >2015	

Zoekverantwoording

Database	Aantallen treffers	Aantallen treffers na ontdubbelen
Medline 29 mei 2023	337	335
Embase 29 mei 2023	545	472
Totaal	882	807

➔ **Aantal SRs: 427; aantal RCT's: 380.**

OVID/Medline 29 mei 2023
Ovid MEDLINE(R) ALL <1946 to May 25, 2023>

1	Stomach Neoplasms/ or exp Esophageal Neoplasms/ or linitis-plastica.ti,ab,kf. or ((carcinoma* or neoplas* or adenoma* or adenocarcinoma* or tumor* or tumour* or cancer* or oncolog* or malignan* or carcinogen* or oncogen* or anticarcinogen* or squamous*) adj5 (esophag* or oesophag* or stomach or gastric* or cardia or gastroesophag* or gastrooesophag* or oesogast* or esogast*)).ti,ab,kf.	**221200**
2	exp Neoplasm Metastasis/ or exp Palliative Medicine/ or exp Palliative Care/ or Terminal Care/ or (metasta* or seeding* or micrometasta* or unresectab* or advanced or palliati* or terminal* or inoperab* or irresectab* or stage-4 or stage-four or stage-iv or end-of-life).ti,ab,kf.	**1809593**
3	exp Immunotherapy/ or Antineoplastic Agents, Immunological/ or T-Lymphocytes, Cytotoxic/ or Nivolumab/ or exp Immune Checkpoint Proteins/ or Ipilimumab/ or Avelumab/ or Adjuvants, Immunologic/ or Immunotherapy, Adoptive/ or Nivolumab/ or (immunotherap* or radioimmunotherap* or immunopotentiat* or immunostimul* or immunonutrition or immunoactivator* or immunoadjuvant* or donor-lymphocyte-infusion* or chimeric-antigen-receptor-therap* or antigen-B7-H1 or antigen-B7H1 or antigen-CD274 or B7-H1-antigen or B7-H1-protein or B7-homolog-1-protein or B7H1-antigen or B7H1-protein or CD274-antigen* or PDCD1-ligand-1 or PDCD1LG1-protein or programmed-cell-death-1-ligand-1 or programmed-death-1-ligand-1-protein or programmed-death-ligand-1 or program-death-1 or protein-B7-H1 or protein-B7H1 or protein-PDCD1LG1 or checkpoint-inhibitor* or checkpoint-blockade* or anti-PD1 or anti-PD-1 or anti-PDL1 or anti-PD-L1 or anti-CTLA4 or cytotoxic-T-lymphocyte-associated-protein-4 or nivolumab or opdivo or pembrolizumab or keytruda or durvalumab or imfinzi or cemiplimab or libtayo or ipilimumab or yervoy or avelumab or bavencio or ((immun* or BRM or response-modifier or car or cytol*) adj3 (therap* or intervention* or lymphocyte* or cell* or adjuvant*))).ti,ab,kf.	**848787**
4	1 and 2 and 3	**3967**
5	4 not ((Adolescent/ or Child/ or Infant/) not Adult/)	**3962**
6	5 not ((exp animals/ or exp models, animal/) not humans/)	**3915**
7	6 not (comment/ or editorial/ or letter/ or Case Reports/)	**3377**
8	limit 7 to yr="2015 -Current"	**2393**
9	(systematic-review.pt. or (meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or umbrella or "structured literature") adj3 (review* or	**635721**

	overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data extraction" or "data source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.)) not (comment/ or editorial/ or letter/ or ((exp animals/ or exp models, animal/) not humans/))	
10	8 and 9	**156**
11	exp randomized controlled trial/ or random*.ti,ab,kf. or ((pragmatic or practical) adj clinical trial*).ti,ab,kf. or ((non-inferiority or noninferiority or superiority or equivalence) adj3 trial*).ti,ab,kf.	**1554523**
12	8 and 11	**262**
14	12 not 10	**181**

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No.	Query	Results
#12	#8 AND #11 NOT #10	**361**
#11	'randomized controlled trial'/exp OR random*:ti,ab,kw OR (((pragmatic OR practical) NEAR/1 'clinical trial*'):ti,ab,kw) OR (((('non inferiority' OR noninferiority OR superiority OR equivalence) NEAR/3 trial*):ti,ab,kw)	**2051905**
#10	#8 AND #9	**422**
#9	('meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab) NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp) NOT ('conference abstract'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it)	**709516**
#8	#6 NOT ('conference abstract'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'case report'/exp) AND [2015-2023]/py	**4925**
#7	#6 NOT ('conference abstract'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'case report'/exp)	**6688**
#6	#5 NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	**10966**
#5	#4 NOT (('adolescent'/exp OR 'child'/exp) NOT ('adult'/exp OR 'aged'/exp OR 'middle aged'/exp))	**11233**
#4	#1 AND #2 AND #3	**11255**
#3	'immunotherapy'/exp OR 'antineoplastic monoclonal antibody'/exp/mj OR 'programmed death 1 ligand 1'/de OR 'cytotoxic t lymphocyte'/de OR 'nivolumab'/de OR 'pembrolizumab'/de OR 'durvalumab'/de OR 'cemiplimab'/de OR 'ipilimumab'/de OR 'avelumab'/de OR 'immune checkpoint protein'/mj OR 'immunological adjuvant'/mj OR 'adoptive immunotherapy'/mj OR immunotherap*:ti,ab,kw OR radioimmunotherap*:ti,ab,kw OR immunopotentiat*:ti,ab,kw OR immunostimul*:ti,ab,kw OR immunoactivator*:ti,ab,kw OR immunoadjuvant*:ti,ab,kw OR immunonutrition:ti,ab,kw OR 'donor lymphocyte infusion*':ti,ab,kw OR 'chimeric antigen receptor therap*':ti,ab,kw OR 'antigen b7 h1':ti,ab,kw OR 'antigen b7h1':ti,ab,kw OR 'antigen cd274':ti,ab,kw OR 'b7 h1 antigen':ti,ab,kw OR 'b7 h1 protein':ti,ab,kw OR 'b7 homolog 1 protein':ti,ab,kw OR 'b7h1 antigen':ti,ab,kw OR 'b7h1 protein':ti,ab,kw OR 'cd274 antigen*':ti,ab,kw OR 'pdcd1 ligand 1':ti,ab,kw OR 'pdcd1lg1 protein':ti,ab,kw OR 'programmed cell death 1 ligand 1':ti,ab,kw OR 'programmed death 1 ligand 1 protein':ti,ab,kw OR 'programmed death ligand 1':ti,ab,kw OR 'program death 1':ti,ab,kw OR 'protein b7 h1':ti,ab,kw OR 'protein b7h1':ti,ab,kw OR 'protein	**1036011**

	pdcd1lg1':ti,ab,kw OR 'checkpoint inhibitor*':ti,ab,kw OR 'checkpoint blockade*':ti,ab,kw OR 'anti pd1':ti,ab,kw OR 'anti pd 1':ti,ab,kw OR 'anti pdl1':ti,ab,kw OR 'anti pd l1':ti,ab,kw OR 'anti ctla4':ti,ab,kw OR 'cytotoxic t lymphocyte associated protein 4':ti,ab,kw OR nivolumab:ti,ab,kw OR opdivo:ti,ab,kw OR pembrolizumab:ti,ab,kw OR keytruda:ti,ab,kw OR durvalumab:ti,ab,kw OR imfinzi:ti,ab,kw OR cemiplimab:ti,ab,kw OR libtayo:ti,ab,kw OR ipilimumab:ti,ab,kw OR yervoy:ti,ab,kw OR avelumab:ti,ab,kw OR bavencio:ti,ab,kw OR (((immun* OR brm OR 'response modifier' OR car OR cytol*) NEAR/3 (therap* OR intervention* OR lymphocyte* OR cell* OR adjuvant*)):ti,ab,kw)	
#2	'metastasis'/exp OR 'palliative therapy'/exp OR 'terminal care'/de OR 'inoperable cancer'/de OR 'advanced cancer'/de OR metasta*:ti,ab,kw OR seeding*:ti,ab,kw OR micrometasta*:ti,ab,kw OR unresectab*:ti,ab,kw OR advanced:ti,ab,kw OR palliati*:ti,ab,kw OR terminal*:ti,ab,kw OR inoperab*:ti,ab,kw OR irresectab*:ti,ab,kw OR 'stage 4':ti,ab,kw OR 'stage four':ti,ab,kw OR 'stage iv':ti,ab,kw OR 'end of life':ti,ab,kw	**2588179**
#1	'stomach tumor'/exp OR 'esophagus tumor'/exp OR 'linitis plastica':ti,ab,kw OR (((carcinoma* OR neoplas* OR adenoma* OR adenocarcinoma* OR tumor* OR tumour* OR cancer* OR oncolog* OR malignan* OR carcinogen* OR oncogen* OR anticarcinogen* OR squamous*) NEAR/5 (esophag* OR oesophag* OR stomach OR gastric* OR cardia OR gastroesophag* OR gastrooesophag* OR oesogast* OR esogast*)):ti,ab,kw)	**329734**

Startpagina richtlijn maagcarcinoom

Deze richtlijn valt onder het cluster oesofagus- en maagcarcinoom.

Waar gaat deze richtlijn over?
Deze richtlijn richt zich op wat volgens de huidige maatstaven de beste zorg is voor patiënten met maagcarcinoom. In de richtlijn komen de volgende onderwerpen aan de orde:

- Screening en diagnostiek van maagcarcinoom
- Early gastric cancer
- Neoadjuvante en adjuvante behandeling
- Chirurgische behandeling en technieken van maagcarcinoom
- Palliatieve chirurgie
- Pathologie
- Follow-up van patiënten met maagcarcinoom
- Recidief en metastasen
- Voeding bij patiënten met een maagcarcinoom
- TNM stadium

Voor wie is deze richtlijn bedoeld?
Deze richtlijn is bestemd voor alle zorgverleners in de tweede (en derde) lijn die betrokken zijn bij de zorg voor patiënten met maagcarcinoom.

Voor patiënten
Jaarlijks wordt bij ongeveer 4000 Nederlanders de diagnose slokdarm- of maagkanker gesteld. Bij bijna 3000 patiënten gaat het over slokdarmkanker of kanker in het overgangsgebied tussen slokdarm en maag. Ongeveer 1000 patiënten worden per jaar gediagnosticeerd met maagkanker.

- Meer informatie over maagkanker is te vinden op Thuisarts: https://www.thuisarts.nl/maagkanker
- Meer informatie over maagkanker is ook te vinden op de website van de Stichting voor Patiënten met Kanker aan het Spijsverteringskanaal (SPKS): https://spks.nl/

Hoe is de richtlijn tot stand gekomen?
Het initiatief voor deze richtlijn is afkomstig van Nederlandse Vereniging voor Maag-Darm-Leverartsen (NVMDL) en wordt vanaf 2022 modulair herzien door het cluster Oesofagus- en maagcarcinoom. De richtlijn is opgesteld door een multidisciplinaire commissie met vertegenwoordigers vanuit internisten, maag-darm-leverartsen, medisch-oncologen, chirurgen, anesthesiologen, pathologen, radiologen, radiotherapeuten, oncologen, nucleair geneeskundigen en keel-neus-oorartsen. De samenstelling van het cluster kunt u hier (link) vinden. Er werd aandacht besteed aan het patiëntenperspectief door inbreng van de patiëntenvereniging SPKS.

Modulair onderhoud
De richtlijnen in het cluster oesofagus- en maagcarcinoom worden modulair onderhouden. Het cluster oesofagus- en maagcarcinoom omvat de richtlijn oesofaguscarcinoom en de richtlijn maagcarcinoom. In onderstaande tabel is te zien wat de geldigheid is van de richtlijnmodules voor maagcarcinoom. Het cluster Oesofagus- en maagcarcinoom is als houder van deze richtlijn de eerstverantwoordelijke voor de actualiteit van deze richtlijn.

Richtlijn maagcarcinoom	Geautoriseerd in	Laatst beoordeeld in	Geplande herbeoordeling	Wijzigingen meest recente versie
1. Startpagina – Maagcarcinoom			1 jaar	Geüpdatet
2. Screening	2016	2021	2023	n.v.t.
3. Diagnostiek	2016	2021	2023	n.v.t.
4. Early gastric cancer	2017	2021	2023	
4.5 Nieuwe update module: **Module 5**: Endoscopische behandeling vroegcarcinoom maag				Update module vervangt oude module 4.5
5. (Neo-) adjuvante behandelingen	2010	2021	2023	n.v.t.
6. Chirurgie	2009/2017	2021	2023	n.v.t.
7. Palliatieve zorg	2009	2021	2023	Aanpassing titel landingspagina
7.1 Nieuwe module: **Module 4**: Palliatieve immuuntherapie				Nieuwe module (zie module 4 – richtlijn oesofaguscarcinoom)
8. Pathologie	2009	2021	2023	n.v.t.
9. Follow-up	2009	2021	2023	n.v.t.
10. Recidief en metastasen	2016	2021	2023	n.v.t.
11. Voeding				n.v.t.
12. TNM classificatie	2016	2021	2023	n.v.t.

Module 5 Chirurgische resectie na endoscopische behandeling vroegcarcinoom maag

Clinical question
Welke patiënten komen in aanmerking voor chirurgische resectie na endoscopische behandeling voor vroegcarcinoom van de maag?

Inleiding
There is no clarity on which patients with early gastric carcinoma should be considered for surgical resection of the stomach to prevent lymph node metastasis in the future. There is a Japanese guideline that addresses several factors such as tumor size, tumor differentiation, and lymphovascular invasion. The question is whether these factors also apply to the patient population in the Western setting.

Search and select
A systematic review of the literature was performed to answer the following question:
Which prognostic factors have been established for surgery after endoscopic treatment of patients with early gastric cancer (stage T1)?

Vul hier onder de belangrijkste concepten (PICO) van de zoekvraag in.

P	**(Patients)**	**=** Patients with early gastric cancer (stage T1) who have been treated endoscopically
I	**(Intervention)**	**=** Prognostic factors that predict for which patients surgery is necessary in terms of residual tumor, lymph node metastasis and overall survival
C	**(Comparison)**	= a different model/care as usual
O	**(Outcomes)**	= predictive value of the factors
T	**(Timing)**	**=** after endoscopic treatment
S	**(Setting)**	= specialized care

<u>Relevant outcome measures</u>
The guideline development group considered lymph node metastasis, residual tumor and overall survival as critical outcomes.

<u>Search and select (Methods)</u>
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until 26-6-2023. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 146 hits. Studies were selected based on the following criteria:

- Being a systematic review or observational study (cohort study).

- Reporting prediction factors with outcome as dependent variable and independent variables (patient characteristics) determined before the start of the procedure.

Eight studies were initially selected based on title and abstract screening. After reading the full text, 6 studies were excluded (see the table with reasons for exclusion under the tab Methods), and two studies were included.

Results

Two studies were included in the analysis of the literature. Important study characteristics and results are summarized in the evidence table. The assessment of the risk of bias is summarized in the risk of bias table.

Summary of literature

Description of studies

Jiang, 2020: In this systematic review and meta-analysis, a total of 12 cohort studies investigating the risk factors of lymph node metastasis (LNM) and tumor invasion were included, with in total 3015 patients. The study took place in China, and the included studies were all performed in either Japan or South-Korea. All included studies were graded as high quality.

With a score of 7 to 9 on the Newcastle-Ottawa Quality Assessment Scales (NOS). No prediction value of the factors or predictive model was calculated.

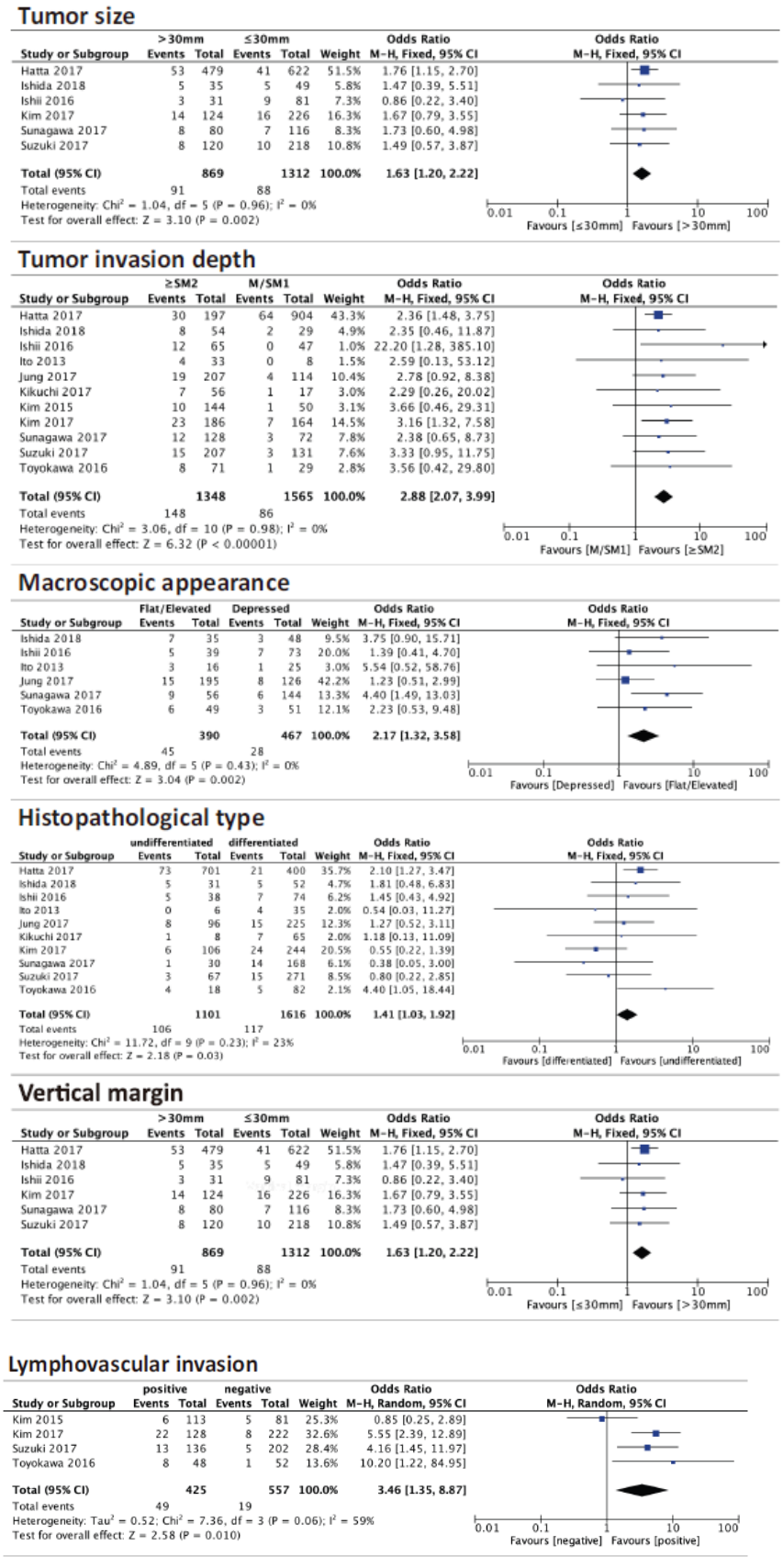
Abdelfatah, 2018: in this meta-analysis a total of 12 studies (11 retrospectives and 1 prospective) were included that compared the incidence of LNM in EGC patients after gastrectomy and lymph node dissection. The total number of included patients was 9798. All of the included studies were executed in Japan, Korea or China.

Results

Preferably describe the results per outcome measure.

LNM: For this outcome, in Jiang, 2020 six predictive factors were found: Tumor size (the risk of LNM was significantly higher in patients with tumor size >30 mm than that of ⩽30 mm (pooled OR = 1.63, 95% CI = 1.20–2.22, p = 0.002)), tumor invasion depth (patients with tumor invasion depth ⩾ SM2 (⩾500 μm from the muscularis mucosae) had significantly higher prevalence of LNM than patients with tumor invasion depth < SM2 (pooled OR = 2.88, 95% CI = 2.07–3.99, p < 0.00001)), macroscopic appearance (patients with flat or elevated tumor macroscopic appearance had significantly higher risk of LNM than patients with depressed tumor macroscopic appearance (pooled OR = 2.17, 95% CI = 1.32–3.58, p = 0.002), histopathological type (prevalence of LNM was significantly higher in patients with histologically undifferentiated type than that of differentiated type (pooled OR = 1.41, 95% CI = 1.03–1.92, p = 0.03)), vertical margin (the prevalence of LNM was significantly higher in patients with positive vertical margin than in patients with negative vertical margin (pooled OR = 2.02, 95% CI = 1.50–2.73, p < 0.00001)), and lymphovasculair invasion (patients with tumor lymphovascular invasion had significantly higher risk of LNM than patients without tumor lymphovascular invasion (pooled OR = 3.46, 95% CI = 1.35–8.87, p = 0.01)). See figure 1 for the forest plots.

Figure 1: Forest plots for the relationship between LNM and tumor size, tumor invasion depth, macroscopic appearance, histopathological type and vertical margin

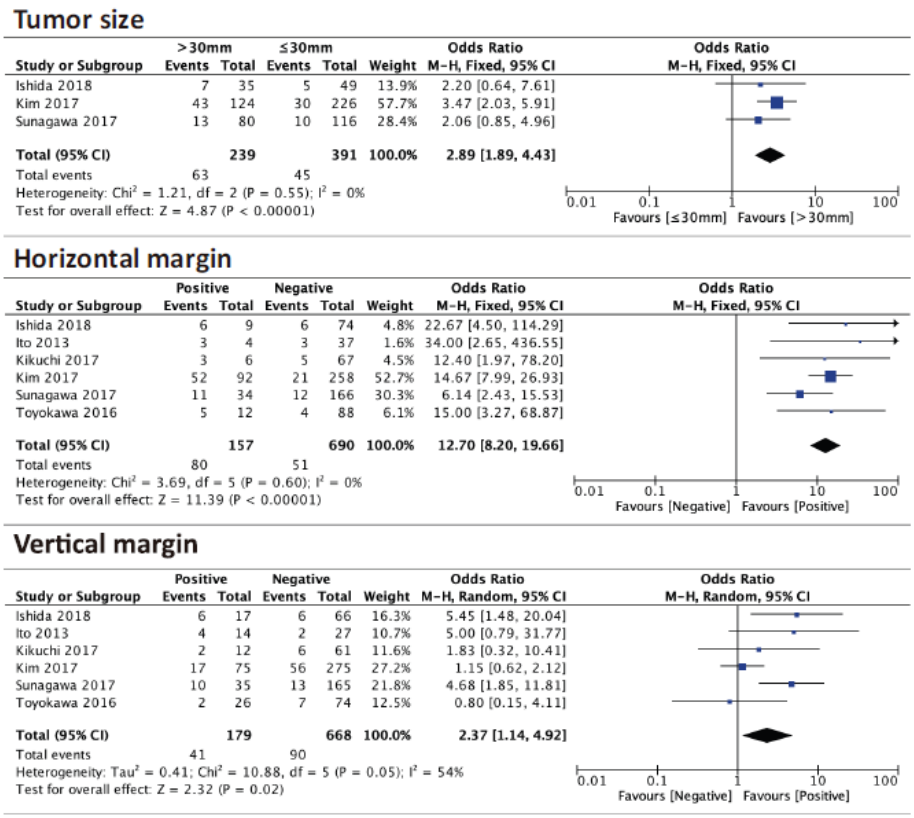


In Abdelfatah, 2018, In patients who underwent gastrectomy with LND, those who met the expanded criteria had a higher incidence of being diagnosed with LNM than patients who met the absolute criteria (68/9798 [0.7%] vs 6/3025 [0.2%]). The relative risk reduction when the absolute indicators were applied instead of the expanded indicators was 2.54 (1.29, 5.01) (P = .007). The expanded indicators were:

- Intramucosal cancer, differentiated type, </=3 cm in size, UL (þ) [Ex-1]
- Intramucosal cancer, differentiated type, >2 cm in size, UL (-) [Ex-2]
- Intramucosal cancer, undifferentiated type, </=2 cm in size, UL (-) [Ex-3]
- SM1 cancer (<500 mm invasion), differentiated type, </=3 cm in size [Ex-SM].

Tumor invasion: For this outcome, three predictive factors were found: Tumor size (the risk of residual tumor was significantly higher in patients with tumor size ⩾30 mm than in patients with tumor size <30 mm (pooled OR = 2.89, 95% CI = 1.89–4.43, p < 0.00001)), horizontal margin (there was a significant difference for the prevalence of residual tumor between patients with positive horizontal margin and patients with negative horizontal margin (pooled OR = 12.70, 95% CI = 8.20–19.66, p < 0.00001)), and vertical margin (the prevalence of residual tumor was significantly higher in patients with positive vertical margin than in patients with negative vertical margin (pooled OR = 2.37, 95% CI = 1.14–4.92, p = 0.02)). See figure 2 for the forest plots.

Figure 2: Forest plot for the relationship between residual tumor and tumor size, horizontal margin, and vertical margin



Overall survival: No results for this outcome was found.

Conclusions

LNM incidence: The level of evidence regarding the outcome LNM incidence started at low (due to the observational nature of the included studies) and was downgraded to very low due to indirectness (the study population was Asian).

Very low GRADE	The evidence is very uncertain about the performance of the expanded indicators model proposed by Abdelfatah, 2018, where • Intramucosal cancer, differentiated type, </=3 cm in size, UL (þ) • Intramucosal cancer, differentiated type, >2 cm in size, UL (-) • Intramucosal cancer, undifferentiated type, </=2 cm in size, UL (-) • SM1 cancer (<500 mm invasion), differentiated type, </=3 cm in size are indicators that predict LNM in EGC patients after gastrectomy. *Sources: Abdelfatah, 2018*

Overwegingen – van bewijs naar aanbeveling

Voor- en nadelen van de interventie en de kwaliteit van het bewijs

De werkgroep heeft een literatuuronderzoek verricht naar predictiemodellen of -factoren die voorspellen bij elke patiënten het risico groter is op lymph node metastase en tumorinvasie na endoscopische behandeling van de maagcarcinoom. Er werd een meta-analyse gevonden van 12 cohortstudies waarin factoren werden gevonden die deze twee uitkomsten voorspellen. Vanwege de opzet van de studie kon geen GRADE-analyse gedaan worden. Daarnaast werd een meta-analyse gevonden waarbij twee modellen met elkaar werden vergeleken met als uitkomstmaat incidentie van LNM. Deze studieopzet was een goede opzet voor het evalueren van dergelijke modellen. Vanwege het observationele design van de studies en gezien het feit dat de populatie Aziatisch was, kan met een zeer lage bewijskracht lastig uitspraak worden gedaan over de prestatie van deze modellen. De werkgroep concludeert dan ook dat er een kennislacune bestaat omtrent het bestaan van beslissingsmodellen voor de Nederlandse populatie welke op basis van risicofactoren voorspellen welke patiënten na endoscopische behandeling van vroegcarcinoom van de maag in aanmerking moeten komen voor chirurgische resectie.

Aanbeveling

Overweeg het expanded indications model toe te passen om de keuze te maken welke patiënten wel en niet voor deze interventie in aanmerking komen. Overweeg een aanvullende resectie te verrichten indien het risico op lymfekliermetastase groter is dan het risico op chirurgische morbiditeit/mortaliteit.

De indicators voor een aanvullende resectie zijn:

- Intramucosaal carcinoom, gedifferentieerd type, </=3 cm groot, UL (þ)
- Intramucosaal carcinoom, gedifferentieerd type, >2 cm groot, UL (-)
- Intramucosaal carcinoom, ongedifferentieerd type, </=2 cm groot, UL (-)
- SM1-carcinoom (<500 mm invasie), gedifferentieerd type, </=3 cm groot

Bespreek met de patiënten die een indicatie hebben voor aanvullende chirurgische resectie de voor- en nadelen van het inzetten van chirurgische resectie na endoscopische behandeling.

Literatuur

Jiang B, Zhou L, Lu J, Wang Y, Guo J. Predictors of lymph node metastasis and residual tumor in early gastric cancer patients after noncurative endoscopic resection: a systematic review and meta-analysis. Therap Adv Gastroenterol. 2020 Jun

23;13:1756284820935033. doi: 10.1177/1756284820935033. PMID: 32636929; PMCID: PMC7313346.

Abdelfatah MM, Barakat M, Lee H, Kim JJ, Uedo N, Grimm I, Othman MO. The incidence of lymph node metastasis in early gastric cancer according to the expanded criteria in comparison with the absolute criteria of the Japanese Gastric Cancer Association: a systematic review of the literature and meta-analysis. Gastrointest Endosc. 2018 Feb;87(2):338-347. doi: 10.1016/j.gie.2017.09.025. Epub 2017 Sep 28. PMID: 28966062.

Table of excluded studies

Author and year	Reason for exclusion
Chang, 2018	Wrong outcome (invasion depth)
Dai, 2015	Wrong outcome (endoscopic treatment)
Hasuike, 2018	Wrong study design (no prognostic models)
Liu, 2021	Wrong outcome (serosial invasion)
Tsolakis, 2019	Wrong population (gastric neuroendocrine neoplasms type 1)
Yang, 2022	Wrong study design (no prognostic models)

Evidence table

Study reference	Study characteristics	Patient characteristics	Prognostic factor(s)	Follow-up	Estimates of prognostic effect	Comments
Jiang, 2020	**Type of study**: Meta-analysis of cohort studies **Setting and country**: Department of General Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Bejing, China **Funding and conflicts of interest**: The study was supported by the National Natural Science Foundation of China (grant number 81972324), the China Academy of Medical Sciences Innovation Fund for Medical Sciences (grant number 2016-I2M-3-019). The authors have declared no conflicts of interest.	**Inclusion criteria**: (1) study design (randomized controlled trial, cohort, or case–control); (2) articles published in English; (3) patients underwent noncurative ER for EGC, with noncurative resection defined by the Japanese gastric cancer treatment guidelines 2010 (version 3);9 (4) patients underwent additional gastrectomy after noncurative ER; (5) adequate information about risk factor for LNM and residual tumor, with available data for extraction to calculate the pooled odds ratio (OR) or mean difference (MD). **Exclusion criteria**: Abstracts, case reports, reviews, letters to editor, editorials, expert opinions, conference abstracts, or meeting proceedings were excluded. N= 3015 **Potential confounders or effect modifiers**: None mentioned.	**Describe prognostic factor(s) and method of measurement:** Risk factors for LNM: - Tumor size - Tumor invasion depth - Macroscopic appearance - Histopathological type - Vertical margin - Lymphovascular invasion Risk factors for residual tumor: - Tumor size - Horizontal margin - Vertical margin	**Duration or endpoint of follow-up**: Not reported **For how many participants were no complete outcome data available?** Not reported **Reasons for incomplete outcome data described?** Not reported	(**Adjusted) Factor-outcome associations (include SEs or 95%CI and p-value if available):** See table 1 and 2 **Incremental predictive value[1]:** None reported	
Abdelfatah, 2018	**Type of study**: Meta-analysis	**Inclusion criteria**: (1) Patients included in the study were diagnosed with EGC by histopathology, and they underwent	**Describe prognostic factor(s) and method of measurement:**	**Duration or endpoint of**	(**Adjusted) Factor-outcome associations (include SEs or**	

	Setting and country: Division of Gastroenterology, Department of Internal Medicine, East Carolina University, Greenville, North Carolina **Funding and conflicts of interest**: Last author is a consultant for Olympus and Boston Scientific. All other authors disclosed no financial relationships relevant to this publication.	gastrectomy with LND. (2) Sufficient data were presented on the lesion, including depth of invasion, size, ulceration, and differentiation, in order to categorize the patients into expanded criteria versus absolute criteria. (3) Adequate details were provided on the total number of patients and percentage of patients involved. **Exclusion criteria**: (1) Publications including meeting abstracts, case reports, review articles, letters to the editor, comments, and editorials. (2) Patients without EGC but with other lesions, such as a precancerous lesion, adenoma, or metastatic gastric cancer and studies referring to patients with recurrent EGCs. (3) Insufficient data provided in the article regarding the details of the lesions to categorize them into expanded criteria versus absolute criteria. (4) Articles that did not report on the frequencies of LNM. N=9798 **Potential confounders or effect modifiers**: None mentioned.	Two models were compared: - **the absolute indicators**: Clinically intramucosal, differentiated type, </=2 cm in size, UL (-) - **the expanded indicators**: Intramucosal cancer, differentiated type, </=3 cm in size, UL (þ) [Ex-1] Intramucosal cancer, differentiated type, >2 cm in size, UL (-) [Ex-2] Intramucosal cancer, undifferentiated type, </=2 cm in size, UL (-) [Ex-3] SM1 cancer (<500 mm invasion), differentiated type, </=3 cm in size [Ex-SM]	**follow-up**: Not reported **For how many participants were no complete outcome data available?** Not reported **Reasons for incomplete outcome data described?** Not reported	**95%CI and p-value if available):** In patients who underwent gastrectomy with LND, those who met the expanded criteria had a higher incidence of being diagnosed with LNM than patients who met the absolute criteria (68/9798 [0.7%] vs 6/3025 [0.2%]). The relative risk reduction when the absolute criteria were applied instead of the expanded criteria was 2.54 (1.29, 5.01) (P = .007) **Incremental predictive value[1]:** None reported	

Risk of bias table

Study reference (first author, year of publication)	**Study participation**[1] Study sample represents the population of interest on key characteristics? (high/moderate/low risk of selection bias)	**Study Attrition**[2] Loss to follow-up not associated with key characteristics (i.e., the study data adequately represent the sample)? (high/moderate/low risk of attrition bias)	**Prognostic factor measurement**[3] Was the PF of interest defined and adequately measured? (high/moderate/low risk of measurement bias related to PF)	**Outcome measurement**[3] Was the outcome of interest defined and adequately measured? (high/moderate/low risk of measurement bias related to outcome)	**Study confounding**[4] Important potential confounders are appropriately accounted for? (high/moderate/low risk of bias due to confounding)	**Statistical Analysis and Reporting**[5] Statistical analysis appropriate for the design of the study? (high/moderate/low risk of bias due to statistical analysis)
Jiang, 2020	Low risk of bias	Unclear	Low risk of bias	Low risk of bias	Unclear	Low risk of bias
Abdelfatah, 2018	Low risk of bias	Unclear	Low risk of bias	Low risk of bias	Unclear	Low risk of bias

Literature search strategy

Zoekverantwoording

Ontdubbelen

Database	Aantallen treffers	Aantallen treffers na ontdubbelen
Medline 26 jun 2023	852	851
Embase 26 jun 2023	751	231
Totaal	1603	1082

Aantal SRs: 61; aantal RCT's: 85; aantal Observationele studies: 936.

OVID/Medline 26 juni 2023

Ovid MEDLINE(R) ALL <1946 to June 22, 2023>

1	Stomach Neoplasms/ or linitis-plastica.ti,ab,kf. or ((carcinoma* or neoplas* or adenoma* or adenocarcinoma* or tumor* or tumour* or cancer* or oncolog* or malignan* or carcinogen* or oncogen* or anticarcinogen* or squamous*) adj5 (stomach or gastric* or cardia or gastroesophag* or gastrooesophag* or oesogast* or esogast*)).ti,ab,kf.	**156252**
2	(t1 or t1a or t1b or t-1 or t-1a or t-1b or n1 or n-1 or type-1 or type-1a or type-1b or ((early or earliest or first or 1st) adj3 (tumor* or tumour* or type or stage or stages or staging* or phase* or tnm))).ti,ab,kf.	**813964**
3	Endoscopy/ or exp Laryngoscopy/ or exp Endoscopy, Gastrointestinal/ or (endoscop* or gastroscop* or laryngoscop*).ti,ab,kf.	**336017**
4	Surgery.sh. or exp Surgical Procedures, Operative/ or (surger* or surgical* or operation* or operative* or resecti* or gastrectom*).ti,ab,kf.	**5067831**
5	1 and 2 and 3 and 4	**1623**
6	5 not ((Adolescent/ or Child/ or Infant/) not Adult/)	**1617**
7	6 not ((exp animals/ or exp models, animal/) not humans/)	**1603**
8	7 not (comment/ or editorial/ or letter/ or Case Reports/)	**1327**
9	limit 8 to yr="2000 -Current"	**1086**
10	(systematic-review.pt. or (meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data extraction" or "data source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.)) not (comment/ or editorial/ or letter/ or ((exp animals/ or exp models, animal/) not humans/))	**641137**
11	9 and 10	**50**
12	exp randomized controlled trial/ or random*.ti,ab,kf. or ((pragmatic or practical) adj clinical trial*).ti,ab,kf. or ((non-inferiority or noninferiority or superiority or equivalence) adj3 trial*).ti,ab,kf.	**1562198**
13	(9 and 12) not 11	**69**
14	exp Epidemiologic Studies/ or (cohort or (case adj5 (control or controll* or comparison or referent)) or risk or causation or causal or odds-ratio or etiol* or aetiol* or natural-history or predict* or prognos* or outcome or course or retrospect* or followup or follow-up).ti,ab,kf.	**8510133**
15	(9 and 14) not (11 or 13)	**733**

Embase.com 26 juni 2023

No.	Query	Results
#15	#9 AND #14 NOT (#11 OR #13)	**748**
#14	'epidemiology'/de OR 'prospective study'/exp OR 'cohort analysis'/exp OR cohort:ti,ab,kw OR ((case NEAR/5 (control OR controll* OR comparison OR referent)):ti,ab,kw) OR risk:ti,ab,kw OR causation:ti,ab,kw OR causal:ti,ab,kw OR 'odds ratio':ti,ab,kw OR etiol*:ti,ab,kw OR aetiol*:ti,ab,kw OR 'natural history':ti,ab,kw OR predict*:ti,ab,kw OR prognos*:ti,ab,kw OR outcome:ti,ab,kw OR course:ti,ab,kw OR retrospect*:ti,ab,kw OR	**11219517**

	'case control':ti,ab,kw OR 'multivariate':ti,ab,kw OR followup:ti,ab,kw OR 'follow up':ti,ab,kw	
#13	#9 AND #12 NOT #11	**64**
#12	'randomized controlled trial'/exp OR random*:ti,ab,kw OR (((pragmatic OR practical) NEAR/1 'clinical trial*'):ti,ab,kw) OR ((('non inferiority' OR noninferiority OR superiority OR equivalence) NEAR/3 trial*):ti,ab,kw)	**2063103**
#11	#9 AND #10	**58**
#10	('meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab) NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp) NOT ('conference abstract'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it)	**715688**
#9	#7 NOT ('conference abstract'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'case report'/exp) AND [2000-2023]/py	**1116**
#8	#7 NOT ('conference abstract'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'case report'/exp)	**1329**
#7	#6 NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	**2564**
#6	#5 NOT (('adolescent'/exp OR 'child'/exp) NOT ('adult'/exp OR 'aged'/exp OR 'middle aged'/exp))	**2587**
#5	#1 AND #2 AND #3 AND #4	**2602**
#4	'surgery'/exp OR surger*:ti,ab,kw OR surgical*:ti,ab,kw OR operation*:ti,ab,kw OR operative*:ti,ab,kw OR resecti*:ti,ab,kw OR gastrectom*:ti,ab,kw	**7289401**
#3	'endoscopy'/de OR 'digestive tract endoscopy'/de OR 'esophagogastroduodenoscopy'/de OR 'gastrointestinal endoscopy'/de OR 'pharyngoscopy'/de OR 'laryngoscopy'/exp OR endoscop*:ti,ab,kw OR gastroscop*:ti,ab,kw OR laryngoscop*:ti,ab,kw	**509334**
#2	t1:ti,ab,kw OR t1a:ti,ab,kw OR t1b:ti,ab,kw OR 't 1':ti,ab,kw OR 't 1a':ti,ab,kw OR 't 1b':ti,ab,kw OR n1:ti,ab,kw OR 'n 1':ti,ab,kw OR 'type 1':ti,ab,kw OR 'type 1a':ti,ab,kw OR 'type 1b':ti,ab,kw OR (((early OR earliest OR first OR 1st) NEAR/3 (tumor* OR tumour* OR type OR stage OR stages OR staging* OR phase* OR tnm)):ti,ab,kw)	**1149161**
#1	'stomach tumor'/exp OR 'linitis plastica':ti,ab,kw OR (((carcinoma* OR neoplas* OR adenoma* OR adenocarcinoma* OR tumor* OR tumour* OR cancer* OR oncolog* OR malignan* OR carcinogen* OR oncogen* OR anticarcinogen* OR squamous*) NEAR/5 (stomach OR gastric* OR cardia OR gastroesophag* OR gastrooesophag* OR oesogast* OR esogast*)):ti,ab,kw)	**234154**

Kennislacunes

Richtlijn oesofaguscarcinoom

Module 1 – Minimaal invasieve chirurgie

Niet gedefinieerd.

Module 2 – Nacontrole na definitieve chemoradiatie

- Wat is de plaats van endoscopische resectie na definitieve chemoradiatie?
- Wat is de meerwaarde van salvage resectie na definitieve chemoradiatie?

Module 3 – Palliatie van dysfagie

- De mate van effect van systemische therapie op dysfagie is niet goed onderzocht.
- Er zijn geen studies die head tot head 5x4 Gy vergelijken met single dose/ een hoge dosis radiotherapie.
- Er zijn geen studies die de behandeling van dysfagie veroorzaakt door een recidief na eerdere (chemo)radiotherapie onderzoeken.
- Er zijn geen studies die het beloop van dysfagie veroorzaakt door een recidief na eerdere (chemo)radiotherapie onderzoeken.
- Bij gemetastaseerde patiënten met beperkte dysfagie is er geen onderzoek naar de meerwaarde van kortdurende radiotherapie voorafgaand aan de systemische therapie op het beloop van dysfagie en overleving.

Module 4 – Palliatieve immuuntherapie

Niet gedefinieerd.

Richtlijn maagcarcinoom

Module 5 – Endoscopische behandeling vroegcarcinoom maag

- Een goed gevalideerd beslissingsmodel welke op basis van risicofactoren kan voorspellen welke patiënten na endoscopische behandeling van vroegcarcinoom van de maag in aanmerking moeten komen voor chirurgische resectie voor de Nederlandse/westerse populatie.

Implementatieplan

Implementatieplan volgt na de commentaarfase.