Update richtlijn Hoofd-halstumoren (10 modules)

Augustus 2022

INITIATIEF
Nederlandse Vereniging voor Keel-Neus-Oorheelkunde en Heelkunde van het Hoofd-Halsgebied

IN SAMENWERKING MET
Nederlandse Internisten Vereniging
Nederlandse Vereniging voor Mondziekten, Kaak- en Aangezichtschirurgie
Nederlandse Vereniging voor Nucleaire Geneeskunde
Nederlandse Vereniging voor Pathologie
Nederlandse Vereniging voor Plastische Chirurgie
Nederlandse Vereniging voor Radiologie
Nederlandse Vereniging voor Radiotherapie en Oncologie
Nederlandse Federatie van Kankerpatiëntenorganisaties | Patiëntenvereniging HOOFD-HALS
Verpleegkundigen en Verzorgenden Nederland | Oncologie

MET ONDERSTEUNING VAN
Kennisinstituut van de Federatie Medisch Specialisten

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

Colofon
UPDATE RICHTLIJN HOOFD-HALSTUMOREN (10 MODULES)

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Inhoudsopgave

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- A.A.M. Goossens, Verpleegkundig specialist oncologie, Haaglanden MC, Den Haag, V&VN
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Met dank aan

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Met ondersteuning van

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Ontwikkelde modules (tot augustus 2021)

In het bijgevoegde document (“*2014 Richtlijn HHT RLDB.pdf”*) treft u de richtlijn uit 2014 aan zoals deze op de Richtlijnendatabase staat. In de onderstaande tabel kunt u terugvinden waar de nieuw ontwikkelde en geüpdate modules in de richtlijn uit 2014 zullen vallen. Op deze wijze is de context van de nieuwe module in de gehele richtlijn te zien alsmede welke delen er van de richtlijn zijn geüpdate.

Hoofdstuk	**Moduletitel**	**Vorm**	**Locatie in Richtlijn 2014 document (geel gemarkeerd)**
Diagnostiek	Diagnostiek afstandsmetastasen	Nieuw ontwikkeld	-
Mondholtecarcinoom	Afkappunt invasiediepte cT1-2N0	Update van bestaande module	Pagina 31
Mondholtecarcinoom	Type beleid negatieve hals cT1-2N0	Update van bestaande module	Pagina 31
Mondholtecarcinoom	Type interventie negatieve hals cT1-2N0	Update van bestaande module	Pagina 31
Hypofarynxcarcinoom	Behandeling T1-T2N0 hypofarynxcarcinoom	Update van bestaande module	Pagina 43
Larynxcarcinoom	Behandeling Tis/T1 glottisch larynxcarcinoom	Update van bestaande module	Pagina 47
Larynxcarcinoom	Behandeling van Tis/T1 supraglottische larynxcarcinomen	Update van bestaande module	Pagina 49
Neus- en neus(bij)holtecarcinoom	Endoscopische chirurgie maligne neus(bij)holtetumoren	Update van bestaande module	Pagina 74
Neus- en neus(bij)holtecarcinoom	Behandeling neus- en neus(bij)holte carcinoom – toevoeging chemotherapie	Nieuw ontwikkeld	-
Nasofarynxcarcinoom	Behandeling nasofarynxcarcinoom – inductie chemotherapie	Nieuw ontwikkeld	-

Verantwoording

Leeswijzer
De verantwoording wordt op de Richtlijnendatabase bij elke nieuwe of geüpdate module opgenomen. Aangezien deze richtlijn gedeeltelijk een herziening betreft, zal het gedeelte 'Autorisatie en geldigheid' in de richtlijn per module (kunnen) verschillen. Het overige gedeelte van de verantwoording is gelijk voor alle herziende of nieuwe modules, en wordt slechts éénmaal bijgevoegd.

Autorisatie en geldigheid
De geldigheid van de richtlijnmodule komt te vervallen indien nieuwe ontwikkelingen aanleiding zijn een herzieningstraject te starten.
NB: Informatie over de autorisatiedatum, autoriserende partij(en), herbevestiging en regiehouder(s) worden ter zijne tijd na autorisatie toegevoegd aan deze alinea.

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 Stichting Kwaliteitsgelden Medisch Specialisten (SKMS). De financier heeft geen enkele invloed gehad op de inhoud van de richtlijnmodule.

Samenstelling werkgroep
Voor het ontwikkelen van de richtlijnmodule is in 2019 een multidisciplinaire werkgroep ingesteld, bestaande uit vertegenwoordigers van alle relevante specialismen (zie hiervoor de Samenstelling van de werkgroep) die betrokken zijn bij de zorg voor patiënten met hoofd-halstumoren.

Belangenverklaringen
De Code ter voorkoming van oneigenlijke beïnvloeding door belangenverstrengeling is gevolgd. Alle werkgroepleden 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 werkgroepleden 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.

Werkgroepl id	Functie	Nevenfuncties	Gemelde belangen	Ondernomen actie
Bree, de	KNO-arts/hoofd-halschirurg, UMC Utrecht	* Lid Algemeen Bestuur Patiëntenvereniging Hoofd-Hals (onbetaald) * Voorzitter Research Stuurgroep NWHHT * Lid Richtlijnen commissie NWHHT	Geen	Geen

		* Lid dagelijks bestuur NWHHT * Lid Clinical Audit Board van de Dutch Head and Neck Audit (DHNA) * Lid wetenschappelijk adviescommissie DORP * Voorzitter Adviescommissie onderzoek hoofd-halskanker (IKNL/PALGA/DHNA/NWHHT)		
Slingerland	Internist-oncoloog, LUMC	* 2018-present: Treasurer of the "Dutch Association of Medical Oncology"(NVMO - vacancy fees) * 2018-present: Member of the "Dutch Working Group for Head-Neck Tumors" (NWHHT-Systemic therapy) * 2016-present: Member of the 'Dutch Working Group for Head-Neck Tumors" (NWHHT - study group steering group (coordinating)) * 2016-present: Member of the "Dutch Working Group for Head-Neck Tumors" (NWHHT - Elderly Platform) * 2012-present: Member "Working Group for Head-Neck Tumors" (WHHT) "University Cancer Centre"(UCK) Leiden - Den Haag * 2019: Member CAB DHNA	Deelname Nationaal expert forum hoofd-halskanker MSD dd 2-5-2018 * Deelname Checkmate studie, sponsor Bristol-Myers Squibb (BMS): An open label, randomized phase 3 clinical trial of nivolumab versus therapy of investigator's choice in recurrent or metastatic platinum-refractory squamous cell carcinoma of the head and neck (SCCHN) * Deelname Commence studie, sponsor Radboud University, in collaboration with Merck Serono International SA (among several Dutch medical centers): A phase lB-II study of the combination of cetuximab and methotrexate in recurrent of metastatic squamous cell carcinoma of the head and neck. A study of the Dutch Head and Neck Society, MOHN01/COMMENCE study. * Deelname HESPECTA studie: Phase I study: to determine the biological activity of two HPV16E6 specific peptides coupled to Amplivant®, a Toll-like receptor ligand in non-metastatic patients treated for HPV16-positive head and neck cancer. * Deelname PINCH studie (nog niet open): PD-L1 ImagiNg to predict durvalumab treatment response in HNSCC (PINCH) trial; patiënten met biopt bewezen locally recurrent of gemetastaseerd HNSCC * Deelname ISA 101b-HN-01-17 studie (nog niet open): A randomized, Double-blind, Placebo-Controlled, Phase 2 Study of Cemiplimab versus the combination of Cemiplimab with	In de werkgroep participeren 2 internist-oncologen, zodat één van beide de voortrekker is van modules over systemische therapie. Actie: werkgroeplid is uitgesloten van besluitvorming bij modules die betrekking hebben op de onderwerpen van de gemelde onderzoeken: nivolumab, cetuximab + methotrexaat, Amplivant, durvalumab, cemiplimab.

			ISA101b in the Treatment of Subjects.	
Meerten, van	Internist-oncoloog, Erasmus MC Kanker Instituut	* 2013-present: Board Member of the "Dutch Working Group for Head-Neck Tumors (NWHHT) * 2016-present: Chair of the "Dutch Working Group for Head-Neck Tumors" (NWHHT)-Systemic therapy * 2016-present: Chair of the "Dutch Working Group for Head-Neck Tumors" (NWHHT)-Guideline committee * 2016-present: Member of the "Dutch Working Group for Head-Neck Tumors" (NWHHT - Elderly Platform) * 2017-present: Executive Board Member of the 'Dutch Working Group for Head-Neck Tumors" (NWHHT)	Op dit moment Principal Investigator voor NL van gerandomiseerde fase III trial naar toegevoegde waarde van pembrolizumab aan chemoradiotherapie bij patiënten met gevorderd hoofdhalskanker. Sponsor: GlaxoSmithKline Research & Development Ltd. Studie is nog lopend, resultaten zullen pas bekend zijn na verschijning van de richtlijn. In toekomst mogelijk participatie aan door industrie gesponsorde studies op gebied van behandeling van hoofdhalskanker	In de werkgroep participeren 2 internist-oncologen, zodat één van beide de voortrekker is van modules over systemische therapie. Actie: werkgroeplid is uitgesloten van besluitvorming bij modules die betrekking hebben op het onderwerp van het gemelde onderzoeken: de toegevoegde waarde van pembrolizumab bij patiënten met gevorderd hoofdhalskanker.
Huijing	Plastisch chirurg, UMC Groningen	Geen	Geen	Geen
Sewnaik	KNO-arts/hoofd-hals chirurg, Erasmus MC	Sectorhoofd Hoofd-Hals chirurgie	Geen	Geen
Vaassen	MKA-chirurg-oncoloog, Maastricht UMC+ / CBT Zuid-Limburg	*Lid Bestuur NVMKA *Waarnemend hoofd MKA-chirurgie MUMC	Geen	Geen
Witjes	MKA-chirurg-oncoloog, UMC Groningen	Geen	PI van KWF grant: RUG 2015 - 8084: Image guided surgery for margin assessment of head & neck Cancer using cetuximab-IRDye800 cONjugate (ICON) geen financieel belang	Geen. Financiering door KWF werd niet als een belang ingeschat.
Bloemena	Klinisch patholoog, Hoogleraar Orale Pathologie, Amsterdam UMC, locatie Vumc 0,6 fte Hoogleraar Orale Pathologie, Academisch Centrum voor Tandheelkunde Amsterdam (ACTA) 0,2 fte	* Voorzitter Wetenschappelijke Raad PALGA – onbezoldigd * Lid juridische commissie NVVP - onbezoldigd	Geen	Geen

Willems	Klinisch patholoog, UMC Groningen	Vice-vz PALGA, AB NWHHT, CAB DHNA, mede-vz en oprichter expertisegroep HH pathologie NL, Hoofdhalspathologie UMC Groningen	PDL1 trainer NL voor MSD Onderzoeksfinanciering van Pfizer, Roche, MSD, BMS, Lilly, Novartis, Bayer, Amge, AstraZeneca	Geen
Karakullukcu	KNO-arts/hoofd-hals chirurg, NKI/AVL	Geen	Geen	Geen
Verschuur	KNO-arts/Hoofd-hals chirurg, Haaglanden MC	* Opleider KNO-artsen * Dagvoorzitter	Geen	Geen
Walenkamp	AIOS KNO, LUMC	Geen	Geen	Geen
Al-Mamgani	Radiotherapeut-oncoloog, NKI/AVL	Geen	Geen	Geen
Terhaard	Radiotherapeut-oncoloog, UMC Utrecht	Niet van toepassing	Geen	Geen
Hoek, van den	Radiotherapeut-oncoloog UMCG	Niet van toepassing	Geen	Geen
Zwijnenburg	Radiotherapeut, Hoofd-hals Radboud UMC	Geen	Geen	Geen
Burdorf	Patiëntvertegenwoordiger	Geen	Geen	Geen
Verdouw	Hoofd Infocentrum patiëntenvereniging HOOFD HALS	Geen	Werkzaam bij de patiëntenvereniging. De achterban heeft baat bij een herziening van de richtlijn	Geen
Karssemakers	Hoofd-hals chirurg NKI/AVL MKA-chirurg-oncoloog Amsterdam UMC (locatie AMC) / vakgroep kaakchirurgie Amsterdam West	Niet van toepassing	Geen	Geen
Goossens	Verpleegkundig specialist, Haaglanden Medisch Centrum (HMC)	* Bestuurslid (penningmeester) PWHHT (onbetaald) * Lid Commissie voorlichting PVHH (onbetaald)	Geen	Geen
Zwezerijnen	Nucleair geneeskundige, Amsterdam UMC (locatie Vumc) PhD kandidaat, Amsterdam UMC (locatie Vumc)	Lid als nucleair geneeskundige in HOVON imaging werkgroep (bespreken van richtlijnen en opzetten/uitvoeren van wetenschappelijke studies met betrekking tot beeldvorming in de hematologie); onbetaald	Geen	Geen

Vogel	Nucleair geneeskundige/radiotherapeut-oncoloog, AVL	Geen	In de afgelopen jaren incidenteel advies of onderwijs, betaald door Bayer, maar niet gerelateerd aan hoofd-hals KWF-grant speekselklier toxiteit na behandeling. Geen belang bij de richtlijn	Geen
Graaf, de	Radioloog, Amsterdam UMC (locatie Vumc)	Bestuurslid sectie Hoofd-Hals radiologie (onbetaald)	Geen	Geen
Weijs	MKA-chirurg-oncoloog, Radboudumc	MKA-chirurg, Weijsheidstand B.V. Werkzaam als algemeen praktiserend MKA-chirurg, betaald (0,1 fte)	Geen	Geen

Inbreng patiëntenperspectief
Er werd aandacht besteed aan het patiëntenperspectief door het uitnodigen van de patiëntenvereniging HOOFD-HALS (PVHH) voor de Invitational conference en met afgevaardigden van de PVHH in de werkgroep. Het verslag hiervan (zie aanverwante producten) is besproken in de werkgroep. De verkregen input is meegenomen bij het opstellen van de uitgangsvragen, de keuze voor de uitkomstmaten en bij het opstellen van de overwegingen. De conceptrichtlijn is tevens voor commentaar voorgelegd aan de patiëntenvereniging HOOFD-HALS en de eventueel aangeleverde commentaren zijn bekeken en verwerkt.

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).

Knelpuntenanalyse en uitgangsvragen
Tijdens de voorbereidende fase inventariseerden de werkgroep de knelpunten in de zorg voor patiënten met hoofd-halstumoren. De werkgroep beoordeelde de aanbeveling(en) uit de eerdere richtlijnmodule (NVKNO, 2014) op noodzaak tot revisie. Tevens zijn er knelpunten aangedragen door de patiëntenvereniging en genodigde partijen tijdens de Invitational conference (zie aanverwante producten voor het verslag van de Invitational conference). Op basis van de uitkomsten van de knelpuntenanalyse zijn door de werkgroep concept-uitgangsvragen opgesteld en definitief vastgesteld.

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

Methode literatuursamenvatting
Een uitgebreide beschrijving van de strategie voor zoeken en selecteren van literatuur en de beoordeling van de risk-of-bias van de individuele studies is te vinden onder 'Zoeken en selecteren' onder Onderbouwing. 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 dicht bij 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 dicht bij 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 dicht bij 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 dicht bij 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).

Overwegingen (van bewijs naar aanbeveling)
Om te komen tot een aanbeveling zijn naast (de kwaliteit van) het wetenschappelijke bewijs ook andere aspecten belangrijk en 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.

Formuleren van aanbevelingen

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 de werkgroep 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. De werkgroep 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. Zie ook het visiedocument Samen beslissen van de Federatie Medisch specialisten.
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.

Commentaar- en autorisatiefase

De conceptrichtlijnmodule werd aan de betrokken (wetenschappelijke) verenigingen en (patiënt) organisaties voorgelegd ter commentaar. De commentaren werden verzameld en besproken met de werkgroep. Naar aanleiding van de commentaren werd de conceptrichtlijnmodule aangepast en definitief vastgesteld door de werkgroep. De definitieve richtlijnmodule werd aan de deelnemende (wetenschappelijke) verenigingen en (patiënt) organisaties voorgelegd voor autorisatie en door hen geautoriseerd dan wel geaccordeerd.

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 kwalitatieve raming	Toelichting
Alle modules	geen substantiële financiële gevolgen	Uit de toetsing volgt dat de aanbeveling(en) niet breed toepasbaar zijn (<5.000 patiënten) en zal daarom naar verwachting geen substantiële financiële gevolgen hebben voor de collectieve uitgaven.

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Module 8.1 Diagnostiek afstandsmetastasen

Uitgangsvraag

Wanneer is aanvullende diagnostiek naar afstandsmetastasen geïndiceerd en hoe moeten deze worden gediagnosticeerd?

De uitgangsvraag omvat de volgende deelvragen:

1. Wat zijn de indicaties voor onderzoek naar afstandsmetastasen ten tijde van de initiële diagnostiek van patiënten met een hoofd-halstumor?
2. Met welke beeldvormende modaliteit(en) moet onderzoek naar afstandsmetastasen verricht worden?

Inleiding

Er is praktijkvariatie met betrekking tot het gebruik van diagnostische strategieën/ verschillende modaliteiten

Search and select

Clinical sub-question 1 - indications during the initial work-up

Systematic searches were not performed for the clinical question concerning indications for diagnosis during the initial work-up.

Clinical sub-question 2 - impact and misclassifications of strategies/modalities

Systematic searches were performed for the second underlying clinical sub-question only, concerning the impact and accuracy of diagnostic tests. Two PICOs were used:

PICO 1 (impact)

What are the (un)beneficial effects of a diagnostic strategy (or modality) to detect distant metastases and secondary primary tumors in the initial work-up on the one-year survival and choice of treatment in patients with head and neck carcinomas?

P: patients with a head and neck carcinoma;
I: Diagnostic strategy or modality (PET-scan, CT-thorax (incl. LODO-CT) or X-thorax) to detect distance metastasis;
C: other diagnostic strategy (PET-scan, CT-thorax (incl. LODO-CT) or X-thorax) to detect distance metastasis;
O: one-year survival, chosen treatment (yes/no, type of treatment).

PICO 2 (diagnostic misclassification)

What is the diagnostic accuracy of diagnostic strategies/modalities to detect distance metastasis and second primary tumors in the initial work-up of patients with head and neck carcinomas?

P: patients with a head and neck carcinoma;
I: diagnostic strategy or modality (PET-scan, CT-thorax (incl. LODO-CT) or X-thorax) to detect distance metastasis;
C: other diagnostic strategy (PET-scan, CT-thorax (incl. LODO-CT) or X-thorax) to detect distance metastasis;
R: disease progression regarding distant metastasis after one year as detected with a PET-scan or pathological report;
O: **number of false negatives**, number of false positives, costs, radiation exposure.

Relevant outcome measures
The guideline development group considered overall survival, number of false negatives and number of false positives as a critical outcome measure for decision making; and chosen treatment, costs, radiation exposure 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 a risk difference of 5% regarding one-year survival as a minimal clinically (patient) important difference.

Search and select (Methods)
Clinical sub-question 1 - indications during the initial work-up
Systematic searches were not performed for the clinical question concerning indications for diagnosis during the initial work-up.

Clinical sub-question 2 - impact and misclassifications of strategies/modalities
The databases (Medline (via OVID) and Embase (via Embase.com)) were searched with relevant search terms until November 28th, ,2019 and December 5th ,2019. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 367 (systematic reviews and RCTs) hits.

Studies were selected based on the following criteria:
For PICO 1 (impact)
- Systematic review (including evidence tables, risk of bias assessments) or RCT.
- Patients with head and neck carcinoma; comparing survival and/or disease progression between different modalities.

For PICO 2 (diagnostic accuracy)
- Systematic review (including evidence tables, risk of bias assessments).
- Patients with head and neck carcinoma.
- Comparing diagnostic accuracy, costs and/or radiation exposure between different modalities within the same population.

Twenty-seven studies were initially selected based on title and abstract screening. After reading the full text, 26 studies were excluded (see the table with reasons for exclusion under the tab Methods) and one study was included.

Results
Clinical sub-question 1 - indications during the initial work-up
Systematic searches were not performed. No studies were selected for the literature analyses concerning indications for diagnosis during the initial work-up.

Clinical sub-question 2 - impact and misclassifications of strategies/modalities
For PICO 1 (impact), no systematic reviews were selected for the literature analysis. However, one relevant observational study (Rohde, 2017) is described in the considerations without GRADEing the outcomes.

For PICO 2 (diagnostic accuracy), one systematic review was included in the literature analysis. Important study characteristics and results of GRADEd studies are summarized in

the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables.

Furthermore, three systematic reviews did not report the outcomes of interest and were excluded from the literature analysis (Blatt, 2016; Li, 2020; Xu, 2012). Due to their relevance they were described in the considerations without GRADEing the outcomes

Summary of literature

Description of studies

Clinical sub-question 1 - indications during the initial work-up

Systematic searches were not performed. No studies were selected for the literature analyses concerning indications for diagnosis during the initial work-up.

Clinical sub-question 2 - impact and misclassifications of strategies/modalities

PICO 1 (impact)

No systematic reviews were included in the literature analysis of PICO 1.

PICO 2 (diagnostic accuracy)

Xu (2017) conducted a meta-analysis of four studies investigating difference in accuracy of F-FDG PET/CT and conventional work-ups (skeletal scintigraphy, chest X-ray examination and liver ultrasound) in a total of 1029 patients with primary nasopharyngeal carcinomas, from which results were compared with biopsy, imaging and clinical follow-up of at least six months. Brief characteristics are shown in Table 8.1. Xu (2017) searched MEDLINE, EMBASE, the Cochrane Library, and the Chinese database CBMDisc, which was last updated on the 3rd of October 2016. Studies were included when: 18F-FDG PET/CT and conventional work-ups were used to detect whole-body distant in patients with nasopharyngeal carcinomas, per patient statistics were reported (including true positives and negatives, and false positives and negatives), and biopsy, imaging, and/or clinical follow-up were used as a reference standard. The largest study was selected when there were multiple cohorts with overlapping data. Studies were excluded when: patients had residual or recurrent nasopharyngeal carcinoma, the study sample contained a mixture of patients with untreated and residual or recurrent disease (if data of untreated patients could not be obtained), the study enrolled patients with no evidence of distant metastasis by conventional work-up, and when the study was a case report/ conference abstract/ review. Two authors independently assessed the study quality using the QUADAS-II tool.

Table 8.1 Characteristics of studies included by Xu (2017)

	Mean age	Number of male/female	Prevalence distant metastasis	Follow-up
Chua 2009	50.00	60/18	7.7%	≥ 6 months
Ng 2009	48.90	84/27	14.4%	≥ 12 months
Zhang 2011	45.00	201/56	15.2%	≥ 36 months
Tang 2013	46.00	474/109	14.8%	≥ 12 months

Results

Clinical sub-question 1 - indications during the initial work-up

Systematic searches were not performed. No studies were selected for the literature analyses concerning indications for diagnosis during the initial work-up.

Clinical sub-question 2 - impact and misclassifications of strategies/modalities

PICO 1 (impact)

No studies could be included for the literature analysis of PICO 1.

PICO 2 (diagnostic misclassification)
False negatives
Xu (2017) reported the false negatives, sensitivity, and prevalence per study. False negatives per 1000 patients were calculated from the pooled sensitivity for FDG-PET/CT (0.84, 95%CI: 0.77 to 0.89) and CWU (0.40, 95%CI: 0.32 to 0.48) reported by Xu (2017) at a pre-test probability of 14.3%. The number of false negatives for FDG-PET/CT was 63 per 1000 patients less than for CWU. FDG-PET/CT had 23 false negatives (95%CI: 15 to 33) compared to 86 false negatives (95%CI: 74 to 97) for CWU.

False positives
Xu (2017) reported the false positives, specificity, and prevalence per study. False positives per 1000 patients were calculated from the pooled specificity for FDG-PET/CT (0.98, 95%CI: 0.96 to 0.99) and CWU (0.98, 95%CI: 0.97 to 0.99) reported by Xu (2017) at a pre-test probability of 14.3%. The number of false positives for FDG-PET/CT was 1 per 1000 patients more than for CWU. FDG-PET/CT had 20 false positives (95%CI: 12 to 30) compared to 19 false positives (95%CI: 11 to 28) for CWU.

Costs
None of the included studies reported costs.

Radiation exposure
None of the included studies reported radiation exposure.

Level of evidence of the literature
Clinical sub-question 1 - indications during the initial work-up
Systematic searches were not performed. No studies were selected for the literature analyses concerning indications for diagnosis during the initial work-up.

Clinical sub-question 2 - impact and misclassifications of strategies/modalities
PICO 1 (impact)
No studies could be included for the literature analysis of PICO 1.

PICO 2 (diagnostic misclassification)
False negatives
Level of evidence for diagnostic studies starts at high level, but was downgraded to low because of risk of bias (one level, see Xu (2017) and risk of bias table: High or unclear risks regarding patient selection, unclear risks regarding reference standard and flow and timing) and imprecision (one level, due to wide confidence intervals of FDG-PET/CT sensitivity). Publication bias was not assessed.

False positives
Level of evidence for diagnostic studies starts at high level, but was downgraded to moderate because of risk of bias (one level, see Xu (2017) and risk of bias table: High or unclear risks regarding patient selection, unclear risks regarding reference standard and flow and timing). Publication bias was not assessed.

Costs
The level of evidence could not be determined as none of the included studies reported costs.

Radiation exposure
The level of evidence could not be determined as none of the included studies reported radiation exposure.

Conclusions
Clinical sub-question 1 - indications during the initial work-up
Literature conclusions could not be drawn for this clinical sub-question. Systematic searches were not performed and no studies were selected for the literature analyses.

Clinical sub-question 2 - impact and misclassifications of strategies/modalities
PICO 1 (impact)

- GRADE	No conclusions could be drawn regarding the impact of different diagnostic strategies on the **one-year survival** and **chosen treatment.** None of the studies met the inclusion criteria.

PICO 2 (diagnostic misclassification)

LOW GRADE	The evidence suggests with low certainty that FDG-PET/CT slightly reduces **the number of false negative detections** of distant metastasis in patients with nasopharyngeal carcinoma compared to conventional work-ups. *Sources: (Xu, 2017)*

- GRADE	No conclusions could be drawn regarding **the number of false negative detections** of distant metastasis in patients with head and neck carcinomas other than nasopharynx carcinomas.

MODERATE GRADE	FDG-PET/CT probably does not reduce **the number of false positive detections** of distant metastasis in patients with nasopharyngeal carcinoma compared to conventional work-ups. Data for other subsites in the head and neck region was not found. *Sources: (Xu, 2017)*

- GRADE	No conclusions could be drawn regarding **the number of false positive detections** of distant metastasis in patients with head and neck carcinomas other than nasopharynx carcinomas.

- GRADE	No conclusions could be drawn regarding the effect of different diagnostic strategies on **costs**. None of the included studies reported costs.

- GRADE	No conclusions could be drawn regarding the effect of different diagnostic strategies on **radiation exposure**. None of the included studies reported radiation exposure outcomes.

Overwegingen - van bewijs naar aanbeveling

Specifieke overwegingen voor Deelvraag 1 - indicaties tijdens de initiële work-up

Er werd geen systematisch literatuuronderzoek verricht naar de deelvraag over de indicaties voor onderzoek ten tijde van de initiële diagnostiek van patiënten met een hoofd-hals tumor. In de door de werkgroepgeïdentificeerde literatuur werd de incidentie van afstandsmetastasen beschreven per subsite van de tumor (Pisani, 2020; Xu, 2017), per stadium (Pisani, 2020), of per indicatie (De Bree, 2000).

Pisani (2020) gaf in een congresrapport per tumor-subsite incidenties van afstandsmetastasen op basis van meerdere referenties. De gerapporteerde subsites waren de neusholte (1,90%), paranasale sinussen (3.50%), mondholte (4.50%), larynx (5,00%), orofarynx (5,90%), nasofarynx (11,00%) en hypofarynx (16,00%).

Xu (2017) includeerde vijf prospectieve diagnostische accuratesse studies die patiënten met nasofaryngeale carcinomen includeerden. De mediane incidentie van afstandsmetastasen in deze studies was 14,4%. Er werd door Pisani (2020) op basis van vier studies een figuur gepresenteerd over het risico per T- en N-stadium. Hierbij kan gezien worden dat het risico toeneemt naar mate de T- en N-stadia avanceren. De hier gerapporteerde risico's werden uit het gepresenteerde figuur benaderd: T1 (1 tot 8%), T2 (7 tot 13%), T3 (12 tot 16%), T4 (15 tot 21%) en N0 (3 tot 5%), N1 (11 tot 20%), N2 (18 tot 22%), N3 (25 tot 30%). Twee studies (Garavello, 2006; Liu, 2018) van de vier studies, door Pisani (2020) beschreven in het figuur, rapporteerden gecorrigeerde relatieve maten ten opzichte van een referentiecategorie. Deze twee studies werden niet formeel beoordeeld op het risico op vertekening.

Garavello (2006) rapporteerde voor het T-stadium relatieve risico's voor T2 (RR = 13,4; 95%BHI: 7,8 tot 24,7), T3 (RR = 15,9; 95%BHI: 8,1 tot 28,5) en T4 (RR = 21,3; 95%BHI: 10,8 tot 34,7) ten opzichte van het T1-stadium. Voor het N-stadium werden relatieve risico's voor N1 (RR = 6,8; 95%BHI: 3,7 tot 13,6), N2 (RR = 7,2; 95%BHI: 4,9 tot 17,5) en N3 (RR = 10,7; 95%BHI: 6,5 tot 21,2) ten opzichte van het N0-stadium. Variabelen in het multivariabele model waren leeftijd, tumorlocatie, T-stadium, N-stadium, histologische differentiatie en locoregionale controle.

Liu (2018) rapporteerde odds ratio's voor T2 (OR = 1,53; 95%BHI: 1,37 tot 1,71), T3 (OR = 2,14; 95%BHI: 1,92 tot 2,39) en T4 (OR = 4,08; 95%BHI: 3,68 tot 4,53) ten opzichte van het T1-stadium. De odds ratio's werden ook per N-stadium gerapporteerd, waarbij N1 (OR = 3,11; 95%BHI: 2,77 tot 3,48), N2 (OR = 5,14; 95%BHI: 4,68 tot 5.64) en N3 (OR = 12,28; 95%BHI: 10,82 tot 13,94) werden vergeleken met het N0-stadium. Variabelen in het multivariabele model waren tumorlocatie, leeftijd, etniciteit, hoog-risico HPV-status, tumor differentiatie, T-stadium en N-stadium.

Pisani (2020) beschreef tevens de risico's per tumor-stadium, gebaseerd op drie studies: stadium I (1%), stadium II (14%), stadium III (15%), stadium IVa (20%) en stadium IVb (24%).

De Bree (2000) beschreef de incidentie van afstandsmetastasen bij verschillende klinische indicaties voor het screenen op afstandsmetastasen. In de steekproef zaten patiënten met carcinomen in de mondholte, orofarynx, hypofarynx, cervicale oesofagus, neus en paranasale sinussen, en een patiënt met lymfeklier metastasen met een onbekende primaire tumor. De incidentie werd gerapporteerd voor de volgende indicaties: totale glossectomie (0% in n=11), lymfeklier metastasen van 6 centimeter of groter (10% in n=10), bilaterale lymfeklier metastasen (13% in n=30), locoregionale terugkeer (18% in n=33), 3 of meer lymfeklier metastasen (21% in n=19), tweede primaire tumor (23% in n=13), 4 of meer lymfe

klier metastasen (33% in n=9), en laag-jugulaire lymfeklier metastasen (33% in n=12). In de steekproef (n=101) werden 17 patiënten (17%) gevonden met één of meerdere afstandsmetastasen. In de thorax werden 16 metastasen gevonden (12 in de longen, 4 in de mediastinale lymfeklieren). Daarnaast werden er 4 botmetastasen gevonden en 1 levermetastase.

Specifieke overwegingen voor Deelvraag 2 - impact en misclassificaties van strategieën/modaliteiten
Er werden voor de vraag over de impact van verschillende diagnostische strategieën op patiënten geen systematische reviews gevonden die voldeden aan de inclusiecriteria. In de literatuuranalyse kon daarom geen conclusies getrokken worden ten aanzien van de impact van verschillende modaliteiten op de overleving of de keuze van behandeling van patiënten met hoofd-hals tumoren. Echter, in een observationele studie van Rohde (2017) werd in Denemarken onderzocht of het type diagnostiek de keuze van de vervolgbehandeling veranderde bij het detecteren van afstandsmetastasen. In de studie werd FDG-PET/CT (4MBq/kg) vergeleken met een gecombineerde thorax röntgenbeelden en MRI bij 303 patiënten met hoofd-hals tumoren (mediane leeftijd: 54 (range: 22 tot 89), 75% mannelijke deelnemers). Alle patiënten ondergingen beide diagnostische strategieën. In een multidisciplinair overleg werden keuzes gemaakt over de behandeling die door de FDG-PET/CT óf door de gecombineerde thorax röntgen afbeelding en MRI werden geïnformeerd. Drie maanden later werd er in een nieuw multidisciplinair overleg de complementaire diagnostiek (dat wil zeggen FDG-PET/CT in het geval de röntgenbeelden en MRI eerst werden besproken, en vice versa). Er werd een verschil in behandelintentie gerapporteerd van 8% (95% BHI: 4.8-11.5%, p<0.01). Na diagnostiek met FDG-PET/CT werden er meer patiënten behandeld met een palliatieve intentie in plaats van een curatieve intentie ten opzichte van gecombineerde diagnostiek met röntgenbeelden en MRI. Rohde (2017) concludeerde dat beslissingen van een multidisciplinair team omtrent de behandelintentie veranderden door een strategie gebaseerd op PET/CT wanneer vergeleken met een standaard strategie met thorax röntgenbeelden en MRI.

Ten aanzien van de accuratesse van verschillende modaliteiten voor het detecteren van afstandsmetastasen zou FDG-PET/CT wellicht minder fout-negatieve classificaties opleveren dan een conventionele work-up bij patiënten met een nasofarynxcarcinoom (Xu, 2017). De testprestatie van FDG-PET ten opzichte van een conventionele work-up werd afgezet in een hypothetisch cohort met een prevalentie van 14.3% (zie Tabel 8.2). FDG-PET lijkt per 1000 personen één persoon meer als fout-positief classificeren dan een conventionele work-up. Echter, FDG-PET lijkt per 1000 personen 63 personen minder te classificeren als fout-negatief. Bij de gerapporteerde sensitiviteit en specificiteit in patiënten met nasofarynxcarcinomen (Xu, 2017) bleek dat er voor een conventionele work-up 2,63 personen (afgerond: 3 personen) nodig zijn om bij één persoon de aandoening te detecteren, tegenover 1.22 personen (afgerond: 2 personen) voor één detectie van de aandoening door FDG-PET.

Tabel 8.2 Test prestaties op basis van de gerapporteerde diagnostische accuratesse in patiënten met een nasofarynxcarcinoom uit Xu (2017)

	Sensitiviteit (95%BHI)	**Specificiteit (95%BHI)**	**Aantal fout-positieven in een hypothetisch cohort van n=1000 bij een prevalentie van 14.3%**	**Aantal fout-negatieven in een hypothetisch cohort van n=1000 bij een prevalentie van 14.3%**	**Aantal benodigd om één keer de ziekte te detecteren (NND)***
Conventioneel	0.40	0.98	19 (95%BHI: 11-28)	86 (95%BHI: 74-97)	2.63

	(95%BHI: 0.32-0.48)	(95%BHI: 0.97-0.99)			
FDG-PET	0.84 (95%BHI: 0.77-0.89)	0.98 (95%BHI: 0.96-0.99)	20 (95%BHI: 12-30)	23 (95%BHI: 15-33)	1.22
***NND: Number Needed to Detect a disease, uit Linn (2006)**					

Uit de literatuuranalyse blijkt dat er waarschijnlijk geen aanvullend risico bestaat op het onterecht detecteren van afstandsmetastasen (dat wil zeggen foutpositief) door modaliteiten als röntgen en ultrasound in vergelijking met FDG-PET/CT bij patiënten met een nasofarynxcarcinoom. Voor andere tumorlocaties in het hoofd-hals gebied werd er geen literatuur gevonden met betrekking tot de diagnostische accuratesse. Er werden tevens drie systematische reviews gevonden die niet aan de selectiecriteria voldeden (dat wil zeggen zij rapporteerden geen fout-positieven en -negatieven), maar wel (deels) relevant werden geacht (Blatt, 2016; Xu, 2012).

Blatt (2016) voerde een review uit waarin één studie (Fakhry, 2012) werd opgenomen die de diagnostische accuratesse van FDG-PET/PET-CT vergeleek met CT in 37 patiënten voor de detectie van afstandsmetastasen of secundaire tumoren. Tumorlocaties waren de mondholte (n=10), orofarynx (n=12, hypofarynx (n=5), larynx (n=8), nasofarynx (n=1) en de sinus maxillaris (n=1). De diagnostiek werd na een behandeling met (radio)chemotherapie ingezet tijdens de work-up vóór salvage chirurgie. Uitkomsten worden in Tabel 8.3 gerapporteerd. De auteurs concludeerden dat het gebruik van PET (FDG-PET/PET-CT) niet de eerste optie lijkt te zijn voor het detecteren van afstandsmetastasen of synchrone tumoren.

Tabel 8.3 Resultaten van Fakhry (2012) (uit Blatt (2016)) voor de detectie van afstandsmetastasen of secundaire tumoren

Type strategie	Sensitiviteit (95%CI)	Specificiteit (95%CI)	Positief voorspellende waarde (95%CI)	Negatief voorspellende waarde (95%CI)
FDG PET/PET-CT	0.92 (NR)	0.87 (NR)	0.74 (NR)	0.97 (NR)
CT	1.00 (NR)	0.94 (NR)	0.86 (NR)	1.00 (NR)
NR: Niet gerapporteerd				

Xu (2012) voerde een meta-analyse uit van acht studies om het verschil in diagnostische accuratesse van 'whole-body' PET/PET-CT en conventionele beeldvorming (inclusief thorax CT, thorax radiologie, abdominale ultrageluid, botscan en abdominale CT) te onderzoeken in 1147 patiënten. De referentietest was histopathologie en/of een klinische of imaging follow-up (veelal na 6 maanden). Enkele steekproefkarakteristieken worden in Tabel 8.4 weergegeven. De gepoolde diagnostische accuratesse uitkomsten worden in Tabel 8.5 beschreven. Het aantal foutpositieven en fout-negatieven werden niet weergegeven en konden niet berekend worden omdat de prevalentie van afstandsmetastasen in de steekproeven niet werd gerapporteerd. De classificaties van de testen werden daarom in een hypothetisch cohort berekend aan de hand van de gerapporteerde sensitiviteit en specificiteit met 5%, 10%, en 15% prevalentie in het hypothetische cohort (Tabel 8.6). De auteurs concludeerden dat gebruik van een 'whole-body' PET/PET-CT ondersteund werd door de resultaten van de meta-analyse en dat conventionele beeldvorming een beperkte sensitiviteit had voor het evalueren van afstandsmetastasen.

Tabel 8.4 Studiekarakteristieken van de geïncludeerde studies in Xu (2012)

Author	Tumor location (n)	Participant age	Number of male/female	Conventional method	Follow-up
Theodoros 2001	Larynx (4)	53 to 78 years	100% male	Chest CT	24 months

	Other, unspecified (8)				
Sigg 2003	Oropharynx (8) Hypopharynx (6) Larynx (5) Oral cavity (9) Other, unspecified (28)	24 to 84 years	66.1% male	Chest CT	Unclear
Chan 2006	Nasopharynx (131)	Unclear	70.2% male	Chest radiography, abdominal ultrasonography, bone scan	≥ 6 months
Liu 2007	Nasopharynx (n=300)	50.5 years	70.0% male	Chest radiography, abdominal ultrasonography, bone scan	≥ 6 months
Ng 2008	Oropharynx (74) Hypopharynx (86)	26 to 87 years	92.5% male	Chest and abdominal CT	≥ 12 months
Krabbe 2009	Oropharynx (40) Hypopharynx (12) Larynx (13) Oral cavity (84)	61 years	68.5% male	Chest CT	Unclear
Ng 2009	Nasopharynx (111)	24 to 83 years	76.7% male	Chest radiography, abdominal ultrasonography, bone scan	12 months
Chua 2009	Nasopharynx (78)	Unclear	83.3% male	Chest radiography, abdominal ultrasonography, bone scan	≥ 12 months

Tabel 8.5 Gepoolde resultaten uit Xu (2012)

Patients	Type of strategy	Sensitivity (95%CI)	Specificity (95%CI)	Positive likelihood ratio (95%CI)	Negative likelihood ratio (95%CI)
All patients, n=1147 (nasopharynx + non-nasopharynx)	Whole body PET/PET-CT	0.83 (0.76–0.88)	0.96 (0.94–0.97)	20.4 (14.5–28.5)	0.17 (0.12–0.25)
	Conventional anatomic imaging, including CT	0.44 (0.29–0.61)	0.96 (0.88–0.98)	9.9 (3.8–25.5)	0.59 (0.44–0.77)
Non-nasopharynx, n=377	Whole body PET/PET-CT	0.85 (0.73-0.93)	0.95 (0.91-0.97)	16.0 (9.8-26.1)	0.15 (0.08-0.30)
	Conventional anatomic imaging, including CT	0.62 (0.43-0.78)	0.93 (0.69-0.99)	8.8 (2.0-40.1)	0.41 (0.27-0.62)

Tabel 8.6 Classificaties van testen uit Xu (2012) in een hypothetisch cohort met een prevalentie van 5%, 10% en 15%

Test	Test classificatie	Aantal patiënten (95%BHI) in een hypothetisch cohort van n=1000		
		Prevalentie: 5%	Prevalentie: 10%	Prevalentie: 15%
Whole body PET/PET-CT (alle patiënten)	*Terecht Positief*	**42** (38 tot 44)	**83** (76 tot 88)	**124** (114 tot 132)
	Fout negatief	**8** (6 tot 12)	**17** (12 tot 24)	**26** (18 tot 36)
	Terecht negatief	**912** (893 tot 922)	**864** (846 tot 873)	**816** (799 tot 825)
	Fout positief	**38** (28 tot 57)	**36** (27 tot 54)	**34** (25 tot 51)
Conventional anatomic imaging, including CT (alle patiënten)	*Terecht Positief*	**22** (14 tot 31)	**44** (29 tot 61)	**66** (44 tot 92)

	Fout negatief	**28** (19 tot 36)	**56** (39 tot 71)	**84** (58 tot 106)
	Terecht negatief	**912** (836 tot 931)	**864** (792 tot 882)	**816** (748 tot 833)
	Fout positief	**38** (19 tot 114)	**36** (18 tot 108)	**34** (17 tot 102)
Whole body PET/PET-CT (zonder nasofarynx)	*Terecht Positief*	**43** (37 tot 47)	**85** (73 tot 93)	**128** (110 tot 140)
	Fout negatief	**7** (3 tot 13)	**15** (7 tot 27)	**22** (10 tot 40)
	Terecht negatief	**903** (864 tot 922)	**855** (819 tot 873)	**808** (774 tot 825)
	Fout positief	**47** (28 tot 86)	**45** (27 tot 81)	**42** (25 tot 76)
Conventional anatomic imaging, including CT (zonder nasofarynx)	*Terecht Positief*	**31** (22 tot 39)	**62** (43 tot 78)	**93** (65 tot 117)
	Fout negatief	**19** (11 tot 28)	**38** (22 tot 57)	**57** (33 tot 85)
	Terecht negatief	**884** (656 tot 941)	**837** (621 tot 891)	**791** (586 tot 842)
	Fout positief	**66** (9 tot 294)	**63** (9 tot 279)	**59** (8 tot 264)

Overkoepelende overwegingen
In een kwalitatieve studie met focusgroepen bestaande uit patiënten met hoofd-halstumoren (n=21) en hun zorgverleners (n=19) werd geconcludeerd dat patiënten het belangrijk vinden om informatie te ontvangen over de levensverwachting (Hoesseini, 2020). In een andere cohortstudie (Windon, 2019) konden patiënten met hoofd-halstumoren (n=150) aangeven wat de hoogste behandelprioriteit voor hen had. Uit 12 onderwerpen werden genezing, overleving, en slikfunctie in deze volgorde als hoogste prioriteit gekozen. In deze studie observeerden de auteurs ook dat de prioriteit voor overleving wellicht af kan nemen bij een toenemende leeftijd van de patiënt (Windon, 2019). De levensverwachting is onder andere afhankelijk van de aanwezigheid van afstandsmetastasen. Het lijkt daarom aannemelijk dat patiënten over het algemeen aanvullend onderzoek naar de aanwezigheid van afstandsmetastasen wensen. Een nadeel van aanvullende onderzoeken is het ondergaan van zowel de emotionele belasting als tijdsbelasting voor de patiënt. Daarnaast kan er sprake zijn van fout-negatieve classificatie door de test, waardoor men onterecht wellicht geen passende interventies ontvangt. Ook kan er sprake zijn van een fout-positieve misclassificatie of de detectie van incidentalomen die geen behandeling behoeven, maar mogelijk wel een verdere emotionele belasting veroorzaken en een vertraging van de start van het behandelproces. De mogelijkheid tot het vinden van incidentalomen, relevante toevalsbevindingen en de mogelijke gevolgen hiervan zouden besproken moeten worden met de patiënt. Zorg waarin de patiënt centraal staat is in toenemende mate terrein aan het winnen binnen onze gezondheidszorg. Met de beschikbare prevalentiegetallen van afstandsmetastasen bij verschillende prognostische factoren en met wellicht een afnemende prioriteit van overleving bij patiënten met een toenemende leeftijd (zie Windon, 2019), zou gedeelde besluitvorming met de patiënt hier uitkomst bieden.

Het is te verwachten dat de wachttijden toe kunnen nemen wanneer er voor elke patiënt een FDG-PET/CT scan wordt aangevraagd. Er moet daarom rekening gehouden worden met de beperkte capaciteit en de hogere kosten van een FDG-PET/CT. Een PET-scan kost op dit moment ongeveer €1200,- tegenover ongeveer €200,- voor een CT-scan. Een echo van de hals kost rond de €86,- en een x-thorax ongeveer €45. Op dit moment worden PET/CT-scans routinematig gebruikt, waardoor er geen implementatieproblemen worden verwacht. Wel wordt opgemerkt dat er op dit moment landelijk nog wisselende indicatiestellen zijn voor het aanvragen van de PET/CT. De werkgroep ziet een CT-thorax als geschikt alternatief bij afweging van beschikbaarheid en kosten. De werkgroep acht dat er geen plaats is voor een routinematig gebruik van een x-thorax.

Aanbevelingen

Aanbeveling-1

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

Patiënten met één of meer dan de volgende kenmerken hebben, ten tijde van de diagnose, een prevalentie van afstandsmetastase van 10% of meer: ≥ 3 lymfekliermetastasen, bilaterale lymfekliermetastasen, kliermetastase ≥ 6 cm, laagjugulaire lymfekliermetastasen, locoregionaal recidief, tweede (synchrone of metachrone) primaire tumor, aanwezigheid van een T3-4 tumor. Bij deze groepen patiënten acht de werkgroep het daarom aangewezen om diagnostiek te verrichten naar afstandsmetastasen.

Verricht diagnostiek naar afstandsmetastasen bij patiënten met ten minste één van de volgende kenmerken:
- Aanwezigheid van drie of meer lymfekliermetastasen.
- Aanwezigheid van bilaterale lymfekliermetastasen.
- Aanwezigheid van een lymfekliermetastase groter of gelijk aan zes centimeter.
- Aanwezigheid van een laag-jugulaire lymfkliermetastase.
- Aanwezigheid van een locoregionaal recidief.
- Aanwezigheid van een tweede (synchrone of metachrone) primaire tumor.
- Aanwezigheid van een T3-4 tumor.

Aanbeveling-2

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

Hoewel het aanvullende bewijs geen formele kwaliteitsbeoordeling onderging, lijkt 'whole-body' PET/CT met diagnostische CT-thorax eventueel een hogere sensitiviteit te hebben dan conventionele diagnostiek in een indirecte vergelijking. Hierdoor zullen er mogelijk minder patiënten fout-negatief geclassificeerd worden. Gezien de indirecte vergelijking in een hypothetisch cohort lijkt de conventionele diagnostiek wellicht gelijkwaardig qua het classificeren van patiënten zonder afstandsmetastasen (dat wil zeggen terecht-negatieven en fout-positieven). De werkgroep is van mening dat een CT-thorax als een alternatief gezien kan worden indien de betere beschikbaarheid en lagere kosten mee worden gewogen.

Gebruik whole-body PET/CT met diagnostische CT-thorax voor de detectie van afstandsmetastasen, waarbij een CT-thorax als alternatief te overwegen is.

Aanbeveling-3

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

Het is belangrijk om samen met de patiënt over de inzet van diagnostiek naar afstandsmetastasen te spreken en te beslissen. Afhankelijk van de (behandel)prioriteiten van de patiënt (bijvoorbeeld genezing, overleving, functiebehoud), de aanwezige co-morbiditeiten, de uitgebreidheid van de eventuele chirurgische behandeling en de eventuele levensverwachting kan er gezamenlijk besloten worden over de inzet van de diagnostiek naar afstandsmetastasen.

Besluit gezamenlijk met de patiënt over de inzet van diagnostiek naar afstandsmetastasen met in achtneming van de (behandel)prioriteiten van de patiënt en indien relevant:
- De eventueel aanwezige co-morbiditeiten.
- De uitgebreidheid van de eventuele chirurgische behandeling.
- De levensverwachting.

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Bijlagen bij module 8.1

Kennislacunes

- Wat zijn de indicaties voor onderzoek naar afstandsmetastasen ten tijde van de initiële diagnostiek van patiënten met een hoofd-halstumor?
- Met welke diagnostische onderzoeken moet onderzoek naar afstandsmetastasen verricht worden?

Implementatieplan

Aanbeveling	Tijdspad voor implementatie: < 1 jaar, 1 tot 3 jaar of > 3 jaar	Verwacht effect op kosten	Randvoorwaarden voor implementatie (binnen aangegeven tijdspad)	Mogelijke barrières voor implementatie[1]	Te ondernemen acties voor implementatie[2]	Verantwoordelijken voor acties[3]	Overige opmerkingen
1e Verricht diagnostiek naar afstandsmetastasen bij patiënten met ten minste één van de volgende kenmerken (..)	<1 jaar	Geen/lichte kostenstijging	Geen	Geen	Geen	Centra	
2e Gebruik PET/CT voor de detectie van afstandsmetastasen, waarbij een CT-thorax als alternatief te overwegen is	1 tot 3 jaar	Kostenstijging	Beschikbaarheid PET-CT	Geen	Geen	Centra	
3e Besluit gezamenlijk met de patiënt over de inzet van diagnostiek naar afstandsmetastasen met in achtneming van de (behandel)prioriteiten van de patiënt en indien relevant (…)	<1 jaar	Geen	Geen	Geen	Geen	Centra	

[1] Barrières kunnen zich bevinden op het niveau van de professional, op het niveau van de organisatie (het ziekenhuis) of op het niveau van het systeem (buiten het ziekenhuis). Denk bijvoorbeeld aan onenigheid in het

land met betrekking tot de aanbeveling, onvoldoende motivatie of kennis bij de specialist, onvoldoende faciliteiten of personeel, nodige concentratie van zorg, kosten, slechte samenwerking tussen disciplines, nodige taakherschikking, et cetera.
[2] Denk aan acties die noodzakelijk zijn voor implementatie, maar ook acties die mogelijk zijn om de implementatie te bevorderen. Denk bijvoorbeeld aan controleren aanbeveling tijdens kwaliteitsvisitatie, publicatie van de richtlijn, ontwikkelen van implementatietools, informeren van ziekenhuisbestuurders, regelen van goede vergoeding voor een bepaald type behandeling, maken van samenwerkingsafspraken.
[3] Wie de verantwoordelijkheden draagt voor implementatie van de aanbevelingen, zal tevens afhankelijk zijn van het niveau waarop zich barrières bevinden. Barrières op het niveau van de professional zullen vaak opgelost moeten worden door de beroepsvereniging. Barrières op het niveau van de organisatie zullen vaak onder verantwoordelijkheid van de ziekenhuisbestuurders vallen. Bij het oplossen van barrières op het niveau van het systeem zijn ook andere partijen, zoals de NZA en zorgverzekeraars, van belang.

Evidence tables

Evidence table for systematic reviews of diagnostic test accuracy studies

Research question:

Study reference	Study characteristics	Patient characteristics	Index test (test of interest)	Reference test	Follow-up	Outcome measures and effect size	Comments
Xu, 2017	SR and meta-analysis *Literature search up to October 2016* **A**: Chua, 2009 **B**: Ng, 2009 **C**: Zhang 2011 **D:** Tang, 2013 <u>Study design</u>: **A:** Prospective **B**: Prospective **C**: Retrospective **D**: Prospective <u>Setting and Country</u>: **A:** Singapore **B**: Taiwan **C**: China **D**: China <u>Source of funding and conflicts of interest:</u> Not reported per study; SR funding: National Science & Technology Pillar Ptrogram during	Inclusion criteria SR: - 18F-FDG PET/CT and CWUs (conventional workups, that is, skeletal scintigraphy, chest X-ray examination, and liver ultrasound) were used for detecting whole-body distant metastasis in NPC (primary nasopharyngeal carcinoma) - Per-patient statistics including true positive, false positive, true negative, and false negative number were reported - Among reports that pertained to overlapping patient cohorts, we retained the largest study to avoid	Describe index and comparator tests* and cut-off point(s): **A-1**: F-FDG PET/CT (dose 370 MBq; uptake time 60 min; analysis method: semi-quantitative (three-point scale)) **A-2:** CWU **A-3:** other modalities (PET alone; CT of thorax & abdomen+skeletal scintigraphy) **B-1**: F-FDG PET/CT (dose 370 MBq; uptake time 50-70 min; analysis method: NR)) **B-2:** CWU **C-1**: F-FDG PET/CT (dose 296-440 MBq; uptake time 45-60 min; analysis method: NR) **C-2:** CWU **D-1**:F-FDG PET/CT (dose 5,5 MBq/kg; uptake time 45-60 min; analysis method: semi-	Describe reference test and cut-off point(s): **A:** biopsy, imaging and clinical follow-up **B**: biopsy, imaging and clinical follow-up **C**: biopsy, imaging and clinical follow-up **D**: biopsy, imaging and clinical follow-up Prevalence (%) (based on refence test at specified cut-off point) **A:** 7.7% **B**: 14.4%	Endpoint of follow-up: **A:** ≥ 6 months **B**: ≥ 12 months **C**: ≥ 36 months **D**: ≥ 12 months	<u>Sensitivity/specificiaty</u> (e.g. sensitivity / specificity (%)) **A-1**: 0.83 (0.36-1.00) / 0.97 (0.90-1.00) **A-2**: 0.33 (0.04-0.78) / 0.90 (0.81-0.96) **B-1**: 0.81 (0.54-96) / 0.97 (0.91-0.99) **B-2**: 0.25 (0.07-0.52) / 0.99 (0.94 – 1.00) **C-1**: 0.87 (0.73-0.96) / 0.98 (0.95-0.99) **C-2**: 0.56 (0.40-0.72) / 0.99 (0.96 – 1.00) **D-1**: 0.83 (0.73-0.90) / 0.98 (0.96-0.99) **D-2**: 0.36 (0.26 – 0.47) / 0.98 (0.97 – 0.99) Pooled characteristic (type of statistical analysis not reported) per index test: **FDG-PET/CT** sensitivity: 0.837 (95% CI 0.767-0.893) I^2=0.0%	<u>Study quality (ROB):</u> assessed by QUADASmethod used and results per individual study. Risk of bias was unclear for reference standards and flow and timing for all studies. <u>Place of the index test in the clinical pathway</u>: detecting distant metastasis in primary NPC during initial staging <u>Choice of cut-off point</u>: not reported

	the Twelfth Five-year Plan Period; Science and Technology Project of Guangzhou City, China; Planned Science and Technology Project of Guangdong Province, China; health & medical collaborative innovation project of Guangzhou City, China; National Natural Science Foundation of China. SR conflicts of interest: none	duplication of information - At least one of the following strategies was used as the reference standard: biopsy, imaging or clinical follow-up. Exclusion criteria SR: - Studies enrolled patients with residual/ recurrent NPC - Studies enrolled mixed patients with untreated and residual/recurrent disease, if relevant data regarding the untreated patients could not be obtained - Studies enrolled patients with no evidence of distant metastasis on CWUs - Case reports, conference abstracts and reviews. *10 studies included (4 included in comparison FDG-*	quantitative (three-point scale)) **D-2:** CWU **D-3:** other modalities (PET/CT + CWU)	**C**: 15.2% **D**:14.8% For how many participants were no complete outcome data available? N (%) Not reported Reasons for incomplete outcome data described? Not reported		Specificity: 0.977 (0.965-0.978) I^2=0.0% **CWU** Sensitivity: 0.401 (0.321-0.485) i^2 = 54.1% p<0.001 specificity: 0.978 (0.967-0.987) I^2=76.5% P=0.892	

		PET/CT versus CWU) Important patient characteristics: N (male/female), mean age **A**: 78 (60/18) patients, 50.00 years **B**: 111 (84/27) patients, 48.90 years **C**: 257 (201/56) patients, 45.00 years **D:** 583 (474/109) patients, 46.00 years					

***comparator test equals the C of the PICO; two or more index/ comparator tests may be compared; note that a comparator test is not the same as a reference test (golden standard)**

Table of quality assessment for systematic reviews of diagnostic studies

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

Research question:

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**	**Assessment of scientific quality of included studies?[5]** **Yes/no/unclear**	**Enough similarities between studies to make combining them reasonable?[6]** **Yes/no/unclear**	**Potential risk of publication bias taken into account?[7]** **Yes/no/unclear**	**Potential conflicts of interest reported?[8]** **Yes/no/unclear**
Xu, 2017	Yes	Yes	No (excluded studies were not reported)	Yes	Yes	Yes	Yes	No (not reported for included studies)

1. **Research question (PICO) and inclusion criteria should be appropriate (in relation to the research question to be answered in the clinical guideline) and predefined.**
2. **Search period and strategy should be described; at least Medline searched.**
3. **Potentially relevant studies that are excluded at final selection (after reading the full text) should be referenced with reasons.**
4. **Characteristics of individual studies relevant to the research question (PICO) should be reported.**

5. **Quality of individual studies should be assessed using a quality scoring tool or checklist (preferably QUADAS-2; COSMIN checklist for measuring instruments) and taken into account in the evidence synthesis.**
6. **Clinical and statistical heterogeneity should be assessed; clinical: enough similarities in patient characteristics, diagnostic tests (strategy) to allow pooling? For pooled data: at least 5 studies available for pooling; assessment of statistical heterogeneity and, more importantly (see Note), assessment of the reasons for heterogeneity (if present)? Note: sensitivity and specificity depend on the situation in which the test is being used and the thresholds that have been set, and sensitivity and specificity are correlated; therefore, the use of heterogeneity statistics (p-values; I^2) is problematic, and rather than testing whether heterogeneity is present, heterogeneity should be assessed by eye-balling (degree of overlap of confidence intervals in Forest plot), and the reasons for heterogeneity should be examined.**
7. **There is no clear evidence for publication bias in diagnostic studies, and an ongoing discussion on which statistical method should be used. Tests to identify publication bias are likely to give false-positive results, among available tests, Deeks' test is most valid. Irrespective of the use of statistical methods, you may score "Yes" if the authors discuss the potential risk of publication bias.**
8. **Sources of support (including commercial co-authorship) should be reported in both the systematic review and the included studies. Note: To get a "yes," source of funding or support must be indicated for the systematic review AND for each of the included studies.**

Table of excluded studies

Author and year	Reason for exclusion
Systematic reviews	
Blatt, 2016	See description of not graded studies PICO 2
de Mones, 2013	French language, methodology not available
Evangelista, 2014	Narrative review
Facey, 2007	PICO1: Relevant outcome on changes in management regarding radiotherapy planning, butnot focusing on disant metastasis. PICO2: Not all relevant data reported, more recent reviews available
Gao, 2013	Individual study data or pooled regarding head and neck carcinoma patients only not reported
Gao, 2014	No comparison
Kolarova, 2012	Wrong PICO (patient)
Li, 2020	See description of not grade studies PICO 2
Liu, 2017	No comparison
Maruyama, 2018	No systematic review
Samuelian, 2013	No systematic review
Shen, 2014	No comparison
Vellayappan, 2014	No comparison
Vermeersch, 2003	Not all relevant data reported, more recent reviews available
Xi, 2015	No comparison
Xu, 2011	No comparison
Xu, 2012a	No comparison
Xu, 2012b	See description of not graded studies PICO 2
RCTs	
Dietl, 2008	No comparison
Dizendorf, 2003	No comparison
Douglas, 2003	Narrative review
Kim, 2017	Wrong PICO (outcome)
Kitagawa, 2002	Wrong PICO (outcome)
Kuta, 2018	Wrong PICO (outcome)
Liao, 2010	No comparison with other modality
Rohde, 2018	No RCT
Sanli, 2018	Narrative review
Schmid, 2003	Wrong PICO (outcome)
Spanu, 2009	Wrong PICO (outcome)

Literature search strategy

Uitgangsvraag: Met welke diagnostische onderzoeken moet onderzoek naar afstandsmetastasen verricht worden?	
Database(s): Ovid/Medline	Datum: 28-11-2019
Periode: 2000-	Talen:
Toelichting:	

	Inclusief dubbele referenties	Ontdubbeld
SR	107	92
RCT	336	244
Observationeel		
Totaal		336

Ovid/Medline

1 "Head and Neck Neoplasms"/ (53024)
2 exp Mouth Neoplasms/ (67318)
3 exp Gingival Neoplasms/ (2356)
4 exp Palatal Neoplasms/ (2995)
5 exp Tongue Neoplasms/ (9890)

6 exp Ear Neoplasms/ (5252)
7 exp Laryngeal Neoplasms/ (27109)
8 exp Nose Neoplasms/ (17258)
9 exp Pharyngeal Neoplasms/ (32994)
10 exp Parathyroid Neoplasms/ (7817)
11 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 (191686)
12 ((adenoma* or anticarcinogen* or blastoma* or cancer* or carcinogen* or carcinom* or carcinosarcoma* or chordoma* or malignan* or melanom* or mesenchymoma* or metasta* or neoplas* or neuroma* or nsclc or oncogen* or oncolog* or paraneoplastic or plasmacytoma* or precancerous or sarcoma* or teratocarcinoma* or teratoma* or tumor* or tumour*) adj6 (gingiva* or head or hypopharyn* or jaw or jaws or lip or lips or mandib* or mouth or nasopharyn* or neck or nose or oral* or oropharyn* or otorhinolaryn* or palatal* or palate or palatum or paranasal* or parathyr* or paroti* or pharyn* or salivar* or sublingual* or submandib* or tongue or tonsil* or uadt)).ti,ab,kf. (175852)
13 11 or 12 (258626)
14 exp Neoplasms, Second Primary/ or ((second* or metachronous* or 'therapy associated' or 'therapy related' or 'treatment related' or 'treatment associated') adj3 (adenoma* or anticarcinogen* or blastoma* or cancer* or carcinogen* or carcinom* or carcinosarcoma* or chordoma* or malignan* or melanom* or mesenchymoma* or neoplas* or neuroma* or oncolog* or paraneoplastic or plasmacytoma* or sarcoma* or teratocarcinoma* or teratoma* or tumor* or tumour*)).ti,ab,kf. or (distant adj3 (malignan* or metastas*)).ti,ab,kf. (89191)
15 exp Tomography, X-Ray Computed/ (416326)
16 exp Positron-Emission Tomography/ or exp Tomography, Emission-Computed/ or computed tomograph*.ti,ab,kf. or ct.ti,ab,kf. or cts.ti,ab,kf. or cat scan*.ti,ab,kf. or computer assisted tomograph*.ti,ab,kf. or computerized tomograph*.ti,ab,kf. or computerised tomograph*.ti,ab,kf. or computed x ray tomograph*.ti,ab,kf. or computed xray tomograph*.ti,ab,kf. or petscan*.ti,ab,kf. or pet.ti,ab,kf. or radionuclid*.ti,ab,kf. (620162)
17 15 or 16 (786961)
18 13 and 14 and 17 (1567)
19 limit 18 to yr="2000 -Current" (1329)
20 (meta-analysis/ or meta-analysis as topic/ or (meta adj analy$).tw. or ((systematic* or literature) adj2 review$1).tw. or (systematic adj overview$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (421081)
21 (exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (1920845)
22 19 and 20 (63)
23 19 and 21 (97)

Embase

No.	Query	Results
#16	#12 OR #14	**8**
#15	#9 AND #14	**1**
#14	spector AND distant AND metastasis AND 2012	**6**
#13	#6 AND #12	**2**
#12	goerres AND impact AND whole AND body AND 2003	**2**
#11	#8 AND #9	**233**
#10	#7 AND #9	**44**
#9	#6 NOT ('conference abstract'/it OR 'conference paper'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	**2016**

#8	('clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti) NOT 'conference abstract':it	**2316355**
#7	('meta analysis'/de OR cochrane:ab OR embase:ab OR psycinfo:ab OR cinahl:ab OR medline:ab OR ((systematic NEAR/1 (review OR overview)):ab,ti) OR ((meta NEAR/1 analy*):ab,ti) OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/de) NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	**464560**
#6	#1 AND #4 AND #5	**2970**
#5	#2 OR #3	**139436**
#4	'x-ray computed 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 OR 'computer assisted emission tomography'/exp OR 'gated single photon emission computed tomography'/exp OR 'single photon emission computer tomography'/exp OR petscan*:ti,ab,kw OR pet:ti,ab,kw OR radionuclid*:ti,ab,kw	**996817**
#3	'distant metastasis'/exp OR ((distant NEAR/3 (malignan* OR metastas*)):ab,ti)	**66686**
#2	'second cancer'/exp OR (((second* OR metachronous* OR 'therapy associated' OR 'therapy related' OR 'treatment related' OR 'treatment associated') NEAR/3 (adenoma* OR anticarcinogen* OR blastoma* OR cancer* OR carcinogen* OR carcinom* OR carcin osarcoma* OR chordoma* OR malignan* OR melanom* OR mesenchymoma* OR neoplas* OR neu roma* OR oncolog* OR paraneoplastic OR plasmacytoma* OR sarcoma* OR teratocarcinoma* OR t eratoma* OR tumor* OR tumour*)):ti,ab,kw)	**74683**
#1	'head and neck tumor'/de OR 'ear tumor'/exp OR 'head and neck cancer'/exp OR 'head tumor'/exp OR 'jaw tumor'/exp OR 'lip tumor'/exp OR 'mouth tumor'/exp OR 'neck tumor'/exp OR 'neoplasms of the eye, lacrimal gland and orbit'/exp OR 'nose tumor'/exp OR 'paranasal sinus tumor'/exp OR hnscc:ab,ti,kw OR scchn:ab,ti,kw OR (((adenoma* OR anticarcinogen* OR blastoma* OR cancer* OR carcinogen* OR carcinom* OR carci nosarcoma* OR chordoma* OR malignan* OR melanom* OR mesenchymoma* OR metasta* OR ne oplas* OR neuroma* OR nsclc OR oncogen* OR oncolog* OR paraneoplastic OR plasmacytoma* O R precancerous OR sarcoma* OR teratocarcinoma* OR teratoma* OR tumor* OR tumour*) NEAR/6 (gingiva* OR head OR hypopharyn* OR jaw OR jaws OR lip OR lips OR mandib* OR mouth OR naso pharyn* OR neck OR nose OR oral* OR oropharyn* OR otorhinolaryn* OR palatal* OR palate OR pa latum OR paranasal* OR parathyr* OR paroti* OR pharyn* OR salivar* OR sublingual* OR submand ib* OR tongue OR tonsil* OR uadt)):ti,ab,kw)	**394952**

Uitgangsvraag: HHT, afstandsmetastasen, accuratesse	
Database(s): Ovid/Medline, Embase	Datum: 5-12-2019, 23-6-2020
Periode: 2000-	Talen: niet van toepassing
Toelichting: 23-6-2020 Op verzoek is een update gedaan van de zoekopdracht van 5-12-2019 en zijn de observationele studies uitgevoerd zonder het diagnostisch filter sensitivity, specificity. De referenties zijn ontdubbeld zowel t.o.v. de databases alsook t.o.v. het reeds eerder gevonden materiaal in Rayyan.	

De ontdubbelde referenties zijn opgenomen in Rayyan.

5-12-2019
Op basis van de vorige uitgangsvraag waarin is gezocht naar afstandsmetastasen en het effect op langere termijn en waarbij alleen de systematische reviews en RCT's zijn meegenomen is besloten om voor deze zoekstrategie alleen de observationele studies toe te voegen in combinatie met het diagnostisch filter. De vorige vraag is in opzet namelijk exact hetzelfde met de uitzondering van het diagnostisch filter dat het resultaat specifieker maakt.
Ten behoeve van het modulair onderhoud wordt er daarna voor gekozen om de bredere zoekstrategie te hanteren waarmee zowel de lange termijn keuzes als de accuratesse worden gevonden.
De referenties zijn toegevoegd aan Rayyan HHT diagnostiek afstandsmetastasen (impact) onder de naam observationeel afstandsmetastasen accuratesse.

Met vriendelijke groet,
Ingeborg van Dusseldorp

23-6-2020	Inclusief dubbele referenties	Ontdubbeld
SR	85	17
RCT	314	14
Observationeel	1139	366
Totaal		

5-12-2019	Inclusief dubbele referenties	Ontdubbeld
SR		
RCT		
Observationeel	641	490
Totaal		

Zoekverantwoording

Ovid/Medline 23 juni 2020

1 "Head and Neck Neoplasms"/ (54319)
2 exp Mouth Neoplasms/ (68632)
3 exp Gingival Neoplasms/ (2373)
4 exp Palatal Neoplasms/ (3001)
5 exp Tongue Neoplasms/ (10026)
6 exp Ear Neoplasms/ (5298)
7 exp Laryngeal Neoplasms/ (27386)
8 exp Nose Neoplasms/ (17490)
9 exp Pharyngeal Neoplasms/ (33760)
10 exp Parathyroid Neoplasms/ (7910)
11 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 (195534)
12 exp Palatal Neoplasms/ or ((adenoma* or anticarcinogen* or blastoma* or cancer* or carcinogen* or carcinom* or carcinosarcoma* or chordoma* or malignan* or melanom* or mesenchymoma* or metasta* or neoplas* or neuroma* or nsclc or oncogen* or oncolog* or paraneoplastic or plasmacytoma* or precancerous or sarcoma* or teratocarcinoma* or teratoma* or tumor* or tumour*) adj6 (gingiva* or head or hypopharyn* or jaw or jaws or lip or lips or mandib* or mouth or nasopharyn* or neck or nose or oral* or oropharyn* or otorhinolaryn* or palatal* or palate or palatum or paranasal* or parathyr* or paroti* or pharyn* or salivar* or sublingual* or submandib* or tongue or tonsil* or uadt)).ti,ab,kf. (183541)
13 11 or 12 (265841)
14 exp Neoplasms, Second Primary/ or ((second* or metachronous* or 'therapy associated' or 'therapy related' or 'treatment related' or 'treatment associated') adj3 (adenoma* or anticarcinogen* or blastoma* or cancer* or carcinogen* or carcinom* or carcinosarcoma* or chordoma* or malignan* or melanom* or mesenchymoma* or neoplas* or neuroma* or oncolog* or paraneoplastic or plasmacytoma* or sarcoma* or teratocarcinoma* or teratoma* or tumor* or tumour*)).ti,ab,kf. or (distant adj3 (malignan* or metastas*)).ti,ab,kf. (92816)
15 exp Tomography, X-Ray Computed/ or exp Positron-Emission Tomography/ or exp Tomography, Emission-Computed/ or computed tomograph*.ti,ab,kf. or ct.ti,ab,kf. or cts.ti,ab,kf. or cat scan*.ti,ab,kf. or computer assisted tomograph*.ti,ab,kf. or computerized tomograph*.ti,ab,kf. or computerised tomograph*.ti,ab,kf. or computed x ray tomograph*.ti,ab,kf. or computed xray tomograph*.ti,ab,kf. or petscan*.ti,ab,kf. or pet.ti,ab,kf. or radionuclid*.ti,ab,kf. (817781)
16 13 and 14 and 15 (1633)
17 limit 16 to yr="2000 -Current" (1395)

18 (meta-analysis/ or meta-analysis as topic/ or (meta adj analy$).tw. or (systematic*or literature adj2 review$1).tw. or (systematic adj overview$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (292978)
19 (exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (1995924)
20 Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or consecutive*.tw. or Cross sectional.tw. or Cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/ (Onder exp cohort studies vallen ook longitudinale, prospectieve en retrospectieve studies) (3459427)
21 17 not ((exp animals/ or exp models, animal/) not humans/) not (letter/ or comment/ or editorial/) (1381)
22 18 and 21 (24) SR
23 19 and 21 (108)
24 20 and 21 (606)
25 23 not 22 (104) RCT
26 24 not 23 not 22 (525) OBS zonder spec en sens

Ovid/Medline 5 december 2019

1 "Head and Neck Neoplasms"/ (53059)
2 exp Mouth Neoplasms/ (67346)
3 exp Gingival Neoplasms/ (2356)
4 exp Tongue Neoplasms/ (9893)
5 exp Ear Neoplasms/ (5252)
6 exp Laryngeal Neoplasms/ (27125)
7 exp Nose Neoplasms/ (17264)
8 exp Pharyngeal Neoplasms/ (33025)
9 exp Parathyroid Neoplasms/ (7822)
10 ((adenoma* or anticarcinogen* or blastoma* or cancer* or carcinogen* or carcinom* or carcinosarcoma* or chordoma* or malignan* or melanom* or mesenchymoma* or metasta* or neoplas* or neuroma* or nsclc or oncogen* or oncolog* or paraneoplastic or plasmacytoma* or precancerous or sarcoma* or teratocarcinoma* or teratoma* or tumor* or tumour*) adj6 (gingiva* or head or hypopharyn* or jaw or jaws or lip or lips or mandib* or mouth or nasopharyn* or neck or nose or oral* or oropharyn* or otorhinolaryn* or palatal* or palate or palatum or paranasal* or parathyr* or paroti* or pharyn* or salivar* or sublingual* or submandib* or tongue or tonsil* or uadt)).ti,ab,kf. (176064)
11 exp Palatal Neoplasms/ (2995)
12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 (258866)
13 exp Neoplasms, Second Primary/ or ((second* or metachronous* or 'therapy associated' or 'therapy related' or 'treatment related' or 'treatment associated') adj3 (adenoma* or anticarcinogen* or blastoma* or cancer* or carcinogen* or carcinom* or carcinosarcoma* or chordoma* or malignan* or melanom* or mesenchymoma* or neoplas* or neuroma* or oncolog* or paraneoplastic or plasmacytoma* or sarcoma* or teratocarcinoma* or teratoma* or tumor* or tumour*)).ti,ab,kf. or (distant adj3 (malignan* or metastas*)).ti,ab,kf. (89285)
14 exp Tomography, X-Ray Computed/ or exp Positron-Emission Tomography/ or exp Tomography, Emission-Computed/ or computed tomograph*.ti,ab,kf. or ct.ti,ab,kf. or cts.ti,ab,kf. or cat scan*.ti,ab,kf. or computer assisted tomograph*.ti,ab,kf. or computerized tomograph*.ti,ab,kf. or computerised tomograph*.ti,ab,kf. or computed x ray tomograph*.ti,ab,kf. or computed xray tomograph*.ti,ab,kf. or petscan*.ti,ab,kf. or pet.ti,ab,kf. or radionuclid*.ti,ab,kf. (787821)
15 12 and 13 and 14 (1569)
16 limit 15 to yr="2000 -Current" (1331)
17 (meta-analysis/ or meta-analysis as topic/ or (meta adj analy$).tw. or ((systematic* or literature) adj2 review$1).tw. or (systematic adj overview$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (421990)
18 (exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized

controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (1923027)
19 Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or consecutive*.tw. or Cross sectional.tw. or Cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/ (Onder exp cohort studies vallen ook longitudinale, prospectieve en retrospectieve studies) (3314655)
20 exp "Sensitivity and Specificity"/ or (Sensitiv* or Specific*).ti,ab. or (predict* or ROC-curve or receiver-operator*).ti,ab. or (likelihood or LR*).ti,ab. or exp Diagnostic Errors/ or (inter-observer or intra-observer or interobserver or intraobserver or validity or kappa or reliability).ti,ab. or reproducibility.ti,ab. or (test adj2 (re-test or retest)).ti,ab. or "Reproducibility of Results"/ or accuracy.ti,ab. or Diagnosis, Differential/ or Validation Studies.pt. (6312603)
21 16 and 17 (63)
22 16 and 18 (97)
23 16 and 20 (601)
24 19 and 23 (342)
25 24 not 22 (301)
26 25 not 21 (295)

Embase 23 juni 2020

Embase Session Results (23 Jun 2020)

Embase Session Results (23 Jun 2020)

No.	Query	Results
#16	#15 NOT #13 NOT #12 OBS zonder sens spec	**614**
#15	#9 AND #11	**782**
#14	#13 NOT #12 RCT	**210**
#13	#8 AND #11	**224**
#12	#7 AND #11 SR	**61**
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No.	Query	Results
	test'):ab,ti) OR ((test NEAR/2 'retest'):ab,ti) OR 'reproducibility'/exp OR accuracy:ab,ti OR 'differential diagnosis'/exp OR 'validation study'/de OR 'measurement precision'/exp OR 'diagnostic value'/exp OR 'reliability'/exp	
#9	'major clinical study'/de OR 'clinical study'/de OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR 'prospective study'/de OR 'comparative study'/de OR 'cohort analysis'/de OR ((cohort NEAR/1 (study OR studies)):ab,ti) OR (('case control' NEAR/1 (study OR studies)):ab,ti) OR (('follow up' NEAR/1 (study OR studies)):ab,ti) OR (observational NEAR/1 (study OR studies)) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti)	**5977542**
#8	('clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti) NOT 'conference abstract':it	**2402228**
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#6	#1 AND #4 AND #5	**3099**
#5	#2 OR #3	**144448**
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No.	Query	Results
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#1	'head and neck tumor'/de OR 'ear tumor'/exp OR 'head and neck cancer'/exp OR 'head tumor'/exp OR 'jaw tumor'/exp OR 'lip tumor'/exp OR 'mouth tumor'/exp OR 'neck tumor'/exp OR 'neoplasms of the eye, lacrimal gland and orbit'/exp OR 'nose tumor'/exp OR 'paranasal sinus tumor'/exp OR hnscc:ab,ti,kw OR scchn:ab,ti,kw OR (((adenoma* OR anticarcinogen* OR blastoma* OR cancer* OR carcinogen* OR carcinom* OR carcinosarcoma* OR chordoma* OR malignan* OR melanom* OR mesenchymoma* OR metasta* OR neoplas* OR neuroma* OR nsclc OR oncogen* OR oncolog* OR paraneoplastic OR plasmacytoma* OR precancerous OR sarcoma* OR teratocarcinoma* OR teratoma* OR tumor* OR tumour*) NEAR/6 (gingiva* OR head OR hypopharyn* OR jaw OR jaws OR lip OR lips OR mandib* OR mouth OR nasopharyn* OR neck OR nose OR oral* OR oropharyn* OR otorhinolaryn* OR palatal* OR palate OR palatum OR paranasal* OR parathyr* OR paroti* OR pharyn* OR salivar* OR sublingual* OR submandib* OR tongue OR tonsil* OR uadt)):ti,ab,kw)	**403799**

Embase 5 december 2019

No.	Query	Results
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#19	#18 NOT #15	**337**
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#16	#5 AND #7	**246**
#15	#6 AND #14	**44**
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#13	#5 AND #6	**66**

#12	#10 AND #11	**803**
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#6	('meta analysis'/de OR cochrane:ab OR embase:ab OR psycinfo:ab OR cinahl:ab OR medline:ab OR ((systematic NEAR/1 (review OR overview)):ab,ti) OR ((meta NEAR/1 analy*):ab,ti) OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/de) NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	**465795**
#5	#1 AND (#2 OR #3) AND #4	**2974**
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#1	'head and neck tumor'/de OR 'ear tumor'/exp OR 'head and neck cancer'/exp OR 'head tumor'/exp OR 'jaw tumor'/exp OR 'lip tumor'/exp OR 'mouth tumor'/exp OR 'neck tumor'/exp OR 'neoplasms of the eye, lacrimal gland and orbit'/exp OR 'nose tumor'/exp OR 'paranasal sinus tumor'/exp OR hnscc:ab,ti,kw OR scchn:ab,ti,kw OR (((adenoma* OR anticarcinogen* OR blastoma* OR cancer* OR carcinogen* OR carcinom* OR carcinosarcoma* OR chordoma* OR malignan* OR melanom* OR mesenchymoma* OR metasta* OR neoplas* OR neuroma* OR nsclc OR oncogen* OR oncolog* OR paraneoplastic OR plasmacytoma* OR precancerous OR sarcoma* OR teratocarcinoma* OR teratoma* OR tumor* OR tumour*) NEAR/6 (gingiva* OR head OR hypopharyn* OR jaw OR jaws OR lip OR lips OR mandib* OR mouth OR nasopharyn* OR neck OR nose OR oral* OR oropharyn* OR otorhinolaryn* OR palatal* OR palate OR palatum OR paranasal* OR parathyr* OR paroti* OR pharyn* OR salivar* OR sublingual* OR submandib* OR tongue OR tonsil* OR uadt)):ti,ab,kw)	**395379**

Aanlandpagina 11.4 - Modules over de klinisch negatieve hals

Behandeling van de negatieve hals bij mondholtecarcinomen
Deze module is onderverdeeld in de volgende submodules:

- Afkappunt invasiediepte cT1-2N0
- Type beleid negatieve hals cT1-2N0
- Type interventie negatieve hals cT1-2N0

Waar gaan deze submodules over?
Deze submodules proberen antwoord te geven op de vragen die spelen rondom kleine mondholtetumoren en het management van de klinisch negatieve hals, gedefinieerd als cN0.

Plaveiselcelcarcinomen van de mondholte metastaseren primair naar lymfeklieren in de hals. In het geval van aantoonbare lymfekliermetastase(n) wordt de hals doorgaans behandeld met een halsklierdissectie. Bij een klinisch (en radiologisch) negatieve hals (cN0) zijn er twee opties: een electieve (profylactische) halsklierdissectie om occulte metastasen te verwijderen of een “watchful waiting” beleid waarbij de hals pas behandeld wordt bij manifeste metastasering tijdens follow-up. Van oudsher bestaat bij patiënten met een klein mondholtecarcinoom het dilemma of een electieve halsklierdissectie dient te worden uitgevoerd (overbehandeling voor 70% van de patiënten met hierbij behorende postoperatieve morbiditeit zoals gestoorde schouderklachten) of dat kan worden volstaan met een afwachtend beleid (onderbehandeling voor 30% van de patiënten met het risico dat een occulte metastase zich zal ontwikkelen tot een grotere metastase met mogelijk uitgebreide en zelfs inoperabele ziekte tot gevolg). Met het doel de diagnostiek van occulte metastase dusdanig te verbeteren dat geen electieve halsklierdissecties meer verricht hoeven te worden is de schildwachtklierprocedure geïntroduceerd. Bij de keuze van management van de hals spelen specifieke patiëntfactoren of keuzes uiteraard een rol.

Samenhang tussen de submodules
In 14.4.1 wordt het gebruik van invasiediepte (of tumordikte) van het primaire plaveiselcelcarcinoom van de mondholte van de primaire tumor om het risico op lymfekliermetastase te bepalen geëvalueerd. De mate van invasiediepte kan een rol spelen bij de keuze van management van de hals. Vervolgens worden in 14.4.2 een electieve halsklierdissectie en een watchful waiting beleid bij een klinisch negatieve hals met elkaar vergeleken. In 14.4.3. worden de electieve halsklierdissectie en een beleid gebaseerd op de schildwachtklierprocedure met elkaar vergeleken.

Module 11.4.1 Afkappunt invasiediepte cT1-2N0

Uitgangsvraag

Welke rol speelt de mate van invasiediepte (of tumordikte) van het primaire plaveiselcelcarcinoom van de mondholte voor de behandelbeslissing van de klinisch negatieve hals?

Inleiding

De mate van invasiediepte (en tumordikte) van het primaire plaveiselcelcarcinoom van de mondholte is geassocieerd met de ontwikkeling van cervicale lymfekliermetastasen. Wanneer lymfekliermetastasen klinisch niet gedetecteerd worden, maar de kans aanzienlijk is dat deze wel aanwezig zijn, ontstaat een dilemma om de hals uit voorzorg (electief) te behandelen of af te wachten totdat deze eventueel manifest worden. Het verwijderen van lymfeklieren in de hals kan echter, naast pijn, oedeemvorming en bloedingen, ook potentieel gevolgen hebben voor de nek- en schouderfunctie van de patiënt. Wanneer gewacht wordt totdat de nog niet gedetecteerde (occulte) lymfekliermetastasen manifest worden, is de behandeling vaak uitgebreider of zelfs soms niet meer mogelijk. Het is daarom belangrijk om te bepalen aan de hand van de invasiediepte (en tumordikte) van de primaire tumor hoe hoog het risico op lymfekliermetastasen is, zodat voor een patiënt het beste beleid ten aanzien van de behandeling van de hals (electief behandelen of afwachten en observeren) gekozen kan worden.

Search and select

A systematic review of the literature was performed to answer the following questions:
What is the risk of lymph node metastases, sensitivity, and negative predictive value per millimeter tumor depth of invasion (or tumor thickness) of the primary tumor for a sentinel lymph node biopsy, an elective neck dissection, or a watch and wait strategy in patients with cT1-2N0 oral cavity carcinomas?

P: patients with a cT1-2N0 oral cavity carcinoma;
I/R: watch and wait, sentinel lymph node biopsy or elective neck dissection;
C: -;
O: risk of lymph node metastases (radiologically or pathologically confirmed), sensitivity, and negative predictive value per millimeter depth of invasion (or tumor thickness) of the primary tumor.

<u>Relevant outcome measures</u>

The guideline development group considered sensitivity and negative predictive value as a critical outcome measure for decision making; and the risk of lymph node metastases 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 a minimal clinically relevant difference as:

- 0.8 or 1.25 as borders for clinical decision-making for lymph node metastases risk or odds ratios.

Search and select (Methods)
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms from 2000 until September 23rd ,2020. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 612 hits.

Studies reporting the risk of lymph node metastases to the neck were selected based on the following criteria: patients had a cT1-2N0 oral cavity carcinoma, sentinel lymph node biopsy/ elective neck dissection/ watch and wait was performed, at least one outcome of interest was reported at a specific cut-off (millimeter), and a multivariable model was used to estimate adjusted risk/odds ratios.

Studies reporting the accuracy (sensitivity/negative predictive value) were selected based on the following criteria: patients had a cT1-2N0 oral cavity carcinoma, sentinel lymph node biopsy / elective neck dissection/ watch and wait was performed, and at least one outcome of interest was reported at a specific cut-off (millimeter).

Seventy-one studies were initially selected based on title and abstract screening. After reading the full text, 60 studies were excluded (see the table with reasons for exclusion under the tab Methods) and 11 studies were included.

Results
Eleven 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
Den Toom (2019) included patients with cT1-2N0 oral carcinomas who underwent transoral excision and sentinel lymph node biopsy (examined with histopathology). Exclusion criteria were not reported. Patients (n=199, 100 males, 99 females) had a median age of 63 years (range 27 to 87). Tumor site in the sample was at the tongue (n=121), floor of mouth (n=53), buccal mucosa (n=160), inferior alveolar process (n=5), or other (n=4). T-stage was either T1 (n=132) or T2 (n=67). Persons with a negative sentinel lymph node biopsy were considered positive for metastasis when metastases developed during follow-up (i.e. the SLNB was false negative). There was a follow-up in the sample of 19 months (central tendency measure was unclear, range: 1 to 104). Depth of invasion was measured as being the mass beneath the basement membrane. A theoretical reconstruction of the basement membrane was made for exophytic lesions or ulceration. Depth of invasion was correlated with (true positive and false negative) lymph node metastatic rate. It was argued that the combination of sentinel node biopsy and follow-up was a better reference standard than routine histopathological examination of neck dissections specimens.

Faisal (2018) selected patients with histopathologically proven T1-2 tongue carcinomas from a database. Patients had to have a clinically negative neck and had to be treated with surgery (including level I-III/IV elective neck dissection) followed by adjuvant (chemo)radiotherapy. Exclusion criteria were not reported. Patients (n= 179, 57% male, 43% female) had a mean age of 57.92 years (SD: 11.93). Pathological T-stage was either T1 (63.69%) or T2 (36.31%), with a tumor differentiation of poor (5.59%), moderate (39.66%), or well (54.75%). Postoperative radiotherapy was provided for patients with pathologically involved lymph nodes or close (< 5mm) resection margins. Three patients received re-excision followed by radiotherapy. Patients with extranodal extension received

chemoradiation. Depth of invasion was measured from the basement membrane of adjacent normal mucosa to the deepest point of invasion by a pathologist.

Goerkem (2010) selected patients from a database with biopsy-proven cT1-2 oral cavity carcinomas without evidence of lymph node metastases after physical examination and imaging. Exclusion criteria were not reported. Transoral tumor resection and sentinel lymph node biopsy was performed in all patients. Patients (n=78, 52 males, 26 females) had a mean age of 60 years (range: 34 to 87). T-stage was either T1 (n=40) or T2 (n=38) with the tumor location at the tongue (n=55) or floor of mouth (n=23). Lymphatic invasion was observed in 10 persons, perineural invasion in 15 persons, vascular invasion in 3 persons, and muscular invasion in 55 patients. Mode of infiltration was observed to be grade 1 (n=11), grade 2 (n=12), grade 3 (n=25), grade 4C (n=16), or grade 4D (n=14). Lymphoplasmacytic infiltration in the sample was grade 1 (n=31), grade 2 (n=41), or grade 3 (n=6). Tumor depth was measured from the mucosal surface to the deepest point of infiltration. Tumor thickness was measured from a virtual line (tangentially placed at the most exophytic tumor area) to the deepest point of infiltration.

Melchers (2012) selected patients with a histologically proven T1-2 oral squamous cell carcinoma from a database. Patients had to be treated by resection of the primary tumor without prior head-neck systemic oncological treatment. All clinicopathologic data regarding the nodal status had to be available. Patients were excluded when there were synchronous tumors, when HE-slides were irretrievable, or when there was an unreliable assessment of depth of invasion. Included patients (n=212, 119 males, 93 females) had a mean age of 61.5 years (range: 25 to 94) with tumors at the tongue (n=108), gum (n=15), floor of mouth (n=64), cheek mucosa (n=7), retromolar area (n=12), or other (n=6). Pathological T-stage was T1 (n=123) or T2 (n=89). The patients were treated with neck dissection (n=174, with n=106 with cN0) or underwent an observation period of at least 2 years (n=38). Clinical nodal stage was assessed with palpation and imaging (CT or MRI, while PET or ultrasound could be performed on indication). Patients with cN0 (n=106) were selected for the accuracy analyses. Pathological N-stage was considered as the true N-stage, after neck dissection. Patients who received the observation strategy were examined for the development of nodal metastases in the follow-up with return visits every 6 weeks. Maximum infiltration depth of the tumor below the mucosal surface was considered as the depth of invasion. The mucosal surface was reconstructed for ulcerated or exophytic tumors when measuring the depth of invasion. Of note is that the group of patients who underwent elective neck dissection differs from the observation group, e.g. true N0 status 58% versus 82%. This difference in incidence may affect negative predictive values.

Sahoo (2020) selected patients older than 35 years with histologically proven oral squamous cell carcinomas from a database. Patients had to be treated with a wide excision of the primary tumor and with elective neck dissection. Patients who had metastatic tumors, recurrent tumors in the oral cavity, immune-compromised diseases and tumors, or who were under treatment with chemotherapy or radiotherapy were excluded. The sample (n=150) consisted of 88 men and 51 females, where 110 patients were younger than 40 years old. The tumor stage was either cT1 (n=27) or cT2 (n=41), with a tumor differentiation of well (n=27), moderate (n=60), or poor (n=3). Lymphovascular invasion was present in 35 patients, while perineural invasion was present in 41 patients. Tumor thickness was measured from the level of the surface of the mucosa or the ulcer base to the deepest point of invasion (without superficial keratin or inflammatory debris). Depth of invasion was measured in two ways from the bottom of the adjacent dysplastic rete ridge to the deepest

point of invasion and from the epithelial junction of most superficial adjacent connective tissue papilla to the deepest point of invasion

Van Lanschot (2020) included patients with pT1-2 primary oral squamous cell carcinomas from a database. Patients with synchronous multiple tumors or with clinically positive neck nodes were excluded. Patients (n=300, 158 males, 142 females) were surgically treated and received an elective neck dissection (n=173) or observation (n=127). Median age was 66.5 years (range: 25 to 94). Tumor site was at the tongue (n=162), floor of mouth (n=77), buccal mucosa (n=27), lower (n=12) or upper (n=7) alveolus and gingiva, lip (n=7), retromolar area (n=5), or hard palate (n=3). Infiltrative grows was present in 179 patients, vasoinvasion in 28 patients, and perineural invasion in 52 patients. Pathological T-stage according to the TNM7-staging system was pT1 (n=197) and pT2 (n=90). Some patients were staged according to the TNM8-staging system (pT1: n=5, pT2: n=8). Patients were surgically treated. Elective neck dissection was performed when the depth of invasion of the primary tumor was ≥ 4 millimeters. Patients staged with clinically negative lymph nodes and < 4 millimeters depth of invasion received an observation strategy. The mean follow-up in the observation group was 23.4 months (range: 0 to 62) and consisted of physical examinations and regular ultrasound of the neck in the first two years. Depth of invasion was measured from the basement membrane of the adjacent normal mucosa to the deepest point of infiltration.

Warburton (2007) selected patient with T1-2N0M0 tongue or floor of mouth carcinomas from a database. Patients had to be treated with resection of the primary tumor, without neck dissection or irradiation. Cases were excluded when there was insufficient tumor tissue on the archived slides. The sample consisted of 27 patients (18 males, 9 females) with a mean age of 64 years (range: 39 to 86). T-stage was either T1 (n=19) or T2 (n=8) with tumors located at the floor of mouth (n=15) or tongue (n=12). Depth of invasion was measured from the surface of the epithelium to the deepest points of invading tumor island or cell by using a reconstructed line, excluding exophytic components and including thickness lost to ulceration.

Wu (2019) Included patients with pathologically confirmed tongue squamous cell carcinoma by biopsy. Patients with T1-2 tumors and without cervical lymph node relapse (N0) were included. TNM stage was assessed with a clinical check, CT, and ultrasound. Exclusion criteria were not reported. Patients received neck dissection (n=69) or observation (n=72) after tumor resection. The sample (n=141, 75 males, 66 females) had a mean age of 55 years. Tumor location carcinoma was on the anterior (n=14), middle (n=103) or back (n=24) of the tongue. Tumor differentiation was well (n=48), moderate/poor (n=93). Eighteen patients had neurovascular invasion. Patients were followed for a maximum of 60 months and examined every 3 months (first 24 months), then every 6 months (for the following 36 months). Examination consisted of physical inspection and CT or MRI. Nodal relapses were pathologically proven. It was unclear how the depth of invasion was measured.

Xu (2020) selected adult patients (≥ 18 years) with primary cT1N0M0 tongue squamous cell carcinoma. Patients were selected when MRI and follow-up data were available. Exclusion criteria were not reported. Elective neck dissection was routinely provided after primary tumor excision, while patients with very early-stage disease did not undergo neck dissection. After therapy, the patients were examined every 3 months (in the first 12 months), every 6 months (in the following 12 months), and once yearly thereafter (mean follow-up: 70.4 months, range: 8 to 103). The sample (n=151, 111 males, 40 females) had a mean age of 57.1 years (range: 30 to 78). A portion of the sample had perineural invasion (n=23) and/or lymphovascular invasion (n=19). The observed growth pattern was either ulcerative (n=71),

invasive (n=20), or exogenous (n=49). Depth of invasion as measured on MRI was defined as the distance between the deepest point of invasion and the simulated normal mucosal junction. The depth of invasion was determined by at least two radiologists. Pathological depth of invasion was measured from the level of normal adjacent mucosa to the deepest point of infiltration.

Yeh (2014) recruited 272 consecutive patients with newly diagnosed T1-2 cN0 oral squamous cell carcinoma who underwent curative surgery. Patients were excluded when there was previous cancer, unless the patient was more than 2 years disease-free. Nineteen patients (who underwent observation) were excluded because of adjuvant therapy was provided (n=7), there was local recurrence before neck recurrence (n=1), or the follow-up period was too short (n=11). Included patients (n=253) had either pT1 (n=128) or pT2 (n=125) with a well (n=171) or moderate/poor (n=82) tumor differentiation. The clinically negative neck status was determined with clinical examination and imaging (MRI or CT). A total of n=176 received neck dissection and n=77 received observation. Node positivity was defined as the pathological diagnosis of lymph node metastasis (for neck dissection) or the neck recurrence within 2 years without antecedent or synchronous local recurrence (for observation). Patients with high-risk features in the neck dissection group received postoperative adjuvant treatment (n=31). Patients were followed every month (first year), every 2 months (following year), and every 3 months (thereafter). Persons who received the observation strategy and remained free from neck recurrence had a mean follow-up of 61.9 months (range: 24 to 130). Tumor thickness was measured vertically from the tumor surface or ulcer base to the deepest point of invasion on serial sections.

Zhang (2014) selected patients with a biopsy proven cT1N0M0 squamous cell carcinoma of the tongue without previous treatment. Patients had to be treated with surgery, the staging of the neck was performed with palpation and contrast-enhanced CT, no other malignancies were present in the head and neck, and sufficient data was recorded. Cases were excluded when there was a carcinoma in situ, verrucous carcinoma, or carcinoma at the base of the tongue. The sample (n=65, 32 males, 33 females) had a mean age of 60.7 years (range: 24 to 91). Tumor was located at the dorsal (n=2), lateral (n=54), or ventral (n=9) part of the tongue with a poor (n=5), moderate (n=18), well (n=37), or unknown (n=5) tumor differentiation. Perineural invasion was present in four patients. Patients received observation when biopsy results showed < 3 millimeters depth of invasion. Delayed neck dissection was recommended within 4 to 6 weeks when pathological depth of invasion was ≥ 3 millimeters (while the biopsy showed < 3 mm). When the depth of invasion was ≥ 3mm on biopsy, the patients received selective neck dissection. Thirty-six patients received simultaneous or delayed neck dissection, while the other (n=29) did not receive neck dissection. Pathological tumor depth was measured from the normal adjacent mucosa to the deepest point of invasion.

Overviews of how depth of invasion was measured, whether tumor thickness was measured, and which reference standard(s) were used in the included studies are reported in Tables 11.1 and 11.2.

Table 11.1 Overview of how depth of invasion measured in the included studies and whether tumor thickness was measured

Author, year	Depth of invasion		Tumor thickness
	From basement membrane of intact mucosa	From surface of intact mucosa	
Den Toom 2019	x		
Faisal 2018	x		
Goerkem 2010		x	x

Melchers 2012		x	
Sahoo 2020	x		x
Van Lanschot 2020	x		
Warburton 2007		x	
Wu 2019	Unclear	Unclear	
Xu 2020		x	
Yeh 2014			x
Zhang 2014		x	

Table 11.2 Overview of how the included studies assessed the occurrence (i.e. presence or development) of neck metastases

Author, year	Reference standard			
	Follow-up	Sentinel node biopsy	Sentinel node + follow-up	Neck dissection
Den Toom 2019			x	
Faisal 2018	x			I - III/IV
Goerkem 2010		x		
Melchers 2012	x			x
Sahoo 2020				x
Van Lanschot 2020	x			x
Warburton 2007	x			
Wu 2019	x			x
Xu 2020	x			x
Yeh 2014	x			x
Zhang 2014	x			x

Results

Risk of lymph node metastases

Three studies used a multivariable model (Faisal, 2018; Wu, 2019; Xu 2020). All studies solely included patients with oral tongue carcinomas. Results are summarized in Table 11.3.

Table 11.3 Adjusted odds ratios from multivariable models at specific cut-off points

Author, year, tumor sites	Reference strategy	TT / DOI*	Adjusted risk per cut-off (millimeters		
			4 mm	5 mm	7.5 mm
Faisal 2018 *Tongue*	ND	DOI		≤5 mm (ref) versus 6-10mm OR not reported (95%CI: 0.52 – 2.00) *Other variables in the model: cT-stage, perineural invasion, extracapsular spread* ≤5mm (ref) versus >10mm OR = 1.69 (95%CI: 0.80 – 3.58) *Other variables in the model: cT-stage, perineural invasion, extracapsular spread*	
Wu 2019 *Tongue*	ND/WW*	DOI	<4 mm (ref) versus ≥4 mm OR = 12.23 (95%CI: 1.31 – 113.90) *Other variables in the model: gender, age, mode of invasion,*		

			pathological differentiation, neurovascular invasion, location, T-stage, smoking, drinking, treatment		
Xu 2020 *Tongue*	ND/WW*	DOI		≤5 mm(ref) versus >5 mm (pathological DOI) OR = 3.112 (95%CI: 1.812 – 9.668) *Other variables in the model: lymphovascular invasion, pathologic tumor grade, MRI-measured depth of invasion.*	<7.5mm (ref) versus ≥7.5 mm (MRI-measured DOI) OR = 2.978 (95%CI: 1.574 – 7.332) *Other variables in the model: lymphovascular invasion, pathologic tumor grade, pathologic depth of invasion.*
DOI: Depth of invasion **mm: millimeter(s)** **ND: Neck dissection** **SLNB: Sentinel lymph node biopsy** **TT: Tumor thickness** **WW: Watch and wait** ***: ND and WW were not separately distinguishable from the reported results**					

Sensitivity
Study results for sensitivity using several reference strategies at specific cut-off points are summarized in Table 11.4. Overall the sensitivity ranged from 0.13 to 1.00, depending on the reference strategy and the cut-off point. Studies used tumor thickness measurements and/or depth of invasion measurements for specific cut-off points in millimeters.

Using watch and wait as the reference strategy, the sensitivity ranged from 0.375 to 1.00 (Warburton, 2007; Melchers 2012) depending on the cut-off point.

Two studies reported the sensitivity for both the neck dissection and observation strategies combined as one group (Zhang, 2014; Van Lanschot 2020). From another study, the sensitivity for the group receiving neck dissection or watch and wait could be calculated from the presented data (Yeh, 2014). The sensitivity ranged from 0.545 to 1.00, depending on the cut-off.

When using neck dissection as a reference strategy, two studies reported the sensitivity at various cut-off points (Melchers, 2012; Sahoo, 2020). Depending on the cut-off point, the sensitivity ranged from 0.50 to 1.00.

Sentinel lymph node biopsy was used as a reference strategy in two studies (Goerkem, 2010; Den Toom 2010). The sensitivity ranged from 0.13 to 1.00, depending on the different cut-off points.

Negative predictive value
Study results for the negative predictive value are summarized in Table 11.5. Overall, the negative predictive value using different reference strategies at specific cut-off points ranged from 0.464 to 1.00 in five studies (Warburton, 2007; Goerkem, 2010; Melchers, 2012; Yeh, 2014; Van Lanschot, 2020). Studies used tumor thickness measurements and/or depth of invasion measurements for specific cut-off points in millimeters.

When using watch and wait as a reference strategy in two studies (Warburton, 2007; Melchers, 2012), the negative predictive value ranged from 0.783 to 1.00 depending on the cut-off point.

In two studies, the study samples received neck dissection or watch and wait as a reference strategy which could not be distinguished (Yeh, 2014; Van Lanschot, 2020). One study reported the negative predictive value (Van Lanschot, 2020), while the negative predictive value could be calculated from the reported data in the other study (Yeh, 2014). Depending on the cut-off points, the negative predictive value ranged from 0.815 to 1.00.

One study also used neck dissection as the reference strategy in a study group (Melchers, 2012). The negative predictive value ranged from 0.889 (at the 7 millimeters cut-off point) to 1.00 (at the 1 millimeter cut-off point).

Sentinel lymph node biopsy was used as a reference strategy in one study reporting the negative predictive value (Goerkem, 2010). Here, the negative predictive value ranged from 0.649 to 1.00 (tumor thickness) and from 0.464 to 0.75 (depth of invasion), depending on the cut-off points.

Table 11.4 Summary of the sensitivity for predicting of lymph node metastasis using several reference standards at specific cut-off points of tumor thickness or depth of invasion

Author, year, tumor sites	Reference strategy	TT / DOI	Sensitivity at specific cut-off points																		
			1 mm	1.5 mm	1.6 mm	2 mm	2.2 mm	2.7 mm	3 mm	3.4 mm	3.8 mm	4 mm	4.59 mm	5 mm	6 mm	7 mm	7.64 mm	8 mm	8.64 mm	9 mm	10 mm
Warburton 2007 *Floor of mouth, tongue*	WW	DOI	-	1.00	1.00	0.875	0.875	0.75	0.5	-	0.375	-	-	-	-	-	-	-	-	-	-
Melchers 2012 *Tongue, gum, floor of mouth, cheek mucosa, retromolar area, other (oral)*	WW	DOI	1.00	-	-	0.857	-	-	0.714	-	-	0.714	0.714	0.571	0.571	0.571	-	-	-	-	-
	ND	DOI	1.00	-	-	0.944	-	-	0.889	-	-	0.833	0.833	0.722	0.667	0.50	-	-	-	-	-
Sahoo 2020 *Gingivobuccal sulcus, tongue, floor of mouth, retromolar area, maxilla*	ND	DOI	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0.727 (95%CI 0.575 – 0.838)	-	-	-	-
		TT	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0.72 (95%CI 0.572 – 0.85)	-	-
Van Lanschot 2020	ND/WW*	DOI	1.00	-	-	1.00	-	-	0.951		-	0.951	-	0.878	0.805	-	-	-	-	-	-

Tongue, Floor of mouth, buccal mucosa, lower and upper alveolus and gingiva, lip, retromolar area, hard palate																					
Yeh 2014 *Oral*	ND/WW*	TT	-	-	-	-	-	-	-	-	-	-	-	-	0.545	-	-	-	-	-	-
Zhang 2014 *Tongue*	ND/WW*	DOI	-	-	-	1.00	-	-	0.929	-	-	0.786		0.643	-	-	-	-	-	-	-
Den Toom 2019 *Tongue, floor of mouth, buccal mucosa, inferior alveolar process, other (oral)*	SLNB+follow-up**	DOI	0.97	-	-	0.89	-	-	0.83	0.83	-	0.70	-	0.50	0.34	0.25	-	0.20	-	0.13	0.13
Goerkem 2010 *Tongue, floor of mouth*	SLNB	DOI	0.964	-	-	0.929	-	-	0.857	-	-	0.643	-	0.607	0.464	-	-	-	-	-	-
		TT	1.00	-	-	1.00	-	-	0.964	-	-	0.786	-	0.679	0.536	-	-	-	-	-	-
DOI: Depth of invasion **mm: millimeter(s)**																					

ND: Neck dissection
SLNB: Sentinel lymph node biopsy
TT: Tumor thickness
WW: Watch and wait
***: ND and WW were not separately distinguishable from the reported results**
****: When a regional metastasis developed during follow-up after a negative SLNB, the negative SLNB was considered to be false-negative**

Table 11.5 Summary of negative predictive values for the prediction of lymph node metastasis using several reference standards at specific cut-off points of tumor thickness or depth of invasion

Author, year, tumor sites	Reference strategy	TT / DOI	Negative predictive value at specific cut-off points												
			1 mm	1.5 mm	1.6 mm	2 mm	2.2 mm	2.7 mm	3 mm	3.8 mm	4 mm	4.59 mm	5 mm	6 mm	7 mm
Warburton 2007 *Floor of mouth, tongue*	WW	TT	-	1.00	1.00	0.933	0.938	0.889	0.818	0.783	-	-	-	-	-
Melchers 2012 *Tongue, gum, floor of mouth, cheek mucosa, retromolar are, other (oral)*	WW	DOI	1.00	-	-	0.857	-	-	0.889	-	0.923	0.923	0.889	0.897	0.906
	ND	DOI	1.00	-	-	0.938	-	-	0.939	-	0.943	0.948	0.918	0.915	0.889
Van Lanschot 2020 *Tongue, Floor of mouth, buccal mucosa, lower and upper alveolus and gingiva, lip, retromolar area, hard palate*	ND/WW *	DOI	1.00	-	-	1.00	-	-	0.978	-	0.986	-	0.971	0.958	-
Yeh 2014 *Oral*	ND/WW *	TT	-	-	-	-	-	-	-	-	-	-	-	0.815	-
Goerkem 2010 *Tongue, floor of mouth*	SLNB	DOI	0.75	-	-	0.75	-	-	0.667	-	0.615	-	0.607	0.464	-
		TT	1.00	-	-	1.00	-	-	0.80	-	0.625	-	0.625	0.649	-

DOI: Depth of invasion
mm: millimeter(s)
ND: Neck dissection
SLNB: Sentinel lymph node biopsy

TT: Tumor thickness
WW: Watch and wait
***: ND and WW were not separately distinguishable from the reported results**

Level of evidence of the literature
The level of evidence regarding the outcome measure risk of lymph node metastases was downgraded by two levels because of study limitations (1 levels for risk of bias: confounders were not predefined, but models were developed based on significance as predictors in the model); imprecision (1 level for imprecision: wide confidence intervals); publication bias was not assessed.

The level of evidence regarding the outcome measure sensitivity was downgraded by one level because of study limitations (1 level for risk of bias: unclear whether there were inappropriate exclusions in most studies, and in some studies not every patient received the same reference standard); not downgraded for conflicting results (already downgraded for risk of bias: different reference tests used within one group may explain some heterogeneity); Not downgraded for overall number of included patients (There is imprecision due to a very low number of included patients (n=27) at: 1.5mm/ 1.6mm/ 2.2 mm/ 2.7 mm/ 3.8 mm); publication bias was not assessed.

The level of evidence regarding the outcome measure negative predictive value was downgraded by 1 level because of study limitations (1 level for risk of bias: unclear whether there were inappropriate exclusions in most studies, and in some studies not every patient received the same reference standard); conflicting results (already downgraded for risk of bias: different reference tests used within one group may explain some heterogeneity); number of included patients (There is imprecision due to a very low number of included patients (n=27) at: 1.5mm/ 1.6mm/ 2.2 mm/ 2.7 mm/ 3.8 mm); publication bias.

Conclusions

LOW GRADE	The evidence is uncertain about the **risk of lymph node metastasis** as at various cut-off points of depth of invasion of oral tongue carcinomas using a sentinel node biopsy, elective neck dissection and/ or a watch and wait strategy as reference standard. There was no data included for other subsites of oral cavity carcinomas. *Sources: (Faisal, 2018; Wu, 2019; Xu 2020)*

MODERATE GRADE	There is moderate certainty about the **sensitivity** at various cut-off points of depth of invasion (or tumor thickness) with enough data in oral cavity carcinomas using a sentinel node biopsy, elective neck dissection, or a watch and wait strategy as reference standard for the prediction of lymph node metastases. However, the evidence is very uncertain about specific cut-off points where there is a lack of data (1.5 mm/ 1.6mm/ 2.2mm/ 2.7mm/ 3.8mm). *Sources: (den Toom, 2019; Goerkem, 2010; Melchers, 2012; Sahoo, 2020; van Lanschot, 2020; Warburton, 2007; Yeh, 2014; Zhang, 2014)*

MODERATE GRADE	There is moderate certainty about the **negative predictive value** at various cut-off points of depth of invasion (or tumor thickness) with enough data in oral cavity carcinomas using a sentinel node biopsy, elective neck dissection, or a watch and wait strategy as reference standard for the prediction of lymph node metastases. However, the evidence is very uncertain about specific cut-off points where there is a lack of data (1.5 mm/ 1.6mm/ 2.2mm/ 2.7mm/ 3.8mm).

	Sources: (Goerkem, 2010; Melchers, 2012; van Lanschot, 2020; Warburton, 2007; Yeh, 2014)

Overwegingen - van bewijs naar aanbeveling
De zekerheid in het bewijs uit de geïncludeerde studies met multivariabele modellen was laag voor het risico op de aanwezigheid van metastasen. De geïncludeerde studies bevatten in geen enkel geval vooraf gedefinieerde confounders en de betrouwbaarheidsintervallen waren breed. Voor het classificeren van de aan- of afwezigheid van (occulte) halskliermetastasen aan de hand van een afkapwaarde voor invasiediepte (of tumordikte) was er een redelijk vertrouwen in het gevonden bewijs, met uitzondering van een zeer laag vertrouwen op specifieke afkappunten waar zeer weinig data voor beschikbaar was.

Invasiediepte is voorspellend voor de aanwezigheid van lymfekliermetastasen. In de beschreven studies werd een verhoogd risico gevonden voor lymfekliermetastasen bij een invasiediepte boven de gekozen afkapwaarde. Wanneer deze studies vergeleken worden, is geen duidelijke trend richting een hogere odds ratio te zien bij een hogere afkapwaarde. De studiepopulaties kunnen echter sterk verschillen.

Wanneer invasiediepte of tumordikte gebruikt wordt om de aanwezigheid van lymfekliermetastasen te voorspellen, nemen met een lagere afkapwaarde de sensitiviteit en negatief voorspellende waarde toe. Bij de veel gebruikte afkapwaarde van 4 mm voor het verrichten van een electieve halsklierdissectie is de sensitiviteit 70 tot 95% en de negatief voorspellende waarde 61 tot 99%. Dit betekent dat als een electieve halsklierdissectie alleen wordt verricht wanneer de invasiediepte groter is dan 4 millimeter, het risico op aanwezigheid van (occulte) lymfekliermetastasen 1 tot 39% is in de groep met een invasiediepte kleiner dan 4 millimeter. De sensitiviteit en negatief voorspellende waarde voor een afkapwaarde van 3 mm zijn 71-96% en 67 tot 98%.

Na de zoekactie voor deze module is nog een studie verschenen waarin de waarde van invasiediepte voor het voorspellen van lymfekliermetastasen is onderzocht bij 222 patiënten met een T1-2 mondholtecarcinoom (Aaboubout, 2021). De referentiestandaard was een electieve halsklierdissectie (n=166) of observatie (n=56). Hierbij werd een odds ratio van 1,3 per mm invasiediepte gevonden en was bij een afkapwaarde van 4 mm de sensitiviteit 74% en de negatief voorspellende waarde 81% (zie tabel 11.6).

Tabel 11.6 Sensitiviteit en negatief voorspellende waarde, uit Aaboubout 2021

Accuratesse parameter	Afkapwaarde (millimeter)									
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Sensitiviteit	1.00	1.00	0.90	0.74	0.59	0.54	0.46	0.28	0.13	0.00
Negatief voorspellende waarde	1.00	1.00	0.88	0.81	0.80	0.81	0.82	0.79	0.77	0.77

Belangrijke factoren die van invloed kunnen zijn op de gevonden waarde zijn de onderzoeken die verricht zijn voordat gesproken wordt over een klinisch negatieve hals (d.w.z. geen lymfekliermetastasen gedetecteerd, cN0), de daarmee samenhangende incidentie van lymfekliermetastasen.

Indien de hals na uitgebreid beeldvormend onderzoek negatief is, is de kans dat toch lymfekliermetastasen aanwezig zijn kleiner dan wanneer de hals na palpatie alleen als negatief beschouwd wordt. Aangezien het risico op lymfekliermetastasen ook afhankelijk is van vele andere factoren als T-stadium en tumor lokalisatie, kan de incidentie van lymfekliermetastasen verschillen indien de samenstelling van in studies onderzochte

cohorten anders is. De incidentie van lymfekliermetastasen kan invloed hebben op de negatief voorspellende waarde.

Ook de referentiestandaard kan van invloed zijn op de resultaten. Bij routinematig onderzoek van een halsklierdissectiepreparaat kunnen namelijk tot 15% van de (micro)metastasen gemist worden. Door stapsgewijze doorsnijdingen en immunohistochemie kunnen bij de schildwachtklierprocedure micrometastasen beter gedetecteerd worden. Het is alleen te arbeidsintensief om dit routinematig bij alle lymfeklieren in een halsklierdissectiepreparaat te doen. Bij een watch and wait strategie (observatie) van een onbehandelde hals zullen alle lymfekliermetastasen tijdens follow-up uiteindelijke manifest worden. Derhalve is observatie van de onbehandelde hals de beste referentiestandaard, gevolgd door de schildwachtklierprocedure (die indien negatief gevolgd wordt door observatie) en daarna het histopathologisch onderzoek van een electieve halklierdissectie.

In de beschreven studies zijn met name tumoren van de tong onderzocht. Het is goed mogelijk dat de gevonden resultaten bij andere tumorlokalisaties als de mondbodem anders zullen zijn.

In de beschreven studies wordt invasiediepte op twee verschillende manieren gemeten: van een denkbeeldig intact (alsof er geen ulceratie of exofytische groei aanwezig is) mucosale oppervlak tot het diepste punt van tumorinfiltratie of van de basaalmembraan tot het diepste punt van tumorinfiltratie. Daarnaast is in andere studies tumordikte in plaats van invasiediepte gebruikt. Dikte kan mogelijk als surrogaat voor invasiediepte gebruikt worden aangezien Dirven (2017) in een cohort van 456 patiënten met een mondholtecarcinoom een gemiddeld verschil van 0,7 mm vonden.

Invasiediepte is voorspellend voor het optreden van lymfekliermetastasen. De sensitiviteit en negatief voorspellende waarde (per afkapwaarde) verschilt echter sterk per studie. Naast invasiediepte zijn er andere voorspellende factoren voor aanwezigheid van lymfekliermetastasen. Toch kan invasiediepte gebruikt worden bij de keuze voor het al dan niet electief behandelen van de hals. Invasiediepte kan histopathologisch bepaald worden op het resectiepreparaat en is derhalve voor de patiënt niet belastend. Nadeel is dat de uitslag niet voor of tijdens de operatie van de primaire tumor beschikbaar is, zodat dan in tweede instantie eventueel een halsklierdissectie verricht zou moeten worden. Aangezien een incisiebiopt slechts een sample van de hele tumor is, zal onduidelijk zijn of de gemeten invasiediepte in het biopt ook de maximale invasiediepte van de tumor is. Preoperatief kan de invasiediepte met MRI en echografie betrouwbaar bepaald worden. MRI en echografie van de hals worden vaak al routinematig gemaakt waardoor het weinig belastend voor de patiënt is. Voor bepaling van invasiediepte met echografie is alleen wel een speciale probe voor in de mondholte nodig. Dit laatste is het enige dat extra aangeschaft hoeft te worden. De overige onderzoeken worden routinematig verricht. De metingen zijn gemakkelijk te aan te leren.

Aanbevelingen

Aanbeveling-1

<u>Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies</u>

Invasiediepte is een voorspeller voor de kans op lymfekliermetastasen. Gezien de grote variatie in sensitiviteit en negatief voorspellende waarde kan moeilijk een keuze gemaakt worden voor een optimale afkapwaarde waaronder voor een afwachtend beleid en waarboven voor een electieve halsklierdissectie gekozen dient te worden. Dit is onder

andere afhankelijk van incidentie van lymfekliermetastasen, welke deels bepaald wordt door de accuratesse voor het detecteren van (occulte) lymfekliermetastasen van de tevoren verrichte diagnostische onderzoeken.

Neem bij de besluitvorming om een electieve halsklierdissectie te verrichten dan wel een watchful waiting te volgen de mate van invasiediepte van het primaire mondholtecarcinoom in de afweging mee

Aanbeveling-2

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

Gezien de grote variatie in sensitiviteit en negatief voorspellende waarde kan (wanneer geen schildwachtklierprocedure verricht wordt) moeilijk een keuze gemaakt worden voor een optimale afkapwaarde waaronder voor een afwachtend beleid en waarboven voor een electieve halsklierdissectie gekozen dient te worden. Wanneer de hals alleen op basis van palpatie als klinisch negatief beoordeeld wordt zal waarschijnlijk voor een lagere afkapwaarde gekozen moeten worden om een acceptabel risico op gemiste metastasen te houden. Uit de voorhanden zijnde literatuur ontstaat het beeld dat het risico op metastasen onacceptabel hoog wordt vanaf een invasiediepte tussen 3 en 4 mm.

Overweeg geen watchful waiting in te zetten bij een invasiediepte groter dan 3-4 millimeter door een tot in het algemeen als onaanvaardbaar niveau beschouwd toegenomen risico op lymfekliermetastasen

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Bijlagen bij module 11.4.1

Implementatieplan

Aanbeveling	Tijdspad voor implementatie: < 1 jaar, 1 tot 3 jaar of > 3 jaar	Verwacht effect op kosten	Randvoorwaarden voor implementatie (binnen aangegeven tijdspad)	Mogelijke barrières voor implementatie[1]	Te ondernemen acties voor implementatie[2]	Verantwoordelijken voor acties[3]	Overige opmerkingen
1e Gebruik invasiediepte bij het bepalen van de kans op occulte lymfekliermetastasen van mondholtecarcinomen.	< 1 jaar	Geen	Geen	Geen	Geen	Geen	Verwachting is dat deze aanbeveling al geïmplementeerd is
2e Overweeg geen watchful waiting in te zetten bij een invasiediepte hoger dan 3 tot 4 millimeter door een toenemend risico op lymfekliermetastasen.	< 1 jaar	Geen	Geen	Geen	Geen	Geen	Verwachting is dat deze aanbeveling al geïmplementeerd is

[1] barrières kunnen zich bevinden op het niveau van de professional, op het niveau van de organisatie (het ziekenhuis) of op het niveau van het systeem (buiten het ziekenhuis). Denk bijvoorbeeld aan onenigheid in het land met betrekking tot de aanbeveling, onvoldoende motivatie of kennis bij de specialist, onvoldoende faciliteiten of personeel, nodige concentratie van zorg, kosten, slechte samenwerking tussen disciplines, nodige taakherschikking, et cetera.
[2] Denk aan acties die noodzakelijk zijn voor implementatie, maar ook acties die mogelijk zijn om de implementatie te bevorderen. Denk bijvoorbeeld aan controleren aanbeveling tijdens kwaliteitsvisitatie, publicatie van de richtlijn, ontwikkelen van implementatietools, informeren van ziekenhuisbestuurders, regelen van goede vergoeding voor een bepaald type behandeling, maken van samenwerkingsafspraken.
[3] Wie de verantwoordelijkheden draagt voor implementatie van de aanbevelingen, zal tevens afhankelijk zijn van het niveau waarop zich barrières bevinden. Barrières op het niveau van de professional zullen vaak opgelost moeten worden door de beroepsvereniging. Barrières op het niveau van de organisatie zullen vaak onder verantwoordelijkheid van de ziekenhuisbestuurders vallen. Bij het oplossen van barrières op het niveau van het systeem zijn ook andere partijen, zoals de NZA en zorgverzekeraars, van belang.

Evidence tables

Evidence table for intervention studies (randomized controlled trials and non-randomized *observational* studies (cohort studies, case-control studies, case series))[1]

This table is also suitable for diagnostic studies (screening studies) that compare the effectiveness of two or more tests. This only applies if the test is included as part of a test-and-treat strategy - otherwise the evidence table for studies of diagnostic test accuracy should be used.

Research question:

Study reference	Study characteristics	Patient characteristics [2]	Intervention (I)	Comparison / control (C) [3]	Follow-up	Outcome measures and effect size [4]	Comments
Den Toom 2019	Type of study: Observational Setting and country: head and neck centers, Netherlands Funding and conflicts of interest:	Inclusion criteria: cT1-2N0 oral cancer, underwent transoral excision, underwent sentinel lymph node biopsy Exclusion criteria: Not reported N total at baseline: N=199 Important prognostic factors[2]: *Age, median (range): 63 (27-87)* *Sex: 100M/99F* *Tumor location, n: Tongue: 121 FOM: 53 Buccal mucosa: 16*	Describe intervention (treatment/procedure/test): Transoral excision of oral cancer and sentinel lymph node biopsy was performed. Biopsy was assessed with histopathology. Persons with negative SLNB developing metastases during follow-up were considered positive for metastasis (false negative). DOI was considered to be the mass between the basement membrane and for ulceration/exophytic lesions a theoretical basement membrane was constructed.	Describe control (treatment/procedure/test): 1: >1mm 2: >2mm 3: >3 mm 4: >3.4mm 5: >4mm 6: >5mm 7: >6mm 8: >7mm 9: >8mm 10: >9mm 11: >10mm	Length of follow-up: 19 months (range:1-104) Loss-to-follow-up: NA, database study Incomplete outcome data: NA	Outcome measures and effect size (include 95%CI and p-value if available): Sensitivity at DOI 1mm cut-off: 1mm: 0.97 2mm: 0.89 3mm: 0.83 ≤3.4mm: 0.83 4mm: 0.70 5mm: 0.50 6mm: 0.34 7mm: 0.25 8mm: 0.20 9mm: 0.13 10mm: 0.13	

		Inferior alveolar process: 5 *Other: 4* *T-stage:* *T1: 132* *T2: 67* Groups comparable at baseline?	1: ≤1mm 2: ≤2mm 3: ≤3 mm 4: ≤3.4mm 5: ≤4mm 6: ≤5mm 7: ≤6mm 8: ≤7mm 9: ≤8mm 10: ≤9mm 11: ≤10mm				
Faisal 2018	Type of study: Observational, database Setting and country: Hospital, Pakistan Funding and conflicts of interest: No funding was received. The authors declared that there were no competing interests.	Inclusion criteria: Histopathologically proven T1-2 tongue cancer , clinically negative neck (cN0) with usually MRI and chest x-ray, radiotherapy or chemoradiation in adjuvant setting. Exclusion criteria: Not reported N total at baseline: N=179 Important prognostic factors[2]: *Age, mean (SD): 57.92 (11.93)* *Sex:* *57% M / 43% F* *pT-stage, %:*	Describe intervention (treatment/procedure/test): Primary treatment modality was surgery. Elective neck dissection was performed in all cases. Postoperative radiotherapy was provided for pathologically involved nodes or close surgical margins (<5mm). Patients with extranodal extension received radiochemotherapy. Three patients were managed by re-excision followed by postoperative radiotherapy. DOI was measured by a pathologist from deepest point of invasion to the	Describe control (treatment/procedure/test): 1: 6-10mm 2: >10mm	Length of follow-up: Unclear Loss-to-follow-up: NA Incomplete outcome data: NA	Outcome measures and effect size (include 95%CI and p-value if available): **Risk of nodal metastases with DOI, multivariable model, ≤5mm(ref) versus 6-10mm:** Adjusted OR: not reported (only the 95%CI was reported: 0.52-2.02) Other variables in the model: cT-stage, perineural invasion. Extracapsular spread **Risk of nodal metastases with DOI, multivariable model, ≤5mm(ref) versus >10mm:** Adjusted OR = 1.69 (95%CI: 0.80-3.58)	Group A: ≤5mm Group B: 6-10mm Group C: <10mm

		pT1: 63.69% *pT2: 36.31%* *Tumor differentiation, %:* *Poor: 5.59%* *Moderate: 39.66%* *Well: 54.75%* *Unclear how other characteristics were distributed: some numbers seem to be omitted from the table.* Groups comparable at baseline?	basement membrane of adjacent normal mucosa. 1:≤5mm 2: ≤5mm			Other variables in the model: cT-stage, perineural invasion. Extracapsular spread	
Goerkem 2010	Type of study: Observational / cross-sectional, database Setting and country: Hospital, Switzerland Funding and conflicts of interest: Not reported in the manuscript	Inclusion criteria: Biopsy-proven cT1-2 oral cavity SCC, no evidence of lymph node metastases (cN0) after physical examination and imaging. Exclusion criteria: Not reported. N total at baseline: N=78 Important prognostic factors[2]: *Mean age (range):* *60 (34-87)*	Describe intervention (treatment/procedure/test): Patients received transoral tumor resection and SLNB. Tumor depth was measured from the mucosal surface to the deepest point of infiltration. Tumor thickness was measured from drawing a parallel line to the virtual	Describe control (treatment/procedure/test): 1: ≥1mm 2: ≥2mm 3: ≥3mm 4: ≥4mm 5: ≥5mm 6: ≥6mm	Length of follow-up: None, the study seems to be cross-sectional. Loss-to-follow-up: NA Incomplete outcome data: NA	Outcome measures and effect size (include 95%CI and p-value if available): **Tumor depth:** Cut-off 1 mm for tumor depth: Sensitivity: 0.964 NPV: 0.75 Cut-off 2 mm for tumor depth: Sensitivity: 0.929 NPV: 0.75 Cut-off 3 mm for tumor depth: Sensitivity: 0.85.7	

		Sex: *52M / 26F* Tumor site, n: Tongue: 55 FOM: 23 T-stage, n: T1: 40 T2: 38 Lymphatic invasion, n: Yes: 10 No:68 Perineural invasion: Yes: 15 No: 63 Vascular invasion, n: Yes: 3 No: 75 Muscle invasion, n: Yes: 55 No: 23 Lymphoplasmacytic infiltration: Grade 1: 31 Grade 2: 41 Grade 3: 6 Mode of invasion, n: Grade 1: 11 Grade 2: 12 Grade 3: 25	mucosa (placed tangentially at the most exophytic tumor area) to the deepest point of infiltration. 1: <1mm 2: <2mm 3: <3mm 4: <4mm 5: <5mm 6: <6mm			NPV: 0.667 <u>Cut-off 4 mm for tumor depth:</u> Sensitivity: 0.643 NPV: 0.615 <u>Cut-off 5 mm for tumor depth:</u> Sensitivity: 0.607 NPV: 0.656 <u>Cut-off 6 mm for tumor depth:</u> Sensitivity: 0.464 NPV: 0.674 **Tumor thickness:** <u>Cut-off 1 mm for tumor thickness:</u> Sensitivity: 1.00 NPV: 1.00 <u>Cut-off 2 mm for tumor thickness:</u> Sensitivity: 1.00 NPV: 1.00 <u>Cut-off 3 mm for tumor thickness:</u> Sensitivity: 0.964 NPV: 0.80 <u>Cut-off 4 mm for tumor thickness:</u> Sensitivity: 0.786	

		Grade 4C: 16 Grade 4D: 14 Groups comparable at baseline?				NPV: 0.625 <u>Cut-off 5 mm for tumor thickness:</u> Sensitivity: 0.679 NPV: 0.625 <u>Cut-off 6 mm for tumor thickness:</u> Sensitivity: 0.53.6 NPV: 0.649	
Melchers 2012	Type of study: Observational, database Setting and country: Hospital, Netherlands Funding and conflicts of interest: Funding not reported. The authors declare that there are no conflicts of interest.	<u>Inclusion criteria</u>: Oral primary tumor location, histologically proven SCC, treated by resection of the primary tumor without prior head-neck or systemic oncological treatment, pT1-2 tumors, all clinicopathologic data regarding nodal status available. <u>Exclusion criteria</u>: Synchronous multiple tumors, irretrievable HE-slides, unreliable assessment of DOI. <u>N total at baseline</u>: N=212 <u>Important prognostic factors[2]</u>: *Median age (range): 61.5 (25-94*	Describe intervention (treatment/procedure/test): Patients were treated by excision for their primary oral tumor. 174 patients received a neck dissection (n=106 with cN0), while 38 patients received a watchful waiting-strategy. Clinical nodal stage was assessed with palpation combined with imaging (CT or MRI). PET or ultrasound may be performed on indication. Pathological N-stage was considered the 'true' N-stage after neck dissection. For patients in the watchful waiting-group, two years of	Describe control (treatment/procedure/test): 1: 1mm 2: 2mm 3: 3mm 4: 4mm 5: 4.49 mm 6: 5mm 7: 6mm 8: 7mm	<u>Length of follow-up</u>: At least 2 years (for watchful waiting) <u>Loss-to-follow-up</u>: NA <u>Incomplete outcome data</u>: NA, none other than the cases excluded from the sample	Outcome measures and effect size (include 95%CI and p-value if available): **Accuracy of neck dissection in cN0 (n=106)** <u>Cut-ff 1 mm for DOI:</u> Sensitivity: 1.00 NPV: 1.00 <u>Cut-ff 2 mm for DOI:</u> Sensitivity: 0.944 NPV: 0.938 <u>Cut-ff 3 mm for DOI:</u> Sensitivity: 0.889 NPV: 0.939 <u>Cut-ff 4 mm for DOI:</u> Sensitivity: 0.833 NPV: 0.94.3 <u>Cut-ff 4.59 mm for DOI:</u> Sensitivity: 0.833	For the accuracy analyses, only cases with clinical negative neck nodes were used.

		Sex: *119 M / 93 F* Tumor site, n: Tongue: 108 Gum: 15 FOM: 64 Cheek mucosa: 7 Retromolar area: 12 Other: 6 pT-stage, n: pT1: 123 pT2: 89 Groups comparable at baseline?	follow-up were examined for the development of nodal metastases. Watchful waiting consisted of return visits every 6 weeks. Infiltration depth was measured as the maximum tumor infiltration below the mucosal surface. (mucosal surface was reconstructed for ulcerated or exophytic tumors) 1: 1mm 2: 2mm 3: 3mm 4: 4mm 5: 4.49 mm 6: 5mm 7: 6mm 8: 7mm			NPV: 0.948 <u>Cut-ff 5 mm for DOI:</u> Sensitivity: 0.722 NPV: 0.918 <u>Cut-ff 6 mm for DOI:</u> Sensitivity: 0.667 NPV: 0.915 <u>Cut-ff 7 mm for DOI:</u> Sensitivity: 0.5 NPV: 0.889 **Accuracy of watchful waiting in cN0 (n=38)** <u>Cut-ff 1 mm for DOI:</u> Sensitivity: 1.00 NPV: 1.00 <u>Cut-ff 2 mm for DOI:</u> Sensitivity: 0.857 NPV: 0.857 <u>Cut-ff 3 mm for DOI:</u> Sensitivity: 0.714 NPV: 0.889 <u>Cut-ff 4 mm for DOI:</u> Sensitivity: 0.714 NPV: 0.923 <u>Cut-ff 4.59 mm for DOI:</u> Sensitivity: 0.714 NPV: 0.923	

						Cut-ff 5 mm for DOI: Sensitivity: 0.571 NPV: 0.889 Cut-ff 6 mm for DOI: Sensitivity: 0.571 NPV: 0.897 Cut-ff 3 mm for DOI: Sensitivity: 0.571 NPV: 0.906	
Sahoo 2020	Type of study: Observational, database Setting and country: Institute of dental sciences and a diagnostics center, India Funding and conflicts of interest: Funding not reported. The authors declare that there are no conflicts of interest	Inclusion criteria: histologically-proven oral SCC, patients >35 years, treated with wide excision of the primary tumor, treated with END Exclusion criteria: Metastatic tumor, recurrent tumors in the oral cavity, immune-compromised diseases and tumors, tumors under treatment of chemotherapy or radiotherapy. N total at baseline: N=150 Important prognostic factors[2]: *Age, n:* *>60y: 40* *<60y: 110*	Describe intervention (treatment/procedure/test): Patients received excision for the primary tumor and underwent elective neck dissection. Tumor thickness was measured from the level of adjacent normal mucosa to the deepest point of invasion without superficial keratin or inflammatory debris. Depth of invasion was measured from the bottom of the most adjacent dysplastic abnormal rete ridge to the deepest point of invasion.	Describe control (treatment/procedure/test): Tumor thickness: <8.64mm DOI: <7.64mm	Length of follow-up: unclear Loss-to-follow-up: NA Incomplete outcome data: N=14 incomplete for tumor thickness measurements N=27 incomplete for DOI measurements	Outcome measures and effect size (include 95%CI and p-value if available): Accuracy of END, tumor thickness at 8.64mm cut-off (n=136): Sensitivity: 0.72 (95%CI: 0.575-0.838) Accuracy of END, DOI at 7.64mm cut-off (n=123): Sensitivity: 0.727 (95%CI: 0.572-0.85)	

		Sex: *99M / 51F* *Tumor site, n:* *GB sulcus: 113* *Tongue: 29* *FOM: 2* *Retromolar area: 4* *Maxilla: 2* *cT-stage, n:* *cT1: 27* *cT2: 41* *Note: unclear why there was missing data* *Tumor differentiation, n:* *Well: 87* *Moderate: 60* *Poor: 3* *Lymphovscylar invasion, n:* *Yes: 35* *No: 115* *Perineural invasion, n:* *Yes: 41* *No: 109* Groups comparable at baseline?	Tumor thickness: >8.64mm DOI: >7.64mm				

Van Lanschot 2020	Type of study: Observational, database Setting and country: Hospital, Netherlands Funding and conflicts of interest: work was supported by ATOS Medical B.V. (provided financial support for PhD student, no role in the study design). The authors declare there were no competing financial interests.	Inclusion criteria: pT1-2 primary oral SCC Exclusion criteria: Synchronous multiple tumors, patients with clinically positive neck nodes N total at baseline: N=300 (n=173 END, 127 WW) Important prognostic factors[2]: *Media age (range): 66.5 (24-94)* *Sex:* *158M / 142F* *Smoking, n:* *Active: 113* *Quit smoking: 89* *Non-smokers: 65* *Alcohol, n:* *Active: 163* *Quit: 12* *Non-consumer: 85* *pT (tnm7),n:* *T1: 197* *T2: 90* *pT (tnm8), n:* *T1: 5*	Describe intervention (treatment/procedure/test): Patients were surgically treated. END was performed when DOI was ≥4mm. patient staged as cN0 wit DOI <4mm received a watch and wait strategy (5-year follow-up with physical examinations and regular ultrasound of the neck in the first 2 years).. DOI measurement was taken from the basement membrane of the closest adjacent normal mucosa to the deepest point of infiltration. 1: <1mm 2: <2mm 3: <3mm 4: <4mm	Describe control (treatment/procedure/test): 1: 1mm 2: 2mm 3: 3mm 4: 4mm 5: 5mm 6: 6mm	Length of follow-up: Mean follow-up: 23.4 months(range 0-62) Loss-to-follow-up: NA Incomplete outcome data: NA	Outcome measures and effect size (include 95%CI and p-value if available): **Accuracy of DOI (END+WW)** 1mm cut-off for DOI, predicting lymph node metastases: N (<1mm): 10 N (≥1mm): 290 Sensitivity: 1.00 NPV: 1.00 2mm cut-off for DOI, predicting lymph node metastases: N (<2mm): 54 N (≥2mm): 246 Sensitivity: 1.00 NPV:1.00 3mm cut-off for DOI, predicting lymph node metastases: N (<3mm): 93 N (≥3mm): 207 Sensitivity: 0.951 NPV: 0.978 4mm cut-off for DOI, predicting lymph node metastases: N (<4mm): 139 N (≥4mm): 161 Sensitivity: 0.951	

		T2: 8 Tumor site, n: Tongue: 162 FOM: 77 Buccal mucosa: 27 Lower alveolus and gingiva: 12 Upper alveolus and gingiva: 7 Lip: 7 Retromolar area: 5 Hard palate: 3 Infiltrative growth, n: 179 Vasoinvasion, n: 28 Perineural invasion, n: 52 Groups comparable at baseline?	5: <5mm 6: <6mm			NPV: 0.986 <u>5mm cut-off for DOI, predicting lymph node metastases:</u> N (<5mm): 171 N (≥5mm): 129 Sensitivity: 0.878 NPV: 0.971 <u>6mm cut-off for DOI, predicting lymph node metastases:</u> N (<6mm): 190 N (≥6mm): 110 Sensitivity: 0.805 NPV: 0.958	
Warburton 2007	Type of study: Observational, database Setting and country: Hospital, USA Funding and conflicts of interest: Supported by the ivision of	<u>Inclusion criteria</u>: Early stage (T1-2N0M0) tongue or floor of mouth carcinomas, treated by primary tumor resection without neck dissection or neck irradioation. <u>Exclusion criteria</u>: Lack of tumor tissue in the archived tissue	Describe intervention (treatment/procedure/test): Treated by primary tumor resection without neckdissection or irradiation. Tumor thickness was measured from the surface	Describe control (treatment/procedure/test): Tumor thickness 1: ≤1.5mm 2: ≤1.6 mm 3: ≤2.0mm 4: ≤2.2mm 5: ≤2.7mm 6: ≤3.0mm 7: ≤3.8mm	<u>Length of follow-up</u>: Unclear <u>Loss-to-follow-up</u>: NA <u>Incomplete outcome data</u>: none	Outcome measures and effect size (include 95%CI and p-value if available): **Accuracy of tumor thickness cut-offs** <u>>1.5mm versus ≤1.5mm tumor thickness:</u> TP: 8 FP: 10 FN: 0	NPV was calculated from the reported data

	Intramural Researchm National Institute of Dental and Craniofacial Research, National Institutes of Health. Conflicts of interest were not declared in the manuscript.	<u>N total at baseline</u>: N=27 <u>Important prognostic factors[2]</u>: *Mean age (range):* *64 (39-86)* *Sex:* *18 M / 9F* Alcohol use, n: Yes: 15 No: 11 Tumor location, n: FOM: 15 Tongue: 12 T-stage, n: T1: 19 T2: 8 Groups comparable at baseline?	of the epithelium to the deepest invading tumor island or cell using a reconstructed line (including the thickness lost due to ulceration) while excluding exophytic components. Tumor thickness 1: >1.5mm 2: >1.6 mm 3: >2.0mm 4: >2.2mm 5: >2.7mm 6: >3.0mm 7: >3.8mm			TN: 9 Sensitivity: 1.00 NPV: 1.00 <u>>1.6mm versus ≤1.6mm tumor thickness:</u> TP: 8 FP: 8 FN: 0 TN: 11 Sensitivity: 1.00 NPV: 1.00 <u>>2mm versus ≤2mm tumor thickness:</u> TP: 7 FP: 5 FN: 1 TN: 14 Sensitivity: 0.875 NPV: 0.933 <u>>2.2mm versus ≤2.2mm tumor thickness:</u> TP: 7 FP: 4 FN: 1 TN: 15 Sensitivity: 0.875 NPV: 0.938 <u>>2.7mm versus ≤2.7mm tumor thickness:</u> TP: 6 FP: 3 FN: 2 TN: 16	

						Sensitivity: 0.75 NPV: 0.889 <u>>3.0mm versus ≤3.0 mm tumor thickness:</u> TP: 4 FP: 1 FN: 4 TN: 18 Sensitivity: 0.5 NPV: 0.818 <u>>3.8mm versus ≤3.8mm tumor thickness:</u> TP: 3 FP: 1 FN: 5 TN: 18 Sensitivity: 0.375 NPV: 0.783	
Wu 2019	Type of study: Observational Setting and country: Hospital, China Funding and conflicts of interest:	<u>Inclusion criteria</u>: Pathologically confirmed tongue SCC (biopsy), T1-2 tumors, no cervical lymph node relapse (N0) <u>Exclusion criteria</u>: Not described. <u>N total at baseline</u>: N=141 <u>Important prognostic factors[2]</u>: *Age, n:* *<55y: 59*	Describe intervention (treatment/procedure/test): Neck dissection and observation-strategy were randomly assigned. For observation: patients were examined for cervical lymph nodes every 3 months (first 24	Describe control (treatment/procedure/test): 1: <4mm	<u>Length of follow-up</u>: Maximum of 60 months (observation) <u>Loss-to-follow-up</u>: None described <u>Incomplete outcome data</u>: None described	Outcome measures and effect size (include 95%CI and p-value if available): Multivariable analysis of DOI **Risk of nodal metastases with DOI, multivariable model, <4mm(ref) versus ≥4mm:** N (<4mm): 43 N (≥4mm): 98 Adjusted OR: 12.23 (95%CI: 1.31-113.90)	No radiotherapy or chemotherapy had been provided before the collection of tumor samples

		≥55: 82 *Average age = 55 years* *Sex:* *75M / 66F* *Tumor differentiation, n:* *Well: 48* *Moderate /poor: 93* *Neurovascular invasion, n:* *Yes: 18* *No: 123* *Tumor location, n:* *Anterior: 14* *Middle: 103* *Back: 24* *T-stage, n:* *T1: 60* *T2: 81* *Smoking, n:* *Yes: 59* *No: 82* *Drinking, n:* *Yes: 52* *No: 89* *Treatment, n:* *Neck dissection: 69* *Observation: 72*	months), then every 6 months (for the following 36 months). Examination consisted of physical inspection and CT or MRI. Nodal relapses were pathologically proven. Unclear how DOI was measured. 1: ≥4mm			Other variables in the model: gender, age, mode of invasion, pathological differentiation, neurovascular invasion, location, T-stage, smoking, drinking, treatment	

		Groups comparable at baseline?					
Xu 2020	Type of study: Observational, database Setting and country: Hospital, China Funding and conflicts of interest: Funding not reported. Authors declare that there were no conflicts of interest.	Inclusion criteria: ≥18 years old, primary tongue SCC, cT1N0M0 carcinoma according to TNM 7, MRI data was available, follow-up data was available. Exclusion criteria: Not reported N total at baseline: N=151 Important prognostic factors[2]: *Mean age (range):* *57.1 (30-78)* *Smoker, n:* *Yes: 101* *No: 50* *Alcohol users, n:* *Yes: 61* *No: 90* *Perineural invasion, n:* *Yes: 23* *No:128* *Lymphovascular invasion:* *Yes: 19* *No: 131*	Describe intervention (treatment/procedure/test): MRI DOI was measured as the vertical distance between the deepest point of tumor infiltration and the simulated normal mucosal junction. DOI was determined by at least two radiologists. Pathological DOI was measured from the level of adjacent normal mucosa to the deepest point of tumor infiltration. Patients with very early stage disease did not undergo neck dissection. Elective neck dissection was	Describe control (treatment/procedure/test): 1: ≥7.5mm (MRI) 2: >5mm (path)	Length of follow-up: Mean: 70.4 months (range: 8-103) Loss-to-follow-up: NA Incomplete outcome data: NA	Outcome measures and effect size (include 95%CI and p-value if available): **Risk of nodal metastases with MRI-measured DOI, multivariable model, <7.5mm versus ≥7.5mm(ref):** N (<7.5mm): 38 N (≥7.5mm): 113 Adjusted OR: 2.978 (95%CI: 1.574-7.332) Other variables in the model: lymphovascular invasion, pathologic tumor grade, pathologic DOI **Risk of nodal metastases with pathology measured DOI, multivariable model, ≤5mm versus >5mm(ref):** N (≤5mm): 108 N (>5mm): 43 Adjusted OR: 3.112 (95%CI: 1.812-9.668) Other variables in the model: lymphovascular invasion, pathologic	

		Growth pattern: *Ulcer: 72* *Invasive: 20* *Exogenous: 59* *Sex:* *111 M / 40F* Groups comparable at baseline?	routine for other stages. After therapy, the patients were examined every 3 months during the first 12 months, every 6 months during the following 12 months, and once yearly thereafter. Biopsy was performed when in suspicion of disease recurrence. 1: <7.5mm (MRI) 2: ≤5mm (path)			tumor grade, MRI-measured DOI	
Yeh 2014	Type of study: Observational Setting and country: Hospital, Taiwan Funding and conflicts of interest: Funding not stated in the manuscript. Authors declare there were no CoI	Inclusion criteria: Newly diagnosed T1-2 cN0 oral SCC, curative surgery Exclusion criteria: Previous cancer (unless disease-free >2 years). N total at baseline: N=272 (n=253 after excluding n=19 patients who received observation) Important prognostic factors[2]:	Describe intervention (treatment/procedure/test): cN0 status was determined by clinical examination and imaging (including CT or MRI). Patients received END or observation	Describe control (treatment/procedure/test): 1: >6mm	Length of follow-up: 2 year Loss-to-follow-up: Not described. Incomplete outcome data: n=19 patients who received observation Reason: postoperative adjuvant therapy (n=7), local	Outcome measures and effect size (include 95%CI and p-value if available): Accuracy of 0-6mm versus >6mm cut-off point for END+observation as one group: TP: 30 FP: 88 FN: 25 TN: 111 Sensitivity: 0.545 Negative predictive value: 0.815	Sensitivity was calculated from the presented data

		pT-stage, n: *pT1: 128* *pT2: 125* *Tumor differentiation, n:* *Well: 171* *Moderate/poor: 82* Treatment, n: Neck dissection: 176 Observation: 77 Groups comparable at baseline?	pN+ was the pathological diagnosis of lymph node metastasis in the END group, or recurrence within 2 years without antecedent or synchronous local recurrence in the observation group. Tumor thickness was measured vertically from the tumor surface or ulcer base to the deepest point of invasion on serial sections. 1: 0-6mm		recurrence before neck recurrence (n=1), short follow-up period: <2 years (n=11).		
Zhang 2014	Type of study: Observational Setting and country: hospital, USA Funding and conflicts of interest:	<u>Inclusion criteria</u>: Biopsy proven cT1N0M0 SCC of the tongue, primary treatment with surgery, no previous treatment, staging of the neck with palpation and contrast enhanced CT, no other malignancies In the head and neck during treatment of tongue	Describe intervention (treatment/procedure/test): Patients received observation if the tumor depth was <3 mm on biopsy. Patients received selective neck dissection when tumor depth was	Describe control (treatment/procedure/test): 1: 2mm 2: 3mm 3: 4mm 4: 5mm	<u>Length of follow-up</u>: Mean: 56.8 months (range: 4-148) <u>Loss-to-follow-up</u>: None other than due to death (see survival rates) <u>Incomplete outcome data</u>:	Outcome measures and effect size (include 95%CI and p-value if available): **Accuracy of tumor depth (WW/delayed ND/ND)** <u>2mm cut-off for tumor depth, predicting lymph node metastases:</u> Sensitivity: 1.00	

		SCC, sufficient data recorded. Exclusion criteria: Carcinoma in situ, verrucous carcinoma, base of tongue carcinoma N total at baseline: N=65 Important prognostic factors[2]: *Mean age (range):* *60.7 (24-91)* *Sex:* *32M / 33F* Smoking: Yes: 19 No: 46 Non-drinkers / social drinkers: 50 Tumor location, n: Dorsal: 2 Lateral: 54 Ventral: 9 Tumor differentiation, n: Well: 37 Moderate: 18 Poor: 5	≥3mm on biopsy. When pathologic tumor depth was ≥3mm after the biopsy tumor depth was <3mm, delayed neck dissection was recommended within 4-6 weeks. Pathological tumor depth was measured from the level of the adjacent normal mucosa to the deepest point of invasion in to the tongue. 1: 2mm 2: 3mm 3: 4mm 4: 5mm		None.	3mm cut-off for tumor depth, predicting lymph node metastases: Sensitivity: 0.929 4mm cut-off for tumor depth, predicting lymph node metastases: Sensitivity: 0.78.6 5mm cut-off for tumor depth, predicting lymph node metastases: Sensitivity: 0.643	

		Unknown: 5 Perineural invasion, n: Yes: 4 No: 58 Groups comparable at baseline?					

95%CI: 95% Betrouwbaarheidsinterval (confidence interval), cN-stage: Klinisch nodaal stadium (clinical N-stage), CoI: Conflicts of Interest, cT-stage: Klinisch tumor stadium (clinical T-stage), DOI: Invasiediepte (depth of invasion), END: Electieve halsdissectie (Elective neck dissection), F: Vrouw (female), FN: fout negatief, FOM: Floor of Mouth, FP: fout positief, GB: Gingivobuccal, M: Man, mm: Millimeters, MRI: Magnetic Resonance Imaging, N-stage: Lymfeklier stadium (Node), n: aantal deelnemers, NA: Niet beschikbaar (not available), NPV: Negatief voorspellende waarde (Negative predictive value), OR: Odds ratio, pN-stage: Pathologisch lymfeklier stadium (pathologic N-stage), pT-stage: Pathologisch tumor stadium (pathologic T-stage), SCC: Plaveiselcel carcinoom (squamous cell carcinoma), SD: Standard deviatie, T-stage: Tumor stadium (uit de TNM stadiëring), TN: terecht negatief, TP: terecht positief, WW: Watchful waiting/Watch and wait, y: years

Notes:

1. **Prognostic balance between treatment groups is usually guaranteed in randomized studies, but non-randomized (observational) studies require matching of patients between treatment groups (case-control studies) or multivariate adjustment for prognostic factors (confounders) (cohort studies); the evidence table should contain sufficient details on these procedures.**
2. **Provide data per treatment group on the most important prognostic factors ((potential) confounders).**
3. **For case-control studies, provide sufficient detail on the procedure used to match cases and controls.**
4. **For cohort studies, provide sufficient detail on the (multivariate) analyses used to adjust for (potential) confounders.**

Risk of bias table for intervention studies (observational: non-randomized clinical trials, cohort and case-control studies)

Table of quality assessment - prognostic factor (PF) studies

Based on: QUIPS[A] (Haydn, 2006; Haydn 2013)

Research question:

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

	(high/moderate/low risk of selection bias)	(high/moderate/low risk of attrition bias)	(high/moderate/low risk of measurement bias related to PF)	(high/moderate/low risk of measurement bias related to outcome)	(high/moderate/low risk of bias due to confounding)	(high/moderate/low risk of bias due to statistical analysis)
Faisal 2018	Unclear	Low	Low	Unclear	High, stepwise regression method excluded non-significant predictors from the model. There are probably uncontrolled confounders.	low
Wu 2019	Low	Low	Unclear	Unclear	Unclear, confounders were not predefined. Nonetheless all variables seemed to be remained in the model (even when non-significant). There might be residual confounding.	Low
Xu 2020	Low	Low	Low	Unclear	High, it seems that non-significant variables were excluded, instead of adding and keeping plausible confounders in the model. There are probably uncontrolled confounders.	Low

[A] https://methods.cochrane.org/sites/methods.cochrane.org.prognosis/files/public/uploads/QUIPS%20tool.pdf

[1] Adequate description of: source population or population of interest, sampling and recruitment, period and place of recruitment, in- and exclusion criteria, study participation, baseline characteristics.

[2] Adequate response rate, information on drop-outs and loss to follow-up, no differences between participants who completed the study and those lost to follow-up.

[3] Method of measurement is valid, reliable, setting of measurement is the same for all participants.

[4] Important confounders are listed (including treatments), method of measurement is valid, reliable, setting of measurement is the same for all participants, important confounders are accounted for in the design (matching, stratification, initial assembly of comparable groups), or analysis (appropriate adjustment)

[5] Enough data are presented to assess adequacy of the analysis, strategy of model building is appropriate and based on conceptual framework, no selective reporting.

Risk of bias assessment diagnostic accuracy studies (QUADAS II, 2011)

Research question:

Study reference	Patient selection	Index test	Reference standard	Flow and timing	Comments with respect to applicability
Den Toom 2019	Was a consecutive or random sample of patients enrolled? Unclear Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Unclear	Were the index test results interpreted without knowledge of the results of the reference standard? Yes If a threshold was used, was it pre-specified? Probably yes	Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unclear	Was there an appropriate interval between index test(s) and reference standard? Yes Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Yes Were all patients included in the analysis? Yes	Are there concerns that the included patients do not match the review question? No Are there concerns that the index test, its conduct, or interpretation differ from the review question? No Are there concerns that the target condition as defined by the reference standard does not match the review question? No
	CONCLUSION: Could the selection of patients have introduced bias? **RISK: UNCLEAR**	CONCLUSION: Could the conduct or interpretation of the index test have introduced bias? **RISK: LOW**	CONCLUSION: Could the reference standard, its conduct, or its interpretation have introduced bias? After discussion with the working group we decided that there was a low risk. **RISK: LOW**	CONCLUSION Could the patient flow have introduced bias? **RISK: LOW /HIGH/UNCLEAR**	
Goerkem, 2010;	Was a consecutive or random sample of patients enrolled? Unclear Was a case-control design avoided? Yes	Were the index test results interpreted without knowledge of the results of the reference standard? Yes If a threshold was used, was it pre-specified?	Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without	Was there an appropriate interval between index test(s) and reference standard? Yes Did all patients receive a reference standard? Yes	Are there concerns that the included patients do not match the review question? No Are there concerns that the index test, its conduct, or

	Did the study avoid inappropriate exclusions? Unclear	Probably yes	knowledge of the results of the index test? Unclear	Did patients receive the same reference standard? Yes Were all patients included in the analysis? Yes	interpretation differ from the review question? No Are there concerns that the target condition as defined by the reference standard does not match the review question? No
	CONCLUSION: Could the selection of patients have introduced bias? Unclear. **RISK: UNCLEAR**	CONCLUSION: Could the conduct or interpretation of the index test have introduced bias? **RISK: LOW**	CONCLUSION: Could the reference standard, its conduct, or its interpretation have introduced bias? After discussion with the working group we decided that there was a low risk. **RISK: LOW**	CONCLUSION Could the patient flow have introduced bias? **RISK: LOW**	
Melchers, 2012;	Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes	Were the index test results interpreted without knowledge of the results of the reference standard? Yes If a threshold was used, was it pre-specified? Probably yes (although a ROC was used to select 1 specific cut-off as well)	Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unclear	Was there an appropriate interval between index test(s) and reference standard? Yes Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Yes (two groups, separately reported) Were all patients included in the analysis? Yes	Are there concerns that the included patients do not match the review question? No Are there concerns that the index test, its conduct, or interpretation differ from the review question? No Are there concerns that the target condition as defined by the reference standard does not match the review question? No
	CONCLUSION:	CONCLUSION:	CONCLUSION:	CONCLUSION	

	Could the selection of patients have introduced bias? **RISK: LOW**	Could the conduct or interpretation of the index test have introduced bias? **RISK: LOW**	Could the reference standard, its conduct, or its interpretation have introduced bias? After discussion with the working group we decided that there was a low risk. **RISK: LOW**	Could the patient flow have introduced bias? **RISK: LOW**	
Sahoo, 2020	Was a consecutive or random sample of patients enrolled? Unclear Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? No (persons <35 years old were not included)	Were the index test results interpreted without knowledge of the results of the reference standard? Yes If a threshold was used, was it pre-specified? No	Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unclear	Was there an appropriate interval between index test(s) and reference standard? Yes Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Yes Were all patients included in the analysis? Unclear	<u>Are there concerns that the included patients do not match the review question?</u> No <u>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</u> No <u>Are there concerns that the target condition as defined by the reference standard does not match the review question?</u> No
	CONCLUSION: Could the selection of patients have introduced bias? **RISK: HIGH**	CONCLUSION: Could the conduct or interpretation of the index test have introduced bias? **RISK: HIGH**	CONCLUSION: Could the reference standard, its conduct, or its interpretation have introduced bias? After discussion with the working group we decided that there was a low risk. **RISK: LOW**	CONCLUSION Could the patient flow have introduced bias? **RISK: LOW**	
Van Lanschot, 2020;	Was a consecutive or random sample of patients enrolled? Yes	Were the index test results interpreted without knowledge of the results of the reference standard?	Is the reference standard likely to correctly classify the target condition? Yes	Was there an appropriate interval between index test(s) and reference standard? Yes	<u>Are there concerns that the included patients do not match the review question?</u> No

	Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes	Yes If a threshold was used, was it pre-specified? Probably yes	Were the reference standard results interpreted without knowledge of the results of the index test? Unclear	Did all patients receive a reference standard? Yes Did patients receive the same reference standard? No (WW/ND) Were all patients included in the analysis? Unclear (probably eys)	Are there concerns that the index test, its conduct, or interpretation differ from the review question? No Are there concerns that the target condition as defined by the reference standard does not match the review question? No
	CONCLUSION: Could the selection of patients have introduced bias? **RISK: LOW**	CONCLUSION: Could the conduct or interpretation of the index test have introduced bias? **RISK: LOW**	CONCLUSION: Could the reference standard, its conduct, or its interpretation have introduced bias? After discussion with the working group we decided that there was a low risk. **RISK: LOW**	CONCLUSION Could the patient flow have introduced bias? Two different reference standards were used. **RISK: HIGH**	
Warburton, 2007;	Was a consecutive or random sample of patients enrolled? Unclear Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Unclear	Were the index test results interpreted without knowledge of the results of the reference standard? Yes If a threshold was used, was it pre-specified? Unclear	Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unclear	Was there an appropriate interval between index test(s) and reference standard? Yes Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Yes Were all patients included in the analysis? Unclear (probably yes)	Are there concerns that the included patients do not match the review question? No Are there concerns that the index test, its conduct, or interpretation differ from the review question? No Are there concerns that the target condition as defined by the reference standard does not match the review question? No

	CONCLUSION: Could the selection of patients have introduced bias? **RISK: UNCLEAR**	CONCLUSION: Could the conduct or interpretation of the index test have introduced bias? **RISK: LOW /HIGH/UNCLEAR**	CONCLUSION: Could the reference standard, its conduct, or its interpretation have introduced bias? After discussion with the working group we decided that there was a low risk. **RISK: LOW**	CONCLUSION Could the patient flow have introduced bias? **RISK: LOW**	
Yeh, 2014	Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes	Were the index test results interpreted without knowledge of the results of the reference standard? Yes If a threshold was used, was it pre-specified? Unclear	Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unclear	Was there an appropriate interval between index test(s) and reference standard? Yes Did all patients receive a reference standard? Yes Did patients receive the same reference standard? No (ND/WW) Were all patients included in the analysis? Yes	Are there concerns that the included patients do not match the review question? No Are there concerns that the index test, its conduct, or interpretation differ from the review question? No Are there concerns that the target condition as defined by the reference standard does not match the review question? No
	CONCLUSION: Could the selection of patients have introduced bias? **RISK: LOW**	CONCLUSION: Could the conduct or interpretation of the index test have introduced bias? **RISK: UNCLEAR**	CONCLUSION: Could the reference standard, its conduct, or its interpretation have introduced bias? After discussion with the working group we decided that there was a low risk. **RISK: LOW**	CONCLUSION Could the patient flow have introduced bias? **RISK: HIGH**	
Zhang, 2014	Was a consecutive or random sample of patients enrolled? Yes	Were the index test results interpreted without knowledge	Is the reference standard likely to correctly classify the target condition?	Was there an appropriate interval between index test(s) and reference standard?	Are there concerns that the included patients do not match the review question?

	Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Unclear	of the results of the reference standard? Yes If a threshold was used, was it pre-specified? Probably yes	Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unclear	Yes Did all patients receive a reference standard? Yes/No/Unclear Did patients receive the same reference standard? No (ND/WW) Were all patients included in the analysis? Unclear (probably yes)	No <u>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</u> No <u>Are there concerns that the target condition as defined by the reference standard does not match the review question?</u> No
	CONCLUSION: Could the selection of patients have introduced bias? **RISK: UNCLEAR**	CONCLUSION: Could the conduct or interpretation of the index test have introduced bias? **RISK: LOW**	CONCLUSION: Could the reference standard, its conduct, or its interpretation have introduced bias? After discussion with the working group we decided that there was a low risk. **RISK: LOW**	CONCLUSION Could the patient flow have introduced bias? **RISK: HIGH**	

Judgments on risk of bias are dependent on the research question: some items are more likely to introduce bias than others, and may be given more weight in the final conclusion on the overall risk of bias per domain:

Patient selection:

- **Consecutive or random sample has a low risk to introduce bias.**
- **A case control design is very likely to overestimate accuracy and thus introduce bias.**
- **Inappropriate exclusion is likely to introduce bias.**

Index test:

- **This item is similar to "blinding" in intervention studies. The potential for bias is related to the subjectivity of index test interpretation and the order of testing.**
- **Selecting the test threshold to optimise sensitivity and/or specificity may lead to overoptimistic estimates of test performance and introduce bias.**

Reference standard:

- **When the reference standard is not 100% sensitive and 100% specific, disagreements between the index test and reference standard may be incorrect, which increases the risk of bias.**
- **This item is similar to "blinding" in intervention studies. The potential for bias is related to the subjectivity of index test interpretation and the order of testing.**

Flow and timing:

- **If there is a delay or if treatment is started between index test and reference standard, misclassification may occur due to recovery or deterioration of the condition, which increases the risk of bias.**
- **If the results of the index test influence the decision on whether to perform the reference standard or which reference standard is used, estimated diagnostic accuracy may be biased.**
- **All patients who were recruited into the study should be included in the analysis, if not, the risk of bias is increased.**

Judgement on applicability:
Patient selection: there may be concerns regarding applicability if patients included in the study differ from those targeted by the review question, in terms of severity of the target condition, demographic features, presence of differential diagnosis or co-morbidity, setting of the study and previous testing protocols.
Index test: if index tests methods differ from those specified in the review question there may be concerns regarding applicability.
Reference standard: the reference standard may be free of bias but the target condition that it defines may differ from the target condition specified in the review question.

Table of excluded studies

Authors	Year	Reason for exclusion
Ahmed, S. Q. and Junaid, M. and Awan, S. and Kazi, M. and Khan, H. U. and Halim, S.	2018	risk was not adjusted
Al-Rajhi, N. and Khafaga, Y. and El-Husseiny, J. and Saleem, M. and Mourad, W. and Al-Otieschan, A. and Al-Amro, A.	2000	sample consists of oral and oropharynxcarcinomas
Alkureishi, Lee W. T. and Ross, Gary L. and Shoaib, Taimur and Soutar, David S. and Robertson, A. G. and Sorensen, Jens A. and Thomsen, Jorn and Krogdahl, Annelise and Alvarez, Julio and Barbier, Luis and Santamaria, Joseba and Poli, Tito and Sesenna, Enrico and Kovacs, Adorjan F. and Grunwald, Frank and Barzan, Luigi and Sulfaro, Sandro and Alberti, Franco	2008	risk was not adjusted
Bier-Laning, Carol M. and Durazo-Arvizu, Ramon and Muzaffar, Kamil and Petruzzelli, Guy J.	2009	does not report the outcomes of interest per millimeter DOI/tumor thickness for the outcomes of interest
Brockhoff, H. C. and Kim, R. Y. and Braun, T. M. and Skouteris, C. and Helman, J. I. and Ward, B. B.	2017	Unclear whether patient initially presenting positive nodes were excluded or whether they had previously undetected nodes. (Zie tekst voor model C (tumor size en DOI), zie tabel 6 voor accuracy per mm)
Chandler, K. and Vance, C. and Budnick, S. and Muller, S.	2011	Unclear what surgical procedures were given (or whether observation strategy was provided)
Chen, Y. W. and Yu, E. H. and Wu, T. H. and Lo, W. L. and Li, W. Y. and Kao, S. Y.	2008	risk was not adjusted
De Silva, R. K. and Siriwardena, B. S. M. S. and Samaranayaka, A. and Abeyasinghe, W. A. M. U. L. and Tilakaratne, W. M.	2018	Not stated in the selection criteria that the sample must have had a cN0 neck at presentation
Dik, E. A. and Willems, S. M. and Ipenburg, N. A. and Rosenberg, A. J. W. P. and Van Cann, E. M. and van Es, R. J. J.	2016	does not report the outcomes of interest per millimeter DOI/tumor thickness for the outcomes of interest
Ettl, Tobias and Irga, Serkan and Muller, Steffen and Rohrmeier, Christian and Reichert, Torsten E. and Schreml, Stephan and Gosau, Martin	2014	concerns resection margin instead of infoltration depth/tumorthickness
Feng, Z. and Cheng, A. and Alzahrani, S. and Li, B. and Han, Z. and Ward, B. B.	2020	Results reported in the text concern univariable analyses (See table 3)
Hakeem, Arsheed Hussain and Pradhan, Sultan Ahmed and Kannan, Rajan and Tubachi, Jagadish	2016	risk was not adjusted
Huang, C. and Zhuang, S. M. and Li, J. J. and Chen, S. W. and Zhang, X. W. and Song, M.	2017	Unadjusted results
Huang, C. and Zhuang, S. M. and Li, J. J. and Chen, S. W. and Zhang, X. W. and Song, M.	2017	risk was not adjusted
Imai, T. and Satoh, I. and Matsumoto, K. and Asada, Y. and Yamazaki, T. and Morita, S. and Saijo, S. and Okubo, J. I. and Wakamori, S. and Saijo, S. and Matsuura, K.	2017	Unadjusted results
Imai, T. and Satoh, I. and Matsumoto, K. and Asada, Y. and Yamazaki, T. and Morita, S. and Saijo, S. and Okubo, J. I.	2017	risk was not adjusted

and Wakamori, S. and Saijo, S. and Matsuura, K.		
Jacob, T. E. and Malathi, N. and Rajan, S. T. and Augustine, D. and Manish, N. and Patil, S.	2016	tumor depth, not tumor thicknes/DOI
Jayasankaran, S. C. and Chelakkot, P. G. and Karippaliyil, M. and Thankappan, K. and Iyer, S. and Moorthy, S.	2017	does not report the outcomes of interest per millimeter DOI/tumor thickness for the outcomes of interest
Jin, W. L. and Ye, W. M. and Zheng, J. W. and Zhou, L. and Zhu, H. G. and Zhang, Z. Y. and Tian, J.	2008	does not report the outcomes of interest per millimeter DOI/tumor thickness for the outcomes of interest
Jing, Jie and Li, Longjiang and He, Wei and Sun, Gang	2006	Did not exclude patients presenting with positive neck nodes
Jung, J. and Cho, N. H. and Kim, J. and Choi, E. C. and Lee, S. Y. and Byeon, H. K. and Park, Y. M. and Yang, W. S. and Kim, S. H.	2009	risk was not adjusted
Kozak, M. M. and Shah, J. and Chen, M. and Schaberg, K. and von Eyben, R. and Chen, J. J. and Bui, T. and Kong, C. and Kaplan, M. and Divi, V. and Hara, W.	2019	risk was not adjusted, does not report the outcomes of interest per millimeter DOI/tumor thickness for the outcomes of interest in multivriable analysis
Kumar, Tarun and Patel, Mahesh D.	2013	risk was not adjusted
Kunzel, J. and Psychogios, G. and Koch, M. and Mantsopoulos, K. and Kapsreiter, M. and Iro, H.	2013	Unadjusted results
Kurokawa, H. and Yamashita, Y. and Takeda, S. and Zhang, M. and Fukuyama, H. and Takahashi, T.	2002	does not report the outcomes of interest per millimeter DOI/tumor thickness for the outcomes of interest
Li, Q. L. and Chen, F. J. and Zeng, Z. Y. and Yang, A. K. and Wu, Q. L. and Zhang, H. Z. and Wu, G. H. and Xu, G. P. and Guo, Z. M. and Zhang, Q.	2003	Article in Chinese
Lin, M. J. and Guiney, A. and Iseli, C. E. and Buchanan, M. and Iseli, T. A.	2011	Did not exclude patients presenting with positive neck nodes
Mair, M. D. and Shetty, R. and Nair, D. and Mathur, Y. and Nair, S. and Deshmukh, A. and Thiagarajan, S. and Pantvaidya, G. and Lashkar, S. and Prabhash, K. and Chaukar, D. and Pai, P. and Cruz, A. D. and Chaturvedi, P.	2018	Not all patients underwent radiology or histopathology to assess the nodal status of the neck at presentation: clinical or radiological detected metastases. From the article: "it is important to note that all patients did not underwent radiological examination for detection of occult metastasis as per our institute policy which would not insist for radiological neck assessment in early oral cancer unless essentially required"
Mark Taylor, S. and Drover, C. and MacEachern, R. and Bullock, M. and Hart, R. and Psooy, B. and Trites, J.	2010	risk was not adjusted
Mark Taylor, S. and Drover, C. and MacEachern, R. and Bullock, M. and Hart, R. and Psooy, B. and Trites, J.	2009	duplicate
Masood, M. M. and Farquhar, D. R. and Vanleer, J. P. and Patel, S. N. and Hackman, T. G.	2018	Did not exclude patients presenting with positive neck nodes
Mattalitti, S. F. O. and Kawazu, T. and Kawano, S. and Ikari, T. and Wada, H. and Yoshiura, K.	2017	does not report the outcomes of interest per millimeter DOI/tumor thickness for the outcomes of interest
Melchers, L. J. and Schuuring, E. and Van Dijk, B. A. C. and De Bock, G. H. and Witjes, M. J. H. and Van Der Laan, B. F. A. M. and Van Der Wal, J. E. and Roodenburg, J. L. N.	2012	duplicate

Melkane, A. E. and Mamelle, G. and Wycisk, G. and Temam, S. and Janot, F. and Casiraghi, O. and Lumbroso, J.	2012	does not report the outcomes of interest per millimeter DOI/tumor thickness for the outcomes of interest
Moe, J. and McHugh, J. B. and Udager, A. M. and Braun, T. M. and Helman, J. I. and Ward, B. B.	2019	does not report the outcomes of interest per millimeter DOI/tumor thickness
Morand, G. B. and Ikenberg, K. and Vital, D. G. and Cardona, I. and Moch, H. and Stoeckli, S. J. and Huber, G. F.	2019	Risk from DOI in the multivariable regression was continuous, risk from categorized DOI was not adjusted
Nair, A. V. and Meera, M. and Rajamma, B. M. and Anirudh, S. and Nazer, P. K. and Ramachandran, P. V.	2018	risk was not adjusted
Nayanar, Sangeetha Keloth and Tripathy, Jaya Prasad and Duraisamy, Karthickeyan and Babu, Sajith	2019	seems to be univariable, for the multivariable analysis it seems that only the risk scores were calculated/reported and not the model or per mm (or cutoff mm)
O'Brien, C. J. and Lauer, C. S. and Fredricks, S. and Clifford, A. R. and McNeil, E. B. and Bagia, J. S. and Koulmandas, C.	2003	Did not exclude patients presenting with positive neck nodes
Otsuru, M. and Ota, Y. and Yanamoto, S. and Okura, M. and Umeda, M. and Kirita, T. and Kurita, H. and Ueda, M. and Komori, T. and Yamakawa, N. and Kamata, T. and Hasegawa, T. and Shibahara, T. and Ohiro, Y. and Yamashita, Y. and Noguchi, K. and Noguchi, T. and Karakida, K. and Naito, H. and Aikawa, T. and Yamashita, T. and Kabata, D. and Shintani, A.	2019	does not report the outcomes of interest per millimeter DOI/tumor thickness for the outcomes of interest
Pentenero, M. and Gandolfo, S. and Carrozzo, M.	2005	not a systematic review
Prabu, N. P. and Swaranapriya and Sargunar, B. and Shamugapriyan and Mohan, R.	2017	does not report the outcomes of interest per millimeter DOI/tumor thickness for the outcomes of interest
Reddy, V. and Wadhwan, V. and Reddy, M. and Venkatesh, A.	2018	Figures and tables are not published on the journal's website and not printed in the fulltext PDF file
Seki, M. and Sano, T. and Yokoo, S. and Oyama, T.	2017	Did not exclude patients presenting with positive neck nodes
Sheahan, P. and O'Keane, C. and Sheahan, J. N. and O'Dwyer, T. P.	2003	logistic regression seems to be performed for composite outcomes ("occult metastases or outcome XYZ"), outcomes of the multiple regression do not seem to be reported besides a p-value
Shin, J. H. and Yoon, H. J. and Kim, S. M. and Lee, J. H. and Myoung, H.	2020	risk was not adjusted
Shin, Jung-Hyun and Yoon, Hye-Jung and Kim, Soung-Min and Lee, Jong-Ho and Myoung, Hoon	2020	Unadjusted results
Sparano, A. and Weinstein, G. and Chalian, A. and Yodul, M. and Weber, R.	2004	multivariable model uses TT as a continuous variable (no dichotomization/cut-off was used)
Subramaniam, N. and Balasubramanian, D. and Low, T. H. H. and Murthy, S. and Anand, A. and Prasad, C. and Vijayan, S. N. and Thankappan, K. and Iyer, S.	2018	does not report the outcomes of interest per millimeter DOI/tumor thickness for the outcomes of interest
Subramaniam, N. and Balasubramanian, D. and Murthy, S. and Kumar, N. and Vidhyadharan, S. and Vijayan, S. N. and Nambiar, A. and Thankappan, K. and Iyer, S.	2019	does not report the outcomes of interest per millimeter DOI/tumor thickness for the outcomes of interest
Suzuki, Mitsuya and Suzuki, Tsunemiti and Asai, Masao and Ichimura, Kei-Ichi and Nibu, Ken-Ichi and Sugasawa, Masashi and Kaga, Kimitaka	2007	Did not exclude patients presenting with positive neck nodes

Tai, S. K. and Li, W. Y. and Chu, P. Y. and Chang, S. Y. and Tsai, T. L. and Wang, Y. F. and Huang, J. L.	2012	Unadjusted results
Tam, Samantha and Amit, Moran and Zafereo, Mark and Bell, Diana and Weber, Randal S.	2019	multivariable model uses TT as a continuous variable (no dichotomization/cut-off was used)
Tanaka, K. and Hanai, N. and Eba, J. and Mizusawa, J. and Asakage, T. and Homma, A. and Kiyota, N. and Fukuda, H. and Hayashi, R.	2018	study protocol
Tarsitano, Achille and Del Corso, Giacomo and Tardio, Maria Lucia and Marchetti, Claudio	2016	risk was not adjusted
Terada, H. and Sasaki, E. and Suzuki, H. and Nishikawa, D. and Beppu, S. and Hanai, N.	2020	Only approximable from a figure
Tsai, C. Y. and Lai, Y. S. and Chen, M. K.	2014	does not report the outcomes of interest per millimeter DOI/tumor thickness for the outcomes of interest
Tsang, R. K. Y. and Chung, J. C. K. and Howe To, V. S. and Chan, J. Y. W. and Ho, W. K. and Wei, W. I.	2011	does not report the outcomes of interest per millimeter DOI/tumor thickness for the outcomes of interest
Veness, M. J. and Morgan, G. J. and Sathiyaseelan, Y. and Gebski, V.	2005	Participants were not clinically node-negative (cN0) in 43% at recruitment
Vijayakumar, M. and Burrah, R. and Sabitha, K. S. and Nadimul, H. and Rajani, B. C.	2011	does not report the outcomes of interest per millimeter DOI/tumor thickness for the outcomes of interest
Wermker, Kai and Belok, Friederike and Schipmann, Stephanie and Klein, Martin and Schulze, Hans-Joachim and Hallermann, Christian	2015	postive neck nodes at presentation were not excluded
Zenga, J. and Divi, V. and Stadler, M. and Massey, B. and Campbell, B. and Shukla, M. and Awan, M. and Schultz, C. J. and Shreenivas, A. and Wong, S. and Jackson, R. S. and Pipkorn, P.	2019	does not report the outcomes of interest per millimeter DOI/tumor thickness for the outcomes of interest
Zou, H. and Zhang, W. F. and Lu, T. T. and Chen, X. M. and Zhao, Y. F.	2005	Did not seem to exclude patients presenting with positive neck nodes

Literature search strategy

Algemene informatie

Richtlijn: HHT	
Uitgangsvraag: Wat zijn (on)gunstige effecten van een schildwachtklierprocedure vergeleken met electieve halsklierdissectie bij patiënten met een crT1-2N0 mondholtecarcinoom PICO1	
Database(s): Ovid/Medline, Embase	Datum: 6-7-2020, 15-7-2020, 23-9-2020
Periode: 2000-	Talen: niet van toepassing
Literatuurspecialist: Ingeborg van Dusseldorp	
Toelichting en opmerkingen: **23-9-2020** Op basis van onderstaande mail is de zoekstrategie opnieuw bekeken. Er ontstond enige verwarring welke PICO deze vraag betrof omdat in PICO 1 is uitgegaan van de vergelijking schildwachtklierprocedure AND selectieve halsklierdissectie. In PICO 2 is uitgegaan van schildwachtklierprocedure OF selectieve halsklierdissectie AND watchful waiting. Omdat de sleutelartikelen uit de mail niet worden gevonden in de definitie van PICO 1 is ervoor gekozen om uit te gaan van PICO 2 zonder watchful waiting en is er een verdere beperking toegepast op tumor diepte en early cancer. De eenvoudig vertaalde zoekstrategie wordt dan als volgt: Mondholtecarcinoom EN (schildwachtklierprocedure OF selectieve halsklierdissectie) EN (tumor diepte OF T1, T2 stadium) Op basis van deze zoekstrategie worden de artikelen van den Toom en Melchers gevonden. Ook eerder genoemde artikelen van den Toom 2020 en Cramer 2019 worden gevonden, evenals het artikel van Cao over wait and watch.	

Het totaal aantal referenties dat wordt gevonden is 441 in 1 database (34 SR, 99 RCT, 308 Observationeel)
Als de werkgroep besluit dat deze zoekstrategie kan worden uitgevoerd dan kan ik de nieuw gevonden referenties ten opzichte van de reeds gevonden referenties ontdubbelen.

Sleutelartikelen
Sentinel Lymph Node Biopsy Versus Elective Neck Dissection for Stage I to II Oral Cavity Cancer
Cramer J.D., Sridharan S., Ferris R.L., Duvvuri U., Samant S.
Laryngoscope (2019) 129:1 (162-169). Date of Publication: 1 Jan 2019

Elective neck dissection or sentinel lymph node biopsy in early stage oral cavity cancer patients: The dutch experience
Den Toom I.J., Boeve K., Lobeek D., Bloemena E., Donswijk M.L., de Keizer B., Klop W.M.C., Leemans C.R., Willems S.M., Takes R.P., Witjes M.J.H., de Bree R.
Cancers (2020) 12:7 (1-13) Article Number: 1783. Date of Publication: 1 Jul 2020

Mail 15-9-2020
De werkgroep heeft voor PICO 1 van de uitgangsvraag 11.4 'Wat is het management van de negatieve hals bij patiënten met een mondholtecarcinoom stadium 1 of 2 (schildwachtklierprocedure of selectieve halsklierdissectie)?' aangegeven dat de volgende artikelen toch cruciale sleutelartikelen zijn die uit de search zouden moeten komen:

den Toom, I. J., Janssen, L. M., van Es, R., Karagozoglu, K. H., de Keizer, B., van Weert, S., Willems, S. M., Bloemena, E., Leemans, C. R., & de Bree, R. (2019). Depth of invasion in patients with early stage oral cancer staged by sentinel node biopsy. Head & neck, 41(7), 2100–2106. https://doi.org/10.1002/hed.25665

Melchers, L. J., Schuuring, E., Van Dijk, B. A. C., De Bock, G. H., Witjes, M. J. H., Van Der Laan, B. F. A. M., ... & Roodenburg, J. L. N. (2012). Tumour infiltration depth⩾ 4 mm is an indication for an elective neck dissection in pT1cN0 oral squamous cell carcinoma. Oral oncology, 48(4), 337-342.

Zou het mogelijk zijn om de search aan te passen zodat deze artikelen in de search zitten?

15-7-2020
De keuze is gemaakt voor watchful waiting. Er worden nog een tweetal termen toegevoegd watch and scan en neck observation. De extra sleutelartikelen worden allemaal gevonden.

6-7-2020
In onderstaande zoekstrategie zijn verschillende scenario's uitgewerkt voor 1 database:

PICO 1 P (mondholtecarcinoom) EN I (schildwachtklier OF halsklierdissectie)
(Te) groot aantal referenties

PICO 1 P(mondholtecarcinoom EN vroeg stadium t1/t2 EN I (schildwachtklier OF halsklierdissectie)
Minder resultaten. Er is een kans dat referenties worden gemist als early stage of t1/t2 niet specifiek wordt benoemd. Sleutelartikel wordt wel gevonden.

PICO 1 P (mondholtecarcinoom EN I (schildwachtklier OF halsklierdissectie) EN C watchful waiting
Te weinig referenties. Kans om refererenties te missen is aanzienlijk. Sleutelartikel wordt wel gevonden

PICO2 P (mondholtecarcinoom) EN I (schildwachtklier) EN C (halsklierdissectie)
Het resultaat van deze zoekstrategie bevindt zich volledig in de strategie van PICO 1. Er valt te overwegen om de strategieën samen te voegen en via labeling in Rayyan de keuze voor de verschillende PICO's te maken.

Er moet rekening mee worden gehouden dat het aantal referenties met 30% zal stijgen vanwege het toevoegen van een tweede database.

Zoekopbrengst

	EMBASE	OVID/MEDLINE	Ontdubbeld
SRs	2	5	6
RCTs	9	11	9
Observationele studies	41	41	39
Overig	15	11	17

Totaal			71

Zoekverantwoording

Ovid/Medline 15 juli 2020

1 (meta-analysis/ or meta-analysis as topic/ or (meta adj analy$).tw. or (systematic*or literature adj2 review$1).tw. or (systematic adj overview$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (295283)

2 (exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (2004168)

3 Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or consecutive*.tw. or Cross sectional.tw. or Cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/ (Onder exp cohort studies vallen ook longitudinale, prospectieve en retrospectieve studies) (3476010)

4 exp Tongue neoplasms/ or exp Mouth neoplasms/ or ((mouth or oral or intraoral or tongue or lingual) adj3 (cancer or tumor* or tumour* or malignan* or neoplasm* or carcinoma*)).ti,ab,kf. (82540)

5 exp sentinel lymph node biopsy/ or ((sentinel node or sentinal lymph*) adj3 (procedure* or assessment* or biop*)).ti,ab,kf. (12216)

6 exp Neck dissection/ or neck dissection.ti,ab,kf. or neck radical dissection.ti,ab,kf. (12274)

7 5 or 6 (24097)

8 4 and 7 (3486)

9 exp Watchful Waiting/ or ((watch* or scan) adj3 (wait* or see*)).ti,ab,kw. or neck observation.ti,ab,kf. (7631)

10 8 and 9 (63)

11 10 not ((exp animals/ or exp models, animal/) not humans/) not (letter/ or comment/ or editorial/) (61)

12 limit 11 to yr="2000 -Current" (56)

13 1 and 12 (5)

14 2 and 12 (11)

15 3 and 12 (41)

16 12 not (13 or 14 or 15) (11)

Embase 23 september 2020

No.	Query	Results
#23	#20 NOT #19 NOT #18	308
#22	#19 NOT #18	99
#21	#18 OR #19 OR #20	441
#20	#16 AND #17	401
#19	#15 AND #17	116
#18	#14 AND #17	34
#17	#9 AND (1-1-2000)/sd NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	601
#16	'major clinical study'/de OR 'clinical study'/de OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR 'prospective study'/de OR 'cohort analysis'/de OR ((cohort NEAR/1 (study OR studies)):ab,ti) OR	5421900

	(('case control' NEAR/1 (study OR studies)):ab,ti) OR (('follow up' NEAR/1 (study OR studies)):ab,ti) OR (observational NEAR/1 (study OR studies)) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti)	
#15	('clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti) NOT 'conference abstract':it	2340458
#14	('meta analysis'/de OR cochrane:ab OR embase:ab OR psycinfo:ab OR cinahl:ab OR medline:ab OR ((systematic NEAR/1 (review OR overview)):ab,ti) OR ((meta NEAR/1 analy*):ab,ti) OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/de) NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	473856
#13	(elective AND neck AND dissection OR sentinel) AND lymph AND node AND biopsy AND in AND early AND stage AND oral AND cavity A ND cancer AND patients AND the AND dutch AND experience AND toom AND 2020	1
#12	sentinel AND lymph AND node AND biopsy AND versus AND elective AND neck AND dis section AND for AND stage AND i AND to AND ii AND oral AND cavity AND cancer AND 2019 AND cramer	1
#11	4 AND mm AND is AND indication AND for AND an AND elective AND neck AND dissecti on AND in AND pt1cn0 AND oral AND squamous AND cell AND carcinoma	2
#10	depth AND of AND invasion AND in AND patients AND with AND early AND stage AND oral AND cancer AND staged AND by AND sentinel AND node AND biopsy	1
#9	#5 AND #8	852
#8	#6 OR #7	257310
#7	'early cancer'/exp OR ((early NEAR/3 (cancer OR tumor* OR tumour* OR malignan* OR neoplasm* OR carcinoma* OR stage OR staging)):ti,ab,kw) OR 'ct1 2no':ti,ab,kw OR 't1/t2':ti,ab,kw OR 't1-t2':ti,ab,kw OR 'stage i/ii':ti,ab,kw	243461
#6	'tumor depth'/exp OR ((depth NEAR/4 (invasi* OR tumor* OR tumour*)):ti,ab,kw)	16652
#5	#1 AND #4	5193
#4	#2 OR #3	39308
#3	'neck dissection'/exp OR 'neck dissection':ti,ab,kw OR 'neck radical dissection':ti,ab,kw	19068
#2	'sentinel lymph node metastasis'/exp AND (biop*:ti,ab,kw OR 'biopsy'/de) OR 'sentinel lymph node biopsy'/exp OR ((('sentinel node' OR 'sentinal lymph*') NEAR/3 (procedure* OR assessment* OR biop*)):ti,ab,kw)	20949
#1	'tongue cancer'/exp OR 'mouth cancer'/exp OR (((mouth OR oral OR intraoral OR tongue OR lingual) NEAR/3 (cancer OR tumor* OR tumour* OR malignan* OR neoplasm* OR carcinoma*)):ti,ab,kw)	88134

Embase 15 juli 2020

No.	Query	Results
#16	#12 NOT (#13 OR #14 OR #15)	15
#15	#4 AND #12	41
#14	#3 AND #12	9
#13	#2 AND #12	6
#12	#10 AND #11	63
#11	'watchful waiting'/exp OR (((watch* OR scan) NEAR/3 (wait* OR see*)):ti,ab,kw) OR 'neck observation':ti,ab,kw	9632
#10	#9 AND (1-1-2000)/sd NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	3461
#9	#5 AND #8	5043
#8	#6 OR #7	38389
#7	'neck dissection'/exp OR 'neck dissection':ti,ab,kw OR 'neck radical dissection':ti,ab,kw	18734
#6	'sentinel lymph node biopsy'/exp OR ((('sentinel node' OR 'sentinal lymph*') NEAR/3 (procedure* OR assessment* OR biop*)):ti,ab,kw)	20494
#5	'tongue cancer'/exp OR 'mouth cancer'/exp OR (((mouth OR oral OR intraoral OR tongue OR lingual) NEAR/3 (cancer OR tumor* OR tumour* OR malignan* OR neoplasm* OR carcinoma*)):ti,ab,kw)	86485
#4	'major clinical study'/de OR 'clinical study'/de OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR 'prospective study'/de OR 'cohort analysis'/de OR ((cohort NEAR/1 (study OR studies)):ab,ti) OR (('case control' NEAR/1 (study OR studies)):ab,ti) OR (('follow up' NEAR/1 (study OR studies)):ab,ti) OR (observational NEAR/1 (study OR studies)) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti)	5304359
#3	('clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti) NOT 'conference abstract':it	2340458
#2	('meta analysis'/de OR cochrane:ab OR embase:ab OR psycinfo:ab OR cinahl:ab OR medline:ab OR ((systematic NEAR/1 (review OR overview)):ab,ti) OR ((meta NEAR/1 analy*):ab,ti) OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/de) NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	473856
#1	elective AND neck AND dissection AND versus AND wait AND watch AND policy AND for AND oral AND cavity AND squamous AND cell AND carcinoma AND in AND early AND stag e AND cao AND 2019	1

Embase Session Results (6 julil 2020)

No.	Query	Results
#27	#1 AND #15 PICO 1 **zowel gevonden bij watchful waiting als bij early cancer**	**1**
#26	#1 AND #22 Sleutelartikel PICO 2 **niet gevonden, geen poortwachtersklierprocedure**	**0**
#25	#4 AND #22**Observationeel**	**125**
#24	#3 AND #22 **RCT**	**82**
#23	#2 AND #22 **SR**	**13**
#22	#21 AND (1-1-2000)/sd NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	**268**
#21	#5 AND #6 AND #7 **PICO 2 P (mondholtecarcinoom) EN I (poortwachtersklier) EN C *(halsdissectie)**	**350**
#20	#10 AND #19	**44**
#19	'watchful waiting'/exp OR ((watch* NEAR/3 (wait* OR see*)):ti,ab,kw) **PICO 1 P (mondholtecarcinoom EN I (schildwachtklier OF halsklierdissectie) EN C watchful waiting**	**8298**
#18	#4 AND #15 **Observationele studies**	**328**
#17	#3 AND #15 **RCT**	**103**
#16	#2 AND #15 **SR**	**32**
#15	#10 AND #14	**506**
#14	'early cancer'/exp OR ((early NEAR/3 (cancer OR tumor* OR tumour* OR malignan* OR neoplasm* OR carcinoma* OR stage OR staging)):ti,ab,kw) OR 'ct1 2no':ti,ab,kw OR 't1/t2':ti,ab,kw OR 't1-t2':ti,ab,kw OR 'stage i/ii':ti,ab,kw **PICO 1 P(mondholtecarcinoom EN vroeg stadium t1/t2) EN I (schildwachtklier OF halsklierdissectie)**	**238984**
#13	#4 AND #10 **Observationele studies**	**1760**
#12	#3 AND #10 **RCT**	**467**
#11	#2 AND #10 **SR**	**99**
#10	#9 AND (1-1-2000)/sd NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	**3461**
#9	#5 AND #8	**5043**
#8	#6 OR #7	**38389**
#7	'neck dissection'/exp OR 'neck dissection':ti,ab,kw OR 'neck radical dissection':ti,ab,kw	**18734**
#6	'sentinel lymph node biopsy'/exp OR ((('sentinel node' OR 'sentinal lymph*') NEAR/3 (procedure* OR assessment* OR biop*)):ti,ab,kw)	**20494**

#5	'tongue cancer'/exp OR 'mouth cancer'/exp OR (((mouth OR oral OR intraoral OR tongue OR lingual) NEAR/3 (cancer OR tumor* OR tumour* OR malignan* OR neoplasm* OR carcinoma*)):ti,ab,kw)	**86485**
	PICO1 P (Mondholtecarcinoom) EN I (poortwachtersklierprocedure OF halsklierdissectie)	
#4	'major clinical study'/de OR 'clinical study'/de OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR 'prospective study'/de OR 'cohort analysis'/de OR ((cohort NEAR/1 (study OR studies)):ab,ti) OR (('case control' NEAR/1 (study OR studies)):ab,ti) OR (('follow up' NEAR/1 (study OR studies)):ab,ti) OR (observational NEAR/1 (study OR studies)) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti)	**5304359**
#3	('clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti) NOT 'conference abstract':it	**2340458**
#2	('meta analysis'/de OR cochrane:ab OR embase:ab OR psycinfo:ab OR cinahl:ab OR medline:ab OR ((systematic NEAR/1 (review OR overview)):ab,ti) OR ((meta NEAR/1 analy*):ab,ti) OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/de) NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	**473856**
#1	elective AND neck AND dissection AND versus AND wait AND watch AND policy AND for AND oral AND cavity AND squamous AND cell AND carcinoma AND in AND early AND stage AND cao AND 2019 **Sleutelartikel**	1

Module 11.4.2 Type beleid negatieve hals cT1-2N0

Uitgangsvraag

Welke type beleid dient uitgevoerd te worden bij patiënten met een mondholtecarcinoom en een klinisch negatieve hals?

Inleiding

Plaveiselcelcarcinomen van de mondholte metastaseren primair lymfogeen naar de lymfeklieren van de hals. Aangetoonde metastasen worden doorgaans behandeld met een halsklierdissectie. Voor kleine mondholtetumoren (T1 en T2) die klinisch en radiologisch een negatieve hals (d.w.z. geen lymfekliermetastasen gedetecteerd, cN0) laten zien en waarbij de hals niet geopend hoeft te worden voor resectie van de primaire tumor of reconstructie van het defect zijn verschillende strategieën mogelijk aangaande behandeling van de hals. Er is bekend dat 30% van deze patiënten occulte metastasen heeft. Er kan gekozen worden voor een electieve halsklierdissectie dan wel voor “watch-and-wait” strategie waarbij de hals wordt opgevolgd bijvoorbeeld met echografische controle en pas behandeld wordt bij een manifeste metastase. Elke strategie heeft zijn eigen voor- en nadelen. Bij een electieve halsklierdissectie worden occulte metastasen direct verwijderd. In geval van grote chirurgische ingrepen zoals commando-procedures met of zonder reconstructies, wordt ongeacht de stadiering van de hals meestal een halsklierdissectie uitgevoerd vanwege de noodzakelijke chirurgische benadering. Bij een “watch-and-wait” strategie ondergaan minder patiënten een behandeling van de hals, maar bestaat het risico dat door de verlate diagnose van eventuele lymfekliermetastasen de behandeling uitgebreider moet zijn dan bij een electieve halsklierdissectie (bijvoorbeeld een gemodificeerd radicale halsklierdissectie met opofferen van structuren in de hals (bijvoorbeeld vena jugularis interna, nervus accessorius en/of musculus sternocleidomastoideus). Ook kan een niet-juiste stadiering van de hals leiden tot het niet uitvoeren van een (selectieve) halsklierdissectie of adjuvante radiotherapie of zelfs dat de metastasen door de delay van het ontdekken inoperabele ziekte zou kunnen ontstaan. Verder moet een afweging gemaakt worden op basis van onder andere morbiditeit van een halsklierdissectie, verwijderen van een vangnet voor metastasen van een recidief of tweede primaire tumoren, gebruik van (schaarse) middelen en kosten.

Search and select

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

> What are the (un)beneficial effects of elective neck dissection on neck recurrence, survival, and mortality compared to an observation strategy in patients with cT1-2N0 oral cavity carcinomas?

P: patients with a resected primary cT1-2N0 oral cavity carcinoma;
I: Elective neck dissection;
C: watchful waiting;
O: neck recurrence, overall survival, disease-free survival, disease-specific survival, mortality.

<u>Relevant outcome measures</u>

The guideline development group considered neck recurrence and overall survival as a critical outcome measure for decision making; and disease-free survival, disease-specific survival, and mortality 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 a minimal clinically relevant difference as:

- 0.8 or 1.25 as borders for clinical decision-making for risk or odds ratios of neck recurrence.
- 5% difference or more (absolute) and HR< 0.7 in disease-specific survival.
- 5% difference or more (absolute) and HR< 0.7 in overall survival.
- 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.
- Statistically significant less complications/adverse events.
- Statistically significant better functional outcomes, work participation.

Search and select (Methods)

The working group identified two published systematic reviews that included studies comparing elective neck dissection to watchful waiting (Ibrahim, 2020; Massey, 2019).

The combined reporting of both systematic reviews was used and only data from randomized studies were considered, even though both systematic reviews included observational studies.

Ibrahim (2020) searched Medline, Google Scholar and Scopus for relevant studies published from 1989 up to 2018. Keywords used in the search were reported in the published manuscript (Ibrahim, 2020). Studies were selected when published in English, patients had pathologically proven T1-2N0M0 oral squamous cell carcinoma (oral tongue, buccal mucosa, hard palate, alveolar ridge, floor of mouth, retromolar trigone), patients had a clinically and radiologically negative neck, patients only received surgical treatment without previous neck radiotherapy, and when elective neck dissection was compared to watchful waiting. Exclusion criteria were not reported. Over 1200 studies were identified by Ibrahim (2020) and, finally, 24 studies were selected (including 4 randomized studies).

Massey (2019) searched Medline, Google Scholar, and Scopus up to June 2018. Keywords used in the search were reported in the published manuscript (Massey, 2019). The reference lists of systematic reviews and meta-analyses deemed relevant were hand-searched. Two authors independently screened articles. Potentially relevant articles were assessed in detail by the two reviewers independently. Studies were selected when patients had T1-2N0M0 (clinical negative nodes) squamous cell carcinoma of the oral cavity with a verification of diagnosis, when the sample size was 30 or more, the oral cavity was defined in accordance with the AJCC or UICC, the TNM staging (AJCC or UICC) was used, patients did not have prior head and neck treatment (surgery, radiotherapy, chemotherapy), occult lymph node metastasis was clearly defined (as: the presence of a metastasis in the sampled lymph node of a clinically disease-free neck at elective neck dissection), and the techniques of neck dissection were well defined (as: a neck dissection in a patient without clinically detectable disease). Studies were excluded when cancers of the oral cavity were non-squamous cell, the primary tumor site was outside the oral cavity, patients had signs of clinical nodal disease, or when the study focused on laboratory application. Massey (2019) found 1840 search hits, eventually leading to the inclusion of 39 studies (including 5 randomized studies).

Results

Two systematic reviews (Ibrahim, 2020; Massey, 2019) were used to identify relevant randomized trials to be included in the analysis of the literature. Both systematic reviews included the same four randomized studies (Fakih, 1989; Kligerman, 1994; Yuen, 2009; D'Cruz, 2015). Massey (2019) included one additional randomized study, published in 1980,

which included patients with T3 carcinomas. Ibrahim (2020) did not include that study because of their search period (from 1989 up to 2018). Due to the inclusion of T3 disease in the study's sample (21% in the elective neck dissection group; 6% in the therapeutic neck dissection group), it was decided not to consider the study in the current analysis of literature (Vandenbrouck, 1980). Important study characteristics and results are summarized in the evidence tables from the combined reporting of the two systematic reviews. The assessment of the risk of bias of the systematic reviews is summarized in the risk of bias tables. The risk of bias assessment for the individual randomized studies as reported by Massey (2019) was used for the GRADEing of outcomes.

Summary of literature

Description of studies

Ibrahim (2020) performed a systematic review and included 24 articles, of which 4 were RCTs (Fakih, 1989; Kligerman, 1994; Yuen, 2009; D'Cruz, 2015). An exact search date was not provided and it was unclear how keywords were combined in the search. Excluded studies in the full-text selection phase were not described or referenced and reasons for excluding literature were not provided. Data was extracted by two authors independently and was cross-checked. The authors did not perform a risk of bias appraisal of the included studies. Potential publication bias was assessed and the authors reported that there was no evidence of publication bias.

Massey (2019) included the same four RCTs. An exact search date was not provided, however it was reported that databases were searched from inception to June 2018. It was unclear how the key words were combined in the search. Excluded studies in the full-text selection phase were not described, however reasons for exclusion were provided in the flow-diagram describing the study selection. Some studies containing overlapping datasets were referenced and excluded in some analyses. Three authors extracted data independently which were checked for consistency. Two authors independently assessed the risk of bias of RCTs by using the Cochrane risk of bias tool. Discrepancies in data-extraction and risk of bias assessments were resolved by consensus. Massey (2019) also included one RCT that recruited patients with T3 disease, which was excluded for the current data-analysis. The authors assessed the potential for publication bias and reported that no publication bias was detected.

Study and/or sample characteristics reported by Ibrahim (2020) and Massey (2019) are summarized in Table 11.7. Other data about potentially important prognostic factors in the sample (such as depth of invasion, perineural invasion, extracapsular spread) was not reported in the systematic reviews. Data about the watch and wait procedures were extracted from the original RCT papers, separately from the systematic reviews.

***Table 11.7 Summary of study and sample characteristics as reported in Ibrahim (2020) and/or Massey (2019). Data from the watch and wait strategy was extracted from the original papers* (Fakih, 1989; Kligerman, 1994; Yuen, 2009; D'Cruz, 2015)**

Author, year	Country	Sample size	Tumor location	Pre-operative staging method	Type of neck dissection	Type of watch and wait strategy*	Adjuvant therapy
Fakih 1989	India	END: 30 WW: 40	Tongue	Not reported	Radical neck dissection	**Strategy:** Therapeutic neck dissection **Regime:**	Postoperative radiotherapy for positive resection margin and extracapsular spread

						Patients were seen regularly	
Kligerman 1994	Brazil	END: 34 WW: 33	Tongue, floor of mouth	Not reported	Supraomohyoid neck dissection	**Strategy:** Primary resection alone **Regime:** Not reported	Postoperative radiotherapy for pathologically positive lymph nodes
Yuen 2009	China	END: 36 WW: 35	Tongue	Ultrasound and ultrasound-guided fine needle aspirate cytology	Supraomohyoid neck dissection	**Strategy:** Observation (after transoral glossectomy) **Regime:** Every month in the first year, every two months in the second year, every 3 months in the third year, every 4 months in the fourth and fifth year. Every 6 months thereafter. Ultrasound examination was performed every three months in the first three years.	Postoperative radiotherapy for pathologically positive lymph nodes
D'Cruz 2015	India	END: 243 WW: 253	Tongue, floor of mouth, buccal mucosa	Physical examination and ultrasound	Supraomohyoid neck dissection	**Strategy:** Therapeutic neck dissection **Regime:** Every 4 weeks in the first 6 months, every 6 weeks for the next 6 months, every 8 weeks for the next 12 months, and thereafter every 12 weeks	Postoperative radiotherapy for pathologically positive lymph nodes, positive resection margins, and >10mm depth of invasion
***Extracted from the original RCT papers**							

END: Elective Neck dissection WW: Watch and Wait

Results

Neck recurrence

Ibrahim (2020) pooled data on neck recurrence from the four included RCTs which compared an elective neck dissection (45 events from n=343) to a watch and wait management (158 events from n=361). A pooled relative risk of 0.36 was found (95%CI: 0.20-0.66, random effects, I^2 = 69.24%), favoring an elective neck dissection. For the pooled risk difference, a fixed methods meta-analyses by Ibrahim (2020) found a difference of -0.302 (95%CI: -0.364 to -0.240, I^2 = 0%), favoring an elective neck dissection. A fixed-effects meta-analysis of risk differences by Ibrahim (2020) found a pooled risk difference of -0.302 (95%CI: -0.364 to -0.240, I^2 = 0.0%), favoring elective neck dissection.

Survival

Four randomized controlled trials reported several survival outcomes at different time-points (Fakih, 1989; Kligerman, 1994; Yuen, 2009; D'Cruz, 2015). Data is summarized in Table 11.8.

Table 11.8 Overview of survival outcomes

Variable	Author, year	Follow-up	Sample size	Survival
Overall survival	*D'Cruz 2015*	3 years	END: 243 WW: 253	END: 80% WW: 67.5% HR = 0.64 (95%CI: 0.45-0.92), p=0.01
Disease-free survival	*Fakih 1989*	Minimum of 12 months (median: 20 months)	END: 30 WW: 40	END: 63% WW: 52% Not significant (p-value not reported)
	Kligerman 1994	3 years	END: 34 WW: 33	END: 72% WW: 49% P=0.04
	D'Cruz 2015	3 years	END: 243 WW: 253	END: 69.5% WW: 45.9% HR = 0.45 (0.34-0.59), p<0.001
Disease-specific survival	*Yuen 2009*	5 years	END: 36 WW: 35	END: 89% WW: 87% P=0.89 (log rank test)

Mortality

Klingerman (1994) reported 7 deaths (7/34, 20.6%) in the elective neck dissection group (n=4 death related to the disease, n=2 death due to new primary tumor, n=1 unknown cause) and 15 deaths (15/33, 45.5%) in the observation group (n=14 disease related deaths (of which 2 brain and pleural metastases), n=1 heart failure) over the course of 3 years. From this data we calculated a relative risk of 0.45 (95%CI: 0.21-0.97), favoring an elective neck dissection.

D'Cruz (2015) reported 50 deaths in the elective neck dissection group (50/243, 20.6%) and 79 deaths in the observation group (79/253, 31.2%) over the course of the study (median follow-up: 39 months, IQR: 16-76). From the reported data, a relative risk of 0.66 (95%CI: 0.48-0.90) was calculated, favoring elective neck dissection.

Level of evidence of the literature

The level of evidence regarding the outcome measure neck recurrence was downgraded by 2 levels because of study limitations (2 level for risk of bias: Massey (2019) indicated that two RCTs had a moderate risk of bias and two RCTs had a high risk of bias. However, the authors did not provide reasons or appraisals on the individual domains of the risk of bias tool); publication bias was not assessed (although publication bias was assessed by the authors of both systematic reviews by using both randomized and non-randomized studies together (Ibrahim, 2020; Massey, 2019), we included 4 RCTs which is not enough to reliably assess publication bias).

The level of evidence regarding the outcome measure overall survival was downgraded by 1 level because of study limitations (1 level for risk of bias: Massey (2019) indicated that the RCT had a high risk of bias. However, the authors did not provide reasons or appraisals on the individual domains of the risk of bias tool, however blinding is one of the domains in the tool which probably had a high risk of bias considering the 4 RCTs did not report any procedures regarding blinding. Blinding does not affect a hard outcome such as overall survival, and therefore we only subtracted 1 level); number of included patients (1 level for imprecision: event calculator revealed that for HR= 0.64 about 158 events were needed (alpha=0.05, beta=0.2, q1=0.49, q0=0.51, relative hazard = 0.64), over the course of the whole study 129 events were reported; furthermore the confidence interval crossed the pre-defined border of 0.7); publication bias was not assessed (although publication bias was assessed by the authors of both systematic reviews by using both randomized and non-randomized studies together (Ibrahim, 2020; Massey, 2019), we included 1 RCTs which is not enough to reliably assess publication bias).

The level of evidence regarding the outcome measure disease-free survival was downgraded by 2 levels because of study limitations (2 level for risk of bias: Massey (2019) indicated that one RCT had a moderate risk of bias and 2 RCTs had a high risk of bias. However, the authors did not provide reasons or appraisals on the individual domains of the risk of bias tool); conflicting results (inconsistency); applicability (bias due to indirectness); we did not downgrade for number of included patients (imprecision, because: event calculator revealed that for HR= 0.45 about 49 events were needed (alpha=0.05, beta=0.2, q1=0.49, q0=0.51, relative hazard = 0.45), furthermore the confidence interval of the largest RCT did not cross the pre-defined border of 0.7); publication bias was not assessed (although publication bias was assessed by the authors of both systematic reviews by using both randomized and non-randomized studies together (Ibrahim, 2020; Massey, 2019), we included 3 RCTs which is not enough to reliably assess publication bias).

The level of evidence regarding the outcome measure disease-specific survival was downgraded by 2 levels because of study limitations (2 level for risk of bias: Massey (2019) indicated that the RCT had a moderate risk of bias. However, the authors did not provide reasons or appraisals on the individual domains of the risk of bias tool); number of included patients (2 levels for imprecision: the study only contained a sample of n=71); publication bias was not assessed (although publication bias was assessed by the authors of both systematic reviews by using both randomized and non-randomized studies together (Ibrahim, 2020; Massey, 2019), we included 1 RCT which is not enough to reliably assess publication bias).

The level of evidence regarding the outcome measure mortality was downgraded by 2 levels because of study limitations (1 level for risk of bias: Massey (2019) indicated that the two RCTs had a high risk of bias. The authors did not provide reasons or appraisals on the

individual domains of the risk of bias tool, however blinding is one of the domains in the tool which probably had a high risk of bias considering the 4 RCTs did not report any procedures regarding blinding. Blinding does not affect a hard outcome such as mortality, and therefore we only subtracted 1 level); number of included patients (1 level for imprecision: Confidence intervals cross the pre-defined border of 0.75); publication bias was not assessed (although publication bias was assessed by the authors of both systematic reviews by using both randomized and non-randomized studies together (Ibrahim, 2020; Massey, 2019), we included 2 RCTs which is not enough to reliably assess publication bias).

Conclusions

LOW GRADE	The evidence suggests that elective neck dissection may reduce the number of neck recurrences in patients with an oral cavity carcinoma and a clinically negative neck, when compared to a watch and wait strategy. *Sources: (Ibrahim, 2020 (meta-analysis of: Fakih, 1989; Kligerman, 1994; Yuen, 2009; D'Cruz, 2015)*

LOW GRADE	The evidence suggests that elective neck dissection may improve the overall survival in patients with an oral cavity carcinoma and a clinically negative neck, when compared to a watch and wait strategy. *Sources: (D'Cruz, 2015)*

LOW GRADE	The evidence suggests that elective neck dissection may improve the disease-free survival in patients with an oral cavity carcinoma and a clinically negative neck, when compared to a watch and wait strategy. *Sources: (Fakih, 1989; Kligerman, 1994; D'Cruz, 2015)*

VERY LOW GRADE	The evidence is very uncertain about the effects of elective neck dissection on disease-specific survival in patients with an oral cavity carcinoma and a clinically negative neck, when compared to a watch and wait strategy. *Sources: (Yuen, 2009)*

LOW GRADE	The evidence suggests that elective neck dissection may reduce the mortality in patients with an oral cavity carcinoma and a clinically negative neck, when compared to a watch and wait strategy. *Sources: (Kligerman, 1994; D'Cruz, 2015)*

Overwegingen - van bewijs naar aanbeveling

Uit de meta-analyse van Ibrahim (2020) bleek dat er een significant voordeel was voor een electieve halsklierdissectie op de terugkeer van halskliermetastasen in vergelijking met een 'watch and wait' strategie (RR = 0.36, 95%CI: 0.20 tot 0.66). De zekerheid in dit bewijs was laag, aangezien Massey (2019) het risico op vertekening van de uitkomst in de studies in de meta-analyse beoordeelde als redelijk tot hoog. Twee beoordelaars gaven onafhankelijk van elkaar deze beoordeling met de Cochrane risk of bias-tool, maar er werden geen beoordelingsredenen en individuele beoordelingen op de domeinen van de Cochrane tool gerapporteerd.

In de originele rapportages van de RCT's werden verschillende maten van overleving gerapporteerd. De zekerheid van dit bewijs hing af van welk type overleving er werd gerapporteerd. Algehele overleving is een hardere maat dan ziektevrije overleving, waardoor een eventueel gebrek aan blindering minder risico op vertekening geeft. Daarnaast was er sprake van enige imprecisie door betrouwbaarheidsintervallen die een vooraf gedefinieerde grens van klinische besluitvorming overschreed of wanneer er zeer weinig patiënten in de steekproef zaten (per uitkomstmaat). Er werd een zeer lage (ziekte-specifieke overleving) tot lage (algehele overleving, ziektevrije overleving) zekerheid gevonden in het bewijs met betrekking tot overleving, hoewel de gevonden data een betere overleving lijkt te suggereren (al dan niet significant) bij een electieve halsklierdissectie wanneer vergeleken met een 'watch and wait' strategie.

Twee gerandomiseerde onderzoeken rapporteerden de sterfte (Kligerman, 1994; D'Cruz, 2015). Aan de hand van de gerapporteerde data uit Klingerman (1994) werd een relatief risico van 0,45 (95%BHI: 0,21 tot 0,97) berekend en met de data uit D'Cruz (2015) werd een relatief risico van 0,66 (95%BHI: 0.48-0.90) bepaald. Massey (2019) beoordeelde het risico op vertekening in deze studies als hoog. Daarnaast kruisten de gevonden betrouwbaarheidsintervallen de vooraf gedefinieerde grens van klinische besluitvorming. Het bewijs lijkt daarmee te suggereren dat er mogelijk een lagere mortaliteit zou kunnen zijn bij het uitvoeren van een electieve halsklierdissectie in plaats van een 'watch and wait' beleid.

Belangrijk bij het beoordelen van de verschillende studies is ook hoe de klinisch negatieve hals is vastgesteld. Is dit alleen door palpatie gedaan of met uitgebreid beeldvormend onderzoek inclusief echogeleide cytologische puncties van echografisch afwijkende lymfeklieren. Zo is de incidentie van lymfekliermetastasen in de 'watch and wait' arm in de studie van D'Cruz et al bijvoorbeeld 45%, terwijl 25 tot 30% na echogeleide cytologische puncties gebruikelijk is. Daarbij is het bij de 'watch and wait' strategie belangrijk om zo spoedig mogelijk de lymfekliermetastase tijdens de follow-up te detecteren. In de studie van D'Cruz et al waren de lymfekliermetastasen die tijdens follow-up gedetecteerd werden in 28% > 3cm en 18% > 6 cm en hadden 93% extranodale groei. Hierdoor kunnen bij de stringente follow-up die nodig is voor een goede 'watch and wait' strategie vraagtekens gezet worden in deze studie.

Het doel bij het kiezen voor een manier van management van de klinisch negatieve hals (cN0) is het bereiken van een lange (ziektevrije) overleving. Daarnaast zal vooral voor patiënten de kwaliteit van leven en functie na behandeling een grote rol spelen. Een voordeel van het uitvoeren van een halsklierdissectie is dat eventuele occulte metastasen verwijderd zijn. Het nadeel van het uitvoeren van een halsklierdissectie is de morbiditeit die hierbij een rol kan spelen, zoals bijvoorbeeld schouderklachten en lymfoedeem. Bij een "watch-and-wait" beleid speelt het voordeel dat er geen operatie nodig is met bijkomende risico's en bijwerkingen. Echter zoals reeds beschreven is de mortaliteit mogelijk hoger bij een "watch-and-wait" beleid omdat er een risico genomen wordt met het wachten op het ontstaan van een metastase. Bij ernstige co-morbiditeit van patiënten waarbij bijvoorbeeld een algehele narcose als risico niet opweegt tegen een "watch-and-wait" beleid, bij beperkte levensverwachting, of wanneer persoonlijke voorkeur van patiënt om bijvoorbeeld functionele redenen (muzikanten, mensen werkzaam in de bouw) uitgaat naar "watch-and-wait" kunnen hierin andere beslissingen genomen worden. Denk hierbij ook aan de belasting van de ingreep bij de oudere en functioneel kwetsbare patiënt. Zij zouden een verhoogd risico kunnen hebben op verdere functionele achteruitgang bij een halsklierdissectie. Wanneer gekozen wordt voor een "watch and wait" beleid lijkt met een protocol met echogeleide cytologische puncties de overleving vergelijkbaar te zijn met een beleid met

electieve halsklierdissectie, maar moeten de patiënten met lymfkliermetastasen uitgebreider behandeld (b.v. gemodificeerd radicale halsklierdissectie in plaats van selectieve halsklierdissectie en vaker adjuvante radiotherapie) te worden dan wanneer een electieve halsklierdissectie was verricht. De werkgroep acht een frequentie van een echografie eens per drie á vier maanden gedurende het eerste jaar acceptabel. Deze frequentie in het eerste jaar is gebaseerd op de mening en expertise van de werkgroep.

Uit de literatuur blijkt dat het uitvoeren van een halsklierdissectie een financieel voordeel oplevert ten opzichte van een "watch-and-wait" beleid. (Avecedo, 2016) Echter in de in Nederland uitgevoerde studie van Govers (2013) blijkt dat een "watch-and-wait" beleid en het uitvoeren van een schildwachtklier procedure kosteneffectiever zijn dan het uitvoeren van een electieve halsklierdissectie. De keuze om bij subgroepen zoals eerder genoemd te kiezen voor een "watch-and-wait" beleid zullen in Nederland niet op financiële gronden genomen worden. Het toevoegen van een schildwachtklierprocedure aan de diagnostische fase zou de kosten verder kunnen reduceren.

Een electieve halsklierdissectie of een "watch-and-wait" beleid voor een negatieve hals (cN0) horen reeds bij de standaard mogelijkheden van diagnostiek en behandeling van mondholtecarcinomen. Dit is beschikbaar in alle hoofd-halscentra en voor alle patiënten. Voor beide keuzes spreekt het voor zich dat het belangrijk is dat er behandelaars met voldoende ervaring betrokken zijn bij de behandeling (hoofd-halschirurg en radioloog). Er worden geen problemen verwacht in de aanvaardbaarheid, haalbaarheid en implementatie.

Aanbevelingen

Aanbeveling-1

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

Voor een klinisch negatieve hals (cN0) bij kleine plaveiselcelcarcinomen van de mondholte na beeldvorming ter stadiëring zijn er meerdere wegen om hiermee om te gaan. Twee hiervan zijn: 1) electieve halsklierdissectie, 2) "watch-and-wait" beleid. De electieve halsklierdissectie lijkt hierbij de voorkeur te hebben ten opzichte van een "watch-and-wait" in verband met de betere overleving en minder regionale recidieven. Wanneer er toch gekozen wordt voor een "watch-and-wait" beleid wordt dit bij voorkeur gedaan met regelmatige echografische controle van de hals.

Verricht bij patiënten met een kleine mondholtecarcinoom (cT1-T2) en een klinisch negatieve hals (cN0) bij voorkeur een electieve halsklierdissectie tenzij specifieke patiënt- of tumorfactoren of aanvullende diagnostiek aanleiding geven tot een 'watchful waiting' strategie.

Aanbeveling-2

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

Bij ernstige co-morbiditeit van patiënten waarbij bijvoorbeeld een algehele narcose als risico niet opweegt tegen een "watch-and-wait" beleid of wanneer persoonlijke voorkeur van patiënt om bijvoorbeeld functionele redenen uitgaat naar "watch-and-wait" kunnen hierin andere beslissingen genomen worden.

Neem specifieke tumor- en patiëntfactoren mee bij de keuze voor een "watch-and-wait" beleid.

Aanbeveling 3

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

De electieve halsklierdissectie lijkt de voorkeur te hebben ten opzichte van een “watch-and-wait” in verband met de betere overleving en minder regionale recidieven. Wanneer er toch gekozen wordt voor een “watch-and-wait” beleid wordt dit bij voorkeur gedaan met regelmatige echografische controle van de hals. In een protocol met echogeleide cytologische puncties lijkt de overleving vergelijkbaar te zijn met een beleid met electieve halsklierdissectie, maar moeten de patiënten met lymfkliermetastasen uitgebreider behandeld (bijvoorbeeld gemodificeerd radicale halsklierdissectie in plaats van selectieve halsklierdissectie en vaker adjuvante radiotherapie) te worden dan wanneer een electieve halsklierdissectie was verricht. Een echografische follow-up van eens per drie á vier maanden in het eerste jaar werd door de werkgroep op basis van expert opinie vastgesteld.

Gebruik bij een “watch-and-wait” beleid bij voorkeur eens per drie á vier maanden echografie in het eerste jaar voor het opvolgen van de hals.

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Bijlagen bij module 11.4.2

Implementatieplan

Aanbeveling	Tijdspad voor implementatie: < 1 jaar, 1 tot 3 jaar of > 3 jaar	Verwacht effect op kosten	Randvoorwaarden voor implementatie (binnen aangegeven tijdspad)	Mogelijke barrières voor implementatie[1]	Te ondernemen acties voor implementatie[2]	Verantwoordelijken voor acties[3]	Overige opmerkingen
1e Verricht bij patiënten met een kleine mondholtecarcinoom (cT1-T2) en een klinisch negatieve hals (cN0) bij voorkeur een electieve halsklierdissectie in plaats van een "watch-and-wait" beleid vanwege een betere overleving vanwege een betere overleving.	< 1 jaar	Besparing van kosten	Geen	Uitzondering tumoren met zeer geringe invasiediepte	Geen	Centra	Verwachting is dat deze aanbeveling al geïmplementeerd is
2e Neem specifieke tumor- en patiëntfactoren mee bij de keuze voor een "watch-and-wait" beleid.	< 1 jaar	Bij goede selectie besparing	Geen	Geen	Geen	Centra	Verwachting is dat deze aanbeveling al geïmplementeerd is.
3e Gebruik bij een "watch-and-wait" beleid bij voorkeur echografie voor het opvolgen van de hals.	1-3 jaar	Besparing van kosten ten opzichte van electieve halsklierdissectie als in eerst 1-2 jaar elke 3 tot 4 maanden echografie wordt verricht	Geen	Niet in alle centra voldoende expertise en capaciteit aanwezig	Afhankelijk lokale situatie	Centra	Verwachting is dat in meeste centra als geïmplementeerd

[1] barrières kunnen zich bevinden op het niveau van de professional, op het niveau van de organisatie (het ziekenhuis) of op het niveau van het systeem (buiten het ziekenhuis). Denk bijvoorbeeld aan onenigheid in het land met betrekking tot de aanbeveling, onvoldoende motivatie of kennis bij de specialist, onvoldoende faciliteiten of personeel, nodige concentratie van zorg, kosten, slechte samenwerking tussen disciplines, nodige taakherschikking, et cetera.

[2] **Denk aan acties die noodzakelijk zijn voor implementatie, maar ook acties die mogelijk zijn om de implementatie te bevorderen. Denk bijvoorbeeld aan controleren aanbeveling tijdens kwaliteitsvisitatie, publicatie van de richtlijn, ontwikkelen van implementatietools, informeren van ziekenhuisbestuurders, regelen van goede vergoeding voor een bepaald type behandeling, maken van samenwerkingsafspraken.**
[3] **Wie de verantwoordelijkheden draagt voor implementatie van de aanbevelingen, zal tevens afhankelijk zijn van het niveau waarop zich barrières bevinden. Barrières op het niveau van de professional zullen vaak opgelost moeten worden door de beroepsvereniging. Barrières op het niveau van de organisatie zullen vaak onder verantwoordelijkheid van de ziekenhuisbestuurders vallen. Bij het oplossen van barrières op het niveau van het systeem zijn ook andere partijen, zoals de NZA en zorgverzekeraars, van belang.**

Evidence tables

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

Based on AMSTAR checklist (Shea, 2007; BMC Methodol 7: 10; doi:10.1186/1471-2288-7-10) and PRISMA checklist (Moher, 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/notapplicable**	**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**
Ibrahim 2020	Yes Reason: PICO elements were reasonably defined in the aim of the study. Inclusion criteria were stated.	Unclear Reason: Multiple databases were searched and keywords were provided. However, the exact search date was not provided (search was conducted over a period from	No Reason: 24 out of 45 potentially relevant studies were included. The excluded studies were not referenced and no reason for exclusion was provided besides that the inclusion	Yes Reason: Some characteristics were described, however more sample characteristics from the included studies would probably have been preferred (e.g. depth of invasion).	NA Reason: We were only interested in the included randomized studies	No Reason: Authors did not provide a reason why a quality appraisal was not performed.	Yes Reason: procedures and interventions were probably similar enough.	Yes Reason: Funnel plots were assessed (plot not presented) and the Egger test was performed. Authors found that there was no indication of publication bias.	No Reason: The authors declare that there is no conflict of interest, however do not report the conflicts of interest from their included studies.

		1989-2018) and it was unclear how keywords were combined.	criteria were applied.						
Massey 2018	Yes Reason: PICO elements were reasonably defined in the aim of the study. Inclusion criteria were stated.	Unclear Reason: Multiple databases were searched in June 2016 and keywords were provided. However, it was unclear how keywords were combined.	No Reason: 39 of 186 potentially relevant articles were selected. Exclusion reasons were provided, however excluded studies were not referenced.	Yes Reason: Some relevant characteristics were reported, however some more specific sample characteristics would probably have been preferred (e.g. depth of invasion).	NA Reason: We were only interested in the included randomized studies	Yes Reason: RCTs were assessed by two independent authors using the Cochrane Risk of Bias tool. The authors reported their overall assessment (without providing reasons) and did not report their judgements on the individual domains of the tool.	Yes Reason: procedures and interventions were probably similar enough. However, one study was included which included some T3 carcinomas in the study sample.	Yes Reason: Funnel plots were assessed (plot not presented) and the Egger test was performed. Authors found that there was no indication of publication bias.	No Reason: The authors declare that there is no conflict of interest, funding, or financial relationship to disclose. The authors do not report the conflicts of interest from their included studies.

1. **Research question (PICO) and inclusion criteria should be appropriate and predefined.**
2. **Search period and strategy should be described; at least Medline searched; for pharmacological questions at least Medline + EMBASE searched.**
3. **Potentially relevant studies that are excluded at final selection (after reading the full text) should be referenced with reasons.**
4. **Characteristics of individual studies relevant to research question (PICO), including potential confounders, should be reported.**
5. **Results should be adequately controlled for potential confounders by multivariate analysis (not applicable for RCTs).**
6. **Quality of individual studies should be assessed using a quality scoring tool or checklist (Jadad score, Newcastle-Ottawa scale, risk of bias table et cetera)**
7. **Clinical and statistical heterogeneity should be assessed; clinical: enough similarities in patient characteristics, intervention and definition of outcome measure to allow pooling? For pooled data: assessment of statistical heterogeneity using appropriate statistical tests (for example Chi-square, I^2)?**
8. **An assessment of publication bias should include a combination of graphical aids (for example funnel plot, other available tests) and/or statistical tests (for example Egger regression test, Hedges-Olken). Note: If no test values or funnel plot included, score "no". Score "yes" if mentions that publication bias could not be assessed because there were fewer than 10 included studies.**

9. Sources of support (including commercial co-authorship) should be reported in both the systematic review and the included studies. Note: To get a "yes," source of funding or support must be indicated for the systematic review AND for each of the included studies.

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
[1]Ibrahim, 2020 AND [2]Massey 2019 individual study characteristics deduced from Ibrahim 2020 ([1]) and/or Massey 2018 ([2]), unless stated otherwise	SR and meta-analysis of RCTs (Observational data was not considered) *Ibrahim 2020[1]: Literature search from 1989 up to 2018)* *Massey 2018[2]: Literature search up to July 2018* **A**: Fakih 1989 **B**: Kligerman 1994 **C**: Yuen 2009 **D**: D'Cruz 2015 <u>Study design</u>: **A:** RCT **B**: RCT **C**: RCT **D**: RCT	Inclusion criteria SR (Ibrahim 2020[1]): published in English, patients had pathologically proven T1-2N0M0 oral squamous cell carcinoma (oral tongue, buccal mucosa, hard palate, alveolar ridge, floor of mouth, retromolar trigone), patients had a clinically and radiologically negative neck, patients only received surgical treatment without previous neck radiotherapy, and when elective neck dissection was compared to watchful waiting Exclusion criteria SR (Ibrahim 2020[1]): Not reported *4 RCTs included by Ibrahim 2020[1]* Inclusion criteria SR (Massey 2018[2]): patients had T1-2N0M0 (clinical negative nodes) squamous cell carcinoma of the oral cavity with a verification of diagnosis,	Describe intervention: Type of elective neck dissection (from Massey 2018[2]): **A:** radical neck dissection **B**: supraomohyoid neck dissection **C**: supraomohyoid neck dissection **D**: supraomohyoid neck dissection	Describe control: Watch and wait strategy strategy **A:** therapeutic neck dissection **B**: primary resection alone **C**: observation (after transoral glossectomy) **D**: therapeutic neck dissection Follow-up strategy: **A:** patients were seen regularly **B**: not reported **C**: every month in the first year, every two months in the second year, every 3 months in the third year, every 4 months in the 4th and 5th year. Every 6 months thereafter. Ultrasound examination was performed every three	<u>End-point of follow-up</u>: **Not reported in the systematic reviews** <u>For how many participants were no complete outcome data available?</u> (intervention/control) **Not reported in the systematic reviews**	<u>Outcome measure-1: locoregional recurrence, END versus WW (Results from Ibrahim 2020[1]):</u> A definition of regional recurrence was not provided for the intervention and/or control group by ibrahim 2020[1]. Massey 2020[2] defined neck recurrences as clinically detectable metastatic disease limited to the neck following END or observation. Effect measure: **RR** (95% CI): **A:** 0.58 (0.33-1.03) **B**: 0.56 (0.27-1.15) **C**: 0.15 (0.04-0.62) **D**: 0.24 (0.16-0.36) Pooled effect (random effects model): 0.36 (95% CI 0.20 to 0.66) favoring END Heterogeneity (I^2): 69.24%	<u>Facultative</u>: Brief description of author's conclusion: Ibrahim 2020: END is better than WW in early oral SCC Massey 2019: Observation may be appropriate for T1, END should be reserved for T2 tumors. Risk of bias (from Massey 2019): **A:** Moderate risk **B**: High risk **C**: Moderate risk **D**: High risk Authors do not provide reasons or appraisals on the individual domains of the RoB tool.

	Setting and Country (from Massey 2019[2]): **A:** India (setting not reported) **B**: Brazil (setting not reported) **C**: China (setting not reported) **D**: India (setting not reported) Source of funding and conflicts of interest: Authors from both systematic reviews ([1,2]) declare that there are no conflicts of interest. Conflicts of interest from the included studies are not reported in the systematic reviews.	when the sample size was 30 or more, the oral cavity was defined in accordance with the AJCC or UICC, the TNM staging (AJCC or UICC) was used, patients did not have prior head and neck treatment (surgery, radiotherapy, chemotherapy), occult lymph node metastasis was clearly defined (as: the presence of a metastasis in the sampled lymph node of a clinically disease-free neck at elective neck dissection), and the techniques of neck dissection were well defined (as: a neck dissection in a patient without clinically detectable disease) Exclusion criteria SR (Massey 2018[2]): cnon-SCC oral cavity, the primary tumor site was outside the oral cavity, patients had signs of clinical nodal disease, or when the study focused on laboratory application *5 RCTs included by* Massey 2018[2]. The 5th RCT was not considered for data-extraction due to the inclusion of T3 disease in the RCT's sample.		months in the first three years. **D**: every 4 weeks in the first 6 months, every 6 weeks for the next 6 months, every 8 weeks for the next 12 months, and thereafter every 12 weeks		Effect measure: **RD**, mean difference (95% CI): **A:** -0.242 (-0.470 to -0.014) **B**: -0.189 (-0.410 to 0.032) **C**: -0.316 (-0.493 to -0.139) **D**: -0.324 (-0.396 to -0.252) Pooled effect (fixed effects model): -0.302. (95% CI -0.364 to -0.240) favoring END Heterogeneity (I^2): 0%	

		Important patient characteristics at baseline: *Number of patients (END / WW), from Ibrahim 2020[1]:* **A:** 30/40 **B**: 34/33 **C**: 36/35 **D**: 243/253 N, mean age Not reported in the systematic reviews *Sex:* Not reported in the systematic reviews *Preoperative nodal staging (from Massey 2020[2]):* **A:** Not stated **B**: Not stated **C**: ultrasound and ultrasound-guided fine needle aspirate cytology **D**: Physical examination and ultrasound *Tumor site (from Massey 2020[2]):* **A:** tongue **B**: tongue, floor of mouth **C**: tongue **D**: tongue, floor of mouth, buccal mucosa *Adjuvant therapy (from Massey 2020[2]):*					

		A: Postoperative radiotherapy for positive resection margin and extracapsular spread **B**: postoperative radiotherapy for pathologically positive lymph nodes **C**: postoperative radiotherapy for pathologically positive lymph nodes **D**: postoperative radiotherapy for pathologically positive lymph nodes, positive resection margins, and >10mm depth of invasion Groups comparable at baseline?					

Table of excluded studies
Ibrahim (2020) and Massey (2019) did not reference the excluded studies in the full-text selection phase.

Literature search strategy
The working group identified two published systematic reviews. The search is described in Ibrahim (2020) and Massey (2019).

Module 11.4.3 Type interventie negatieve hals cT1-2N0

Uitgangsvraag

Welke chirurgische interventie dient uitgevoerd te worden bij patiënten met een mondholtecarcinoom en een klinisch negatieve hals?

Inleiding

Plaveiselcelcarcinomen van de mondholte metastaseren primair lymfogeen naar lymfeklieren in de hals. In het geval van aantoonbare lymfekliermetastase(n) wordt de hals van de patiënt doorgaans behandeld met een halsklierdissectie. Bij een klinisch (en bij beeldvorming) negatieve hals (d.w.z. geen lymfekliermetastasen gedetecteerd, cN0) zijn er twee opties: een electieve (profylactische) halsklierdissectie om occulte (dat wil zeggen klinisch en bij beeldvorming niet te detecteren) metastasen te verwijderen of een "watchful waiting" beleid waarbij de hals pas behandeld wordt bij manifeste metastasering tijdens follow-up. Dit dilemma doet zich met name voor bij kleine mondholtecarcinomen (d.w.z. cT1-2) waarbij de hals niet geopend hoeft te worden voor resectie van de primaire tumor of reconstructie van het chirurgisch defect in de mondholte. Van patiënten met een klinisch of bij beeldvorming negatieve hals is het bekend dat ongeveer 30% van de patiënten occulte metastasen heeft. Van oudsher bestaat bij deze patiënten dan ook het dilemma of er een electieve halsklierdissectie dient te worden uitgevoerd (overbehandeling bij 70% van de patiënten met hierbij behorende postoperatieve morbiditeit zoals mogelijk een gestoorde schouderfunctie) of dat kan worden volstaan met een afwachtend beleid (onderbehandeling bij 30% van de patiënten met het risico dat een occulte metastase zich zal ontwikkelen tot een grotere metastase met mogelijk uitgebreide en zelfs inoperabele ziekte tot gevolg). Het risico op het ten onrechte afzien van een behandeling van de hals kan verminderd worden door de diagnostiek voorafgaand aan behandeling te verbeteren. Daarnaast is het als onderdeel van de diagnostische work-up mogelijk om een schildwachtklierprocedure (sentinel node procedure) uit te voeren, wat als voordeel heeft dat er een histologische bevestiging van de oncologische klierstatus (N) van de hals komt. Het nadeel van een schildwachtklierprocedure is dat indien een metastase gevonden wordt in tweede instantie een halsklierdissectie moet worden uitgevoerd. De voorliggende vraag is, indien er gekozen wordt voor een stadierende ingreep voor de hals, is een schildwachtklier procedure dan gelijkwaardig aan een electieve halsklierdissectie bij patiënten met een mondholtecarcinoom en een negatieve hals?

Search and select

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

> What are the (un)beneficial effects of a sentinel lymph node biopsy on neck recurrence, disease specific survival, overall survival, quality of life, shoulder morbidity, hematomas, pain, and postoperative oedema compared to an elective neck dissection in patients with cT1-2N0 oral cavity carcinomas?

P: patients with a cT1-2N0 oral cavity carcinoma;
I: sentinel lymph node biopsy;
C: elective neck dissection;
O: neck recurrence, disease specific survival, overall survival, quality of life, neck and shoulder morbidity, hematomas, pain, and lymph oedema, costs.

<u>Relevant outcome measures</u>

The guideline development group considered neck recurrence, disease-specific survival, and overall survival as critical outcome measures for decision making; and quality of life,

shoulder morbidity, hematomas, pain, and postoperative oedema 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 a minimal clinically relevant difference as:

- 0.8 or 1.25 as borders for clinical decision-making for risk or odds ratios of neck recurrence.
- 5% difference or more (absolute) and HR< 0.7 in disease-specific survival.
- 5% difference or more (absolute) and HR< 0.7 in overall survival.
- 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.
- Statistically significant less complications/adverse events.
- Statistically significant better functional outcomes.

Search and select (Methods)

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms from 2000 until July 15th, 2020. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 201 hits. Six systematic reviews were initially selected and screened for eligibility. Systematic reviews were selected based on the following criteria: concerns patients with a cT1-2N0 oral cavity carcinoma, sentinel lymph node biopsy was compared to (elective) neck dissection, at least one outcome of interest was reported, included randomized trials. The only relevant systematic review (Crocetta, 2019) did not find any randomized studies up to their search date on the 30th of April in 2019. To update their search strategy, we selected all primary studies (n=25) published between the 1st of January 2019 and the 15th of July 2020 from our own search (n=201). Thirteen of these 25 studies were initially selected based on title and abstract screening, using the following criteria: concerns patients with a cT1-2N0 oral cavity carcinoma, sentinel lymph node biopsy was compared to elective neck dissection, at least one outcome of interest was reported, and the study was a randomized trial. None of the 13 studies met the selection criteria.

On the 1st of July 2021 our search strategy was repeated and the databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms, resulting in 25 new hits. Five studies were selected based on title and abstract. Studies were selected using the aforementioned criteria.

After reading the full text, three studies were excluded and two randomized trials were selected.

Results

Two randomized controlled trials were included. 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

Hasegawa (2021) performed a multi-center randomized trial in Japan to assess the hypothesized noninferiority of a sentinel lymph node biopsy (SLNB) compared to elective neck dissection (ND). The border of clinical relevance for noninferiority was set at 12% for

the three-year overall survival of patients with an oral cavity squamous cell carcinoma. Patients were included when they had a T1-2N0M0 oral cavity squamous cell carcinoma (according to the TNM 7th ed.), when there were no lymph node metastases on contrast enhanced CT of the head and neck, when the patient did not receive prior treatment, and when the patient was 18 years or older. Patients with T1 tumors having ≤ 4mm depth of invasion were excluded, as well as patients with a recurrence after definitive treatment, history of radiation to the neck, had planned or were currently pregnant or lactating, or had other disqualifying reasons as judged by the attending physician. Patients were allocated to a treatment through a stratified randomization (T-stage: T1 versus T2, tumor site: tongue versus other). The clinical neck status of patients was examined by CT and supplemented with ultrasound when necessary. The study center could decide to use MRI and PET/CT additionally at their own discretion. Four patients were excluded after randomization (n=3 did not fulfill the eligibility criteria (n=1 ND, n=2 SLNB), n=1 declined treatment (SLNB)). Tumor resection was performed during surgery. For the group undergoing SLNB, the sentinel lymph node identification was performed with ^{99m}Tc phytate and was injected in the peritumoral mucosa the day before surgery. A gamma probe was used to identify the sentinel node on the day of surgery. During surgery a frozen section analysis was performed on 2mm blocks. When the result was negative, the blocks were paraffin embedded for staining analysis on 4μm sections (hematoxylin and eosin, and cytokeratin). Isolated tumor cells were treated as metastasis-positive. Patients with positive sentinel nodes on frozen section immediately underwent neck dissection (level I-IV or I-V). If the resected specimen was positive in pathological analysis, the neck dissection was performed within 6 weeks of the initial surgery. When no metastasis was detected in the sentinel node and if the resection required a pull-through resection, a supraomohyoid neck dissection was performed. Patients with a negative sentinel node on the contralateral side of the neck received a sentinel node basin dissection. The group undergoing neck dissection received a supraomohyoid neck dissection. Patients with a positive resection margin received a reoperation or radiationtherapy (with or without chemotherapy) at the discretion of the study center. Radiotherapy was initiated within 6 weeks when patients had extracapsular spread of the lymph node metastasis. Concomitant chemotherapy was left at the discretion of the study center. Patients were followed up to a median of 3.1 years. Patients in the SLNB-group (n=134, 66.4% males) had a median age of 63 years (range: 21 to 90) and tumors located at the tongue (n=109), floor of mouth (n=13), lower gingiva (n=7), or buccal mucosa (n=5). Tumor stage was either T1 (n=26) or T2 (n=108) with a pN status of pN- (n=86), pN+ (n=46), or pNx (n=4). Four patients received postoperative radiation and/or chemotherapy. The group undergoing elective ND (n=137, 65.7% males) had a mean age of 63 years (range: 28 to 85). The primary tumor was located at the tongue (n=114), floor of mouth (n=14), lower gingiva (n=6), or buccal mucosa (n=3). Patients had a T-stage of either T1 (n=25) or T2 (n=112). The pN status was either pN- (n=99), pN+ (n=34), or pNx (n=4). Three patients received postoperative radiation or chemotherapy.

Garrel (2020) performed a multi-center open-label randomized controlled trial in France to investigate the equivalence of sentinel lymph node biopsy to elective neck lymph node dissection. The border of equivalence was defined at a recurrence rate difference of 0.10 (H_{null}: SLNB-END ≥ 0.10; $H_{alternative}$: SLNB-END < 0.10). Eligible patients had to be older than 18 years with health insurance, signed an informed consent, were not participating in another trial, and had an operable T1-2N0M0 primary oral or oropharyngeal squamous cell carcinomas (diagnosed by biopsy with histopathologic analysis in the month prior to inclusion). Patients were excluded when they had treatment for other cancers, non-invasive tumors (high grade dysplasia, in situ carcinoma), inadequate tumor resection, contraindications (for sentinel lymph node biopsy, lymph node dissection, radiotherapy,

medical imaging), allergy or intolerance to contrast product, pregnancy, refusal to accept full treatment, when follow-up was not possible or when follow-up was refused, when already treated for the tumor, when chemotherapy or immunotherapy was received in the prior 6 months, or when there was a history of neck surgery or radiotherapy. Preoperatively a contrast enhanced CT or MRI (when there were contraindications for CT) was performed to check for the clinically negative neck (cN0). All participants (n=307) received excision of the primary tumor. After randomization 28 participants were excluded (intervention: n=15, control: n=13) due to high grade dysplasia (n=2), carcinoma in situ (n=10), history of surgery for oral cavity carcinoma (n=1), history of radiotherapy for oropharyngeal carcinoma (n=1), R1 margin without completion (n=1), refusal of surgery (n=1), decision for radiotherapy (n=1), refusal of random allocation (n=4), withdrawal of consent (n=1), synchronous lung cancer (n=1), urgent carotid surgery (n=1), erroneous inclusion of T4 tumor (n=2), investigator decision (n=1), or neck dissection despite ITC1 only (n=1). Participants in the intervention group received treatment with sentinel lymph node biopsy and neck dissection in case of positive sentinel lymph nodes (SLNB-group, n= 140 after exclusions). Preoperative sentinel lymph node identification was performed with radiotracer injections and lymphoscintigraphy. A portable gamma probe was used to identify sentinel lymph nodus during surgery and intraoperative histopathology was performed by imprint cytology or frozen sections. Positive tumor invasion was defined as the presence of at least one micrometastasis (tumor tissue 200μm-2mm) or one macrometastasis (tumor tissue > 2mm). Isolated tumor cells (< 200μm) were not considered to be nodal invasion. When sentinel lymph node positivity was detected post-surgery, a neck dissection was performed. Eight persons in the SLNB-group received a neck dissection because sentinel lymph node biopsies failed and twelve patients received a neck dissection after initial negative intraoperative histopathological analysis (total neck dissections in SLNB-group: 21/140, 15%) The control group (END-group, n=139 after exclusion) received neck dissection. Patients received adjuvant radiotherapy if two or more lymph nodes (including the sentinel node, when applicable) were positive. Concomitant adjuvant chemotherapy was proposed when poor prognostic factors were present (for example vascular, perineural, or muscular invasion). Follow-up was performed by the surgeon every 2 months (first year), every 4 months (following year), and once yearly (up to the fifth year). Every visit had a clinical examination. A neck-thorax CT was performed at year 1 and year 2 post-surgery. Functional follow-up was performed at month 2, 4, 6, 12, and 24 post-surgery. Mean follow-up duration was 4.95 years (SD: 2.45).

Results

Neck recurrence

Hasegawa (2021) observed 15 regional recurrences (11.2%) in the sentinel lymph node biopsy-group, while 13 (9.5%) regional recurrences were observed in the neck dissection group. A relative risk was calculated from this data (RR=1.18, 95%CI: 0.58 to 2.38). In natural frequencies (using the baseline risk of 9.5%), a neck dissection results in 95 patients with regional recurrences from a group of 1000 patients compared to 113 patients (95%CI: 56 to 217) with regional recurrences out of 1000 patients for a sentinel lymph node biopsy. According to these numbers, sentinel lymph node biopsy can result in a range of 39 less patients to 122 more patients with regional recurrences per 1000 patients compared to neck dissection.

Garrell (2020) reported 13 recurrences without relapse of the primary tumor in the sentinel lymph node biopsy-group (9.3%), compared to 14 recurrences in the elective neck dissection-group (10.1%). There were no statistically significant differences when tested with a Chi^2-test (p=0.82). From this data a relative risk was calculated: RR = 0.92 (95%CI: 0.45 to

1.89) with the point estimate favoring the sentinel lymph node biopsy procedure. In natural frequencies (using the baseline risk of 10.1%), a neck dissection then results in 101 patients with regional recurrences from a group of 1000 patients compared to 93 patients (95%CI: 46 to 191) with regional recurrences out of 1000 patients for a sentinel lymph node biopsy. According to these numbers, sentinel lymph node biopsy can result in a range of 55 less patients to 90 more patients with regional recurrences per 1000 patients compared to neck dissection.

Disease-specific survival
Garrel (2020) reported the 2-year and 5-year disease specific survival. The 2-year specific survival in the sentinel lymph node biopsy-group was 93.0% (95%CI: 87 to 96), compared to 95.5% (95%CI: 90 to 98) in the neck dissection-group. The 5-year disease-specific survival was 87.1% (95%CI: 79 to 92) in the sentinel lymph node biopsy group versus 88.6 (95%CI: 82 to 93) in the neck dissection group. No statistically significant difference between groups were found (p=0.68).

Overall survival
Hasegawa (2021) reported the 3-year overall survival. In the sentinel lymph node biopsy-group the survival was 87.9% (one-sided lower limit of the 95%CI: 82.4%) compared to 86.6% (one-sided lower limit of the 95%CI: 80.9%) survival in the neck dissection group at three years.

Garrel (2020) investigated the 2-year and 5-year overall survival. The 2-year overall survival in the sentinel lymph node biopsy-group was 88.7% (95%CI: 82 to 93) versus 92.6% (95%CI: 87 to 96) in the neck dissection-group. The 5-year overall survival in the sentinel lymph node biopsy-group was 82.2% (95%CI: 74 to 88) compared to 81.8% (95%CI: 74 to 88) in the neck dissection-group. No statistically significant differences between groups were found (p=0.42).

Quality of life
Hasegawa (2021) reported the quality of life using the Neck Dissection Quality of Life Questionnaire. Subscales in this questionnaire that described outcomes of interest in this guideline module are described under the respective outcome (i.e. the subscales: pain, shoulder drop, reach above). The other quality of life subscales are described in Table 11.9 for 1, 3, 6, and 12 months postoperatively. Medians were calculated from the reported frequency table.

Table 11.9 Median scores on Quality of Life subscales as measured by Hasegawa (2021) with the Neck Dissection Quality of Life Questionnaire

QoL Subscale	Treatment	Median score at 1 month (sample size)	Median score at 3 months (sample size)	Median score at 6 months (sample size)	Median score at 12 months (sample size)
Stiffness	SLNB	4 (n=125)	4 (n=125)	4 (n=123)	4 (n=108)
	ND	3 (n=126)	3 (n=131)	4 (n=128)	4 (n=120)
	p-value*	<0.001	<0.001	0.00105	0.00108
Constriction	SLNB	4 (n=125)	5 (n=125)	5 (n=123)	5 (n=108)
	ND	3 (n=125)	3 (n=131)	4 (n=128)	4 (n=120)
	p-value*	<0.001	<0.001	M0.001	0.00133
Numbness	SLNB	4 (n=124)	5 (n=125)	5 (n=123)	5 (n=108)
	ND	4 (n=126)	4 (n=131)	4 (n=128)	4 (n=120)
	p-value*	0.01345	<0.001	0.00077	<0.001
Neck appearance	SLNB	5	5	5	5
	ND	3	4	4	4
	p-value*	<0.001	<0.001	0.01852	0.04795

Measurement scale ranged from 1 to 5. Higher scores indicate a better quality of life. **ND: Neck dissection** **SLNB: Sentinel Lymph Node Biopsy*P-value: Bonferroni corrected alpha for multiple testing was set at 0.0125**

Neck and shoulder morbidity

Hasegawa (2021) measured 'shoulder drop' and 'reach above' using the Neck Dissection Quality of Life Questionnaire. Since these subscales specifically describe an aspect of shoulder morbidity, these subscales were described here. Hasegawa (2021) also used the shoulder abduction test. Results are presented in Table 11.10 for 1, 3, 6, and 12 months postoperatively. Median scores were derived from the reported data in a frequency table.

Table 11.10 Median scores for shoulder morbidity, from Hasegawa (2021)

Outcome	Treatment	Median score at 1 month (sample size)	Median score at 3 months (sample size)	Median score at 6 months (sample size)	Median score at 12 months (sample size)
Shoulder drop (QoL subscale)*	SLNB	5 (n=125)	5 (n=125)	5 (n=123)	5 (n=108)
	ND	4 (n=126)	4 (n=131)	5 (n=128)	5 (n=119)
	p-value**	<0.001	<0.001	0.004	0.04873
Reach above (QoL subscale)	SLNB	5 (n=124)	5 (n=125)	5 (n=123)	5 (n=108)
	ND	4 (n=126)	4 (n=130)	5 (n=128)	4.5 (n=120)
	p-value*	<0.001	<0.001	0.04327	0.09578
Arm abduction test†	SLNB	3 (n=38)	4 (n=33)	4 (n=26)	4 (n=19)
	ND	4 (n=68)	3 (n=73)	4 (n=41)	5 (n=31)
	p-value*	<0.001	<0.001	0.06219	0.099

ND: Neck dissection
SLNB: Sentinel Lymph Node Biopsy
QoL: Quality of life
***Measurement scale ranged from 1 to 5. Higher scores indicate a better quality of life.**
****P-value: Bonferroni corrected alpha for multiple testing was set at 0.0125**
†Measurement scale ranged from 0 to 5: 0 = up to <90°/ 1 = up to around 90°/ 2 = Up to more than 90° but < 150°/ 3 = Up to more than 150° but < 180°/ 4 = up to 180° with pain or effort/ 5 = up to 180° without pain or effort

Garrel (2020) assessed shoulder mobility with the neck-shoulder impairment scale (self-reported). Results were displayed in a figure and exact scores can only be approximated. Significance tests at different time points on the questionnaire's items are summarized in Table 11.11. Garrell (2020) also reported the proportion of patients capable of reaching 180° shoulder abduction without pain or effort. Results are summarized in Table 11.12.

Table 11.11 Approximated scores and statistical differences between groups on the neck-shoulder impairment scale as reported by Garrel (2020)

Item	2 months	4 months	6 months	12 months
Shoulder stiffness	SLNB: 17% ND: 34% p<0.01 (favouring SLNB)	SLNB: 15% ND: 36% p<0.01 (favouring SLNB)	SLNB: 18% ND: 35% p<0.01 (favouring SLNB)	SLNB: 16% ND: 17% NS
Shoulder pain	SLNB: 20% ND: 32% NS	SLNB: 22% ND: 32% NS	SLNB: 22% ND: 27% NS	SLNB: 22% ND: 13% NS
Constriction of the neck	SLNB: 26% ND: 37% NS	SLNB: 17% ND: 25% NS	SLNB: 20% ND: 39% p<0.01 (favouring SLNB)	SLNB: 17% ND: 24% NS
Limited ability to reach above head	SLNB: 15% ND: 39% p<0.01 (favouring SLNB)	SLNB: 18% ND: 29% NS	SLNB: 13% ND: 26% p=0.03 (favouring SLNB)	SLNB: 14% ND: 15% NS
Neck numbness	SLNB: 23%	SLNB: 19%	SLNB: 19%	SLNB: 10%

	ND: 23% NS	ND: 15% NS	ND: 29% NS	ND: 14% NS
Shoulder drop	SLNB: 6% ND: 11% NS	SLNB: 6% ND: 11% NS	SLNB: 6% ND: 7% NS	SLNB: 5% ND: 5% NS
Bothered by appearance of neck	SLNB: 16% ND: 14% NS	SLNB: 15% ND: 18% NS	SLNB: 11% ND: 10% NS	SLNB: 5% ND: 17 p=0.04 (favouring SLNB)
Difficulty dressing	SLNB: 6% ND: 21% NS	SLNB: 10% ND: 17% NS	SLNB: 6% ND: 12% NS	SLNB: 5% ND: 5% NS
Difficulty combing hair	SLNB: 10% ND: 17% NS	SLNB: 7% ND: 12% NS	SLNB: 5% ND: 9% NS	SLNB: 6% ND: 6% NS
Limited in ability to do work	SLNB: 10% ND: 24% p<0.01 (favouring SLNB)	SLNB: 11% ND: 22% NS	SLNB: 13% ND: 13% NS	SLNB: 8% ND: 9% NS
Limited in ability to do leisure	SLNB: 11% ND: 24% p=0.01 (favouring SLNB)	SLNB: 11% ND: 21% p=0.05 (favouring SLNB)	SLNB: 11% ND: 24% p=0.03 (favouring SLNB)	SLNB: 9% ND: 11% NS
NS: Not significant **SLNB: Sentinel lymph node biopsy** **Lower score indicates less impairment: Percentage of positive responses to the questions**				

Table 11.12 Proportion capable of reaching 180° shoulder abduction without pain or effort, from Garrell (2020)

	2 months	4 months	6 months	12 months	24 months
SLNB-group	71.03%	74.29%	76.29%	84.95%	87.8%
ND-group	50.51%	57.89%	60.23%	76.92%	78.38%
Significance testing	p<0.01	p<0.01	p<0.03	p=0.18	p=0.11
END: Elective Neck Dissection **SLNB: Sentinel Lymph Node Biopsy**					

Hematoma

None of the included studies reported the occurrence of hematomas as an outcome.

Pain

Hasegawa (2021) measured 'pain' using the Neck Dissection Quality of Life Questionnaire. Since this subscale specifically described the outcome of interest, the subscale was reported here. The measurement scale of the instrument was 1 to 5, where higher scores indicated a higher quality of life (i.e. less pain). Table 11.13 summarized the findings of Hasegawa (20201) at 1, 3, 6, and 12 months postoperatively. Median scores were derived from the reported data in a frequency table.

Table 11.13 Median scores of the pain subscale of th Neck Dissection Quality of Life Questionnaire, as measured by Hasegawa (2021)

Outcome	Treatment	Median score at 1 month (sample size)	Median score at 3 months (sample size)	Median score at 6 months (sample size)	Median score at 12 months (sample size)
Pain (QoL subscale)*	SLNB	4 (n=125)	5 (n=125)	5 (n=123)	5 (n=108)
	ND	4 (n=126)	4 (n=130)	4 (n=128)	4 (n=120)
	p-value**	0.00117	0.00086	0.01272	0.6394
ND: Neck dissection **SLNB: Sentinel Lymph Node Biopsy** **QoL: Quality of life** ***Measurement scale ranged from 1 to 5. Higher scores indicate a better quality of life (i.e. less pain).** ****P-value: Bonferroni corrected alpha for multiple testing was set at 0.0125**					

Postoperative oedema
None of the included studies reported the occurrence of postoperative oedema as an outcome.

Costs
None of the included studies reported costs as an outcome.

Level of evidence of the literature
The level of evidence regarding the outcome measure neck recurrence was downgraded by 3 levels because of study limitations (1 level for risk of bias: unclear block size for randomization in one of the RCTs, unclear procedures for random sequence generation, unclear procedures for allocation concealment); number of included patients (2 levels for imprecision: the confidence interval of the pooled estimate crosses both borders of clinical decision-making (0.8 and 1.25)); publication bias was not assessed.

The level of evidence regarding the outcome measure disease-specific survival was downgraded by 2 levels because of study limitations (1 levels for risk of bias: unclear block size for randomization, unclear procedures for random sequence generation, unclear procedures for allocation concealment, no blinding in the RCT); number of included patients (1 level for imprecision: the trial protocol calculated 164 patients per arm in a sample size calculation, this number was not met in the actual inclusion); publication bias was not assessed.

The level of evidence regarding the outcome measure overall survival was downgraded by 2 levels because of study limitations (1 level for risk of bias: unclear block size for randomization in one of the RCTs, unclear procedures for random sequence generation, unclear procedures for allocation concealment); number of included patients (1 level for imprecision: Hasegawa (2021) calculated a sample size for a 12% difference (border of non-inferiority); using the sample size calculation provided in the protocol of Hasegawa (2021) a sample size for a 5% difference was calculated resulting in n=592 participants per arm ($D_{between\text{-}group}$=0.05, $Z_{one\text{-}sided\ alpha\ 0.05}$=1.65, $Z_{two\text{-}sided\ beta\ 0.2}$=1.28 P_a=0.85, P_b=0.85); SLNB arms consisted of n=134/n=137, ND arms consisted of n=137/n=139); publication bias was not assessed.

The level of evidence regarding the outcome measure neck and shoulder morbidity was downgraded by 3 levels because of study limitations (2 levels for risk of bias: unclear block size for randomization in one of the RCTs, unclear procedures for random sequence generation, unclear procedures for allocation concealment, some concerns due to no blinding of the patient in the RCTs, outcomes on the shoulder impairment scale were not reported at 24 months in one RCT); number of included patients (1 level for imprecision: SLNB arms consisted of n=134/n=137, ND arms consisted of n=137/n=139); publication bias was not assessed.

The level of evidence regarding the outcome measure quality of life was downgraded by 3 levels because of study limitations (2 levels for risk of bias: unclear procedures for random sequence generation, unclear procedures for allocation concealment, some concerns due to no blinding of the patient in the RCT, missing data on the subscales at 12 months was 12.4% (ND) and 19.4% (SLNB)); number of included patients (1 level for imprecision: SLNB arms consisted of n=134, ND arms consisted of n=137); publication bias was not assessed.

The level of evidence regarding the outcome measure pain was downgraded by 3 levels because of study limitations (2 levels for risk of bias: unclear procedures for random sequence generation, unclear procedures for allocation concealment, no blinding in the RCT, 13.1% (ND) and 19.4%(SLNB) missing data at 12 months); number of included patients (1 level for imprecision: SLNB arms consisted of n=134, ND arms consisted of n=137); publication bias was not assessed.

The level of evidence regarding the outcome measures hematoma, postoperative oedema, and costs could not be GRADEd, since none of the included studies reported this outcome.

Conclusions

VERY LOW GRADE	The evidence is very uncertain about the effects of a sentinel node biopsy on **neck recurrences** compared to elective neck dissection. *Sources: (Hasegawa, 2021; Garrel, 2020)*

LOW GRADE	The evidence is uncertain about the effects of a sentinel node biopsy on **disease-specific survival** compared to elective neck dissection and may not result in relevant differences between treatments.. *Sources: (Garrel, 2020)*

LOW GRADE	The evidence is uncertain about the effects of a sentinel node biopsy on **overall survival** compared to elective neck dissection and may not result in relevant differences between treatments. *Sources: (Hasegawa, 2021; Garrel, 2020)*

VERY LOW GRADE	The evidence is very uncertain about the effects of a sentinel node biopsy on **neck and shoulder morbidity** compared to elective neck dissection. *Sources: (Hasegawa, 2021; Garrel, 2020)*

VERY LOW GRADE	The evidence is very uncertain about the effects of a sentinel node biopsy on the **quality of life** compared to elective neck dissection. *Sources: (Hasegawa, 2021)*

VERY LOW GRADE	The evidence is very uncertain about the effects of a sentinel node biopsy on **pain** compared to elective neck dissection. *Sources: (Hasegawa, 2021)*

- GRADE	The outcomes **occurrence of hematomas**, **postoperative oedema**, and c**osts** could not be assessed since none of the included studies reported these outcomes.

Overwegingen - van bewijs naar aanbeveling

De zekerheid in het bewijs uit de geïncludeerde gerandomiseerde trials was laag tot zeer laag voor de gerapporteerde uitkomstmaten. Procedures met betrekking tot de randomisatie werden niet (voldoende) beschreven. Daarnaast vonden blindering niet plaats,

wat als risico heeft dat de ‘zachtere’ uitkomsten kunnen vertekenen in tegenstelling tot ‘harde’ uitkomstmaten zoals algehele overleving. Garrel (2020) stelde in het studieprotocol dat de kwaliteit van leven gemeten zou worden met de H&N35, QLQ-C30, SF-36 en EuroQoL EQ-5D, maar rapporteerde hierover geen resultaten in de geïncludeerde studierapportage. De geïncludeerde gerandomiseerde studies in de literatuuranalyse rapporteerden daarnaast geen data over de kosten en het ontstaan van hematomen en lymfoedeemvorming.

In een systematische review van Crocetta (2020) over schildwachtklierprocedures versus halsklierdissecties werden géén gerandomiseerde onderzoeken gevonden tot 30 april 2019. In de geïncludeerde niet-gerandomiseerde onderzoeken werden geen significante verschillen gevonden op de volgende uitkomstmaten: recidief van lymfekliermetastasen in de hals, ziekte-specifieke overleving, algehele overleving, kwaliteit van leven (behalve op één sub-schaal uit één studie: kwaliteit van leven op de sub-schaal ‘swallowing’ was significant lager voor de electieve halsklierdissectie-groep), pijn, en lymfoedeemvorming. Eén studie, geïncludeerd door Crocetta (2020), observeerde dat er proportioneel meer mensen die een schilwachtklierprocedure ondergingen pijn ervaarden dan mensen die een halsklierdissectie ondergingen, maar dit verschil was niet statistisch significant. Voor de schouderfunctie werd gezien dat, indien gerapporteerd, groepen die de schildwachtklierprocedure ondergingen een statistisch significant betere schouderfunctie hadden zoals gemeten met de Constant-Murley score. Eén studie, opgenomen in de systematische review van Crocetta (2020), rapporteerde de schouderbeperkingen zoals gemeten met de Shoulder Disability Questionnaire. Hier leek het wellicht dat mensen die een schildwachtklierprocedure ondergingen minder beperkingen ervaarden, maar er werd geen statistisch significant verschil tussen de groepen geobserveerd. Twee studies in Crocetta (2020) rapporteerden over het ontstaan van bloedingen. Er werd door één studie geen statistisch significant verschil gevonden in het aantal bloedingen die revisie chirurgie noodzakelijk maakten (schildwachtklierprocedure: 0/33, 0%; halsklierdissectie: 5/29, 17.2%; OR=0,067, 95%BHI: 0,004-1,260 (+0,5 in alle cellen in verband met nul-waarde)), terwijl in de andere studie een significant verschil in het vóórkomen van hematomen werd gezien aan de hand van de Fischer’s Exact test (schildwachtklierprocedure: 0/29, 0%; halsklierdissectie: 6/41, 14.6%; OR=0,093, 95%BHI: 0,005 tot 1,712 (+0,5 in alle cellen in verband met nul-waarde)). Beide studies zagen minder events in de groep die de schilwachtklierprocedure ontving ten opzichte van aanvullende halsklierdissectie of electieve halsklierdissectie. De zekerheid in dit bewijs is waarschijnlijk laag tot zeer laag door de observationele aard van de studies. De auteurs van de systematische review rapporteerden voor 4 van de 5 geïncludeerde studies een hoog risico op vertekening doordat de groepen van elkaar verschilden op mogelijke confounders (door middel van de Newcastle-Ottawa Scale). De auteurs concludeerden dat er tot op het moment van zoeken een gebrek was aan gerandomiseerd bewijs. Zij waren van mening dat hun resultaten suggereerden dat er geen significante verschillen zijn tussen een beleid van de hals gebaseerd op de schildwachtklierprocedure en electieve halsklierdissectie op totale overleving, ziektevrije overleving en op het recidief van halskliermetastasen, maar dat de zekerheid in het geïncludeerde bewijs te laag is voor klinische besluitvorming.

Sundaram (2019) voerde een gerandomiseerde trial uit in India om de effecten van een schildwachtklierprocedure te vergelijken met electieve halsklierdissectie. Procedures rondom de randomisatie (bijvoorbeeld de blok-grootte, random sequence generation) werden niet of onvoldoende gerapporteerd. De studie werd geëxcludeerd uit de literatuuranalyse omdat er patiënten met cT3 tumoren werden geïncludeerd en omdat de enige relevante uitkomst als composiet werd gerapporteerd (nodal én distant metastases in de follow-up). Recidief in de halsklier kon niet afzonderlijk worden geanalyseerd. De auteurs

rapporteerden drie recidieven in de halsklierdissectie-groep (3/30, 10%) tegenover één recidief in de schildwachtklierprocedure-groep (1/28, 3.6%). Hiermee is het volgende relatieve risico te berekenen: RR = 0.36 (95%BHI: 0.04-3.24).

Van Hinte (2021) beschreef in een prospectief cohortonderzoek met 69 patiënten (cT1-2N0 mondholtecarcinomen; n= 33 END, n=27 SLNB-, n=9 SLNB+) uitkomsten betreffende de schoudermorbiditeit. Metingen werden verricht tot 12 maanden na de ingreep. De auteurs concludeerden dat de geobserveerde korte termijn voordelen op de schouderfunctie de keuze voor een halsklierdissectie als voorkeursbehandeling versterkt.

De schildwachtklierprocedure is echter niet voor alle mondholtecarcinomen even betrouwbaar. In een studie waarbij retrospectief een cohort patiënten met een vroeg stadium mondholtecarcinoom een schildwachtklierprocedure ondergingen (n=488) werd vergeleken werd met een cohort patiënten die electieve halsklierdissectie ondergingen (n=399), was voor de detectie van occulte lymfekliermetastasen de sensitiviteit bij mondbodemcarcinomen statistisch significant lager: 63% (SLNB) versus 92% (END, p = 0.006). De negatief voorspellende waarde was 90% versus 97% (p = 0.057). De sensitiviteit was bij mondbodemcarcinomen lager dan voor de overige lokalisaties in de mondholte: 63% versus 86% (p = 0.008) (den Toom, 2020). Omdat de oorzaak van de mindere betrouwbaarheid met name gelegen lijkt te zijn in (radioactieve) overstraling van de schildwachtklieren door de hoge activiteit op de nabijgelegen injectielocatie (waardoor deze niet meer separaat detecteerbaar zijn) wordt bij mondbodemcarcinomen een aanvullende dissectie van level I geadviseerd, totdat met nieuwe technieken deze schildwachtklieren beter geïdentificeerd kunnen worden. Zodoende kan bij mondbodemcarcinomen de schildwachtklierprocedure waarschijnlijk even betrouwbaar verricht worden als bij andere tumorlokalisaties in de mondholte (Stoeckli, 2016).

Voordeel van een beleid gebaseerd op de schildwachtklierprocedure is dat een aanzienlijk aantal achteraf onnodige halsklierdissecties worden voorkomen. Een nadeel is dat bij een positieve schildwachtklierprocedure een tweede operatie nodig is voor de halsklierdissectie, terwijl deze bij een electieve ingreep in één keer tegelijk met de resectie van de primaire tumor verricht kan worden.

Seferin (2021) rapporteerde een cross-sectioneel onderzoek waarin de kwaliteit van leven 26 maanden na de ingreep gemeten met de University of Washington Quality of Life Questionnaire. Patiënten met een T1-2N0 mondholtecarcinoom die tussen 2014 en 2015 een ingreep ondergingen (n=51) werden bevraagd, maar slechts een deel kon worden geïncludeerd (n=15 met schildwachtklierprocedure, n=9 met selectieve halsklierdissectie). De auteurs concludeerden dat patiënten die een schildwachtklierprocedure ondergingen op langere termijn een betere kwaliteit van leven ervaarden, specifiek op het gebied van uiterlijk en kauwfunctie.

Flach (2016) interviewde patiënten met een negatieve schildwachtklierprocedure en patiënten met een positieve schildwachtklierprocedure gevolgd door een halsklierdissectie. De meeste van deze patiënten prefereerden een beleid van de klinisch negatieve hals met een schildwachtklierprocedure in plaats van een halsklierdissectie.

De individuele keuze dient door behandelend arts en patiënt gezamenlijk gemaakt te worden.

Govers (2013) toonde modelmatig aan dat de schildwachtklierprocedure kosteneffectief is in vergelijking met electieve halsklierdissectie. Van de Linden (2016) bevestigde dit later in ieder geval voor de korte en middellange termijn. Hoe beter de accuraatheid van de schildwachtklier is hoe kosten-effectiever deze is. Het is mogelijk dat bij een hogere incidentie van occulte lymfekliermetastasen de schildwachtklierprocedure niet meer kosteneffectief is. In de Franse zorg-context werd een kostenanalyse gerapporteerd door De Kerangal (2021) waar de schildwachtklierprocedure (n=94) met de selectieve halsklierdissectie (n=77) vergeleken werd bij patiënten met een T1-2cN0 mondholte tumoren die tussen 2012 en 2017 werden behandeld. De volgende kosten werden gebruikt bij de berekening van de kosten: kosten van de ziekenhuisopname voor de initiële operatie, kosten voor de verlate aangepaste radicale halsklierdissectie en kosten voor elke ziekenhuisopname door postoperatieve complicaties tot 60 dagen na de initiële operatie. Na multivariabele correctie werd geschat dat een schildwachtklierprocedure €9.564,- (95%BHI: 7.646-11.483) kostte, ten opzichte van €10.562,- (95%BHI: 8.985-12.138) voor een selectieve halsklierdissectie. Het gemiddelde verschil was niet statistisch significant.

De verrichtingen schildwachtklierprocedure en electieve halsklierdissectie zijn voor iedereen toegankelijk. Beide vormen van beleid (schildwachtklierprocedure en electieve halsklierdissectie) kunnen in alle hoofd-halscentra routinematig verricht worden nadat door het behandelend team enige ervaring hiermee is opgedaan. De faciliteiten zijn in alle centra aanwezig. Binnen elk centrum kan een afweging gemaakt worden welk beleid de voorkeur in het betreffende centrum heeft. Voorzichtigheid is geboden bij mondbodemcarcinomen aangezien daarbij de schildwachtklierprocedure minder betrouwbaar is. In geval van mondbodem carcinomen is het nog steeds mogelijk een schildwachtklier procedure te doen, echter, vanwege overstraling naar de hals van de tracer vanuit de inspuitplaats in de mondbodem (shine through phenomenon) kan het identificeren van de schildwachtklier lastig blijken. Hierbij wordt in de literatuur een duidelijk lagere negatief voorspellende waarde gevonden dan voor andere mondholte locaties. Indien een schildwachtklier procedure wordt overwogen dan is het mogelijk een selectieve verwijdering van level 1A uit te voeren zoals beschreven door Stoeckli (2016) als onderdeel van de schildwachtklier procedure.

Aanbeveling

Aanbeveling-1

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

Een beleid op basis van de schildwachtklierprocedure heeft als voordeel dat er wellicht een aanzienlijk deel achteraf onnodige halsklierdissecties voorkómen zouden kunnen worden. Het nadeel van een schildwachtklierprocedure is dat er een tweede operatie noodzakelijk is als er een positieve schildwachtklier gevonden wordt. Een electieve ingreep is daartegenover in één verrichting mogelijk, namelijk gezamenlijk met de resectie van de primaire tumor. De zekerheid in het gevonden wetenschappelijk bewijs was laag tot zeer laag en op enkele uitkomstmaten werd geen gerandomiseerde data gevonden. Binnen elk centrum kan er een afweging gemaakt worden welk beleid de voorkeur heeft.

Verricht bij patiënten met een cT1-cT2 plaveiselcelcarcinoom van de mondholte en een klinisch en/of bij beeldvorming negatieve hals een schildwachtklierprocedure of een electieve halsklierdissectie.

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Bijlagen bij module 11.4.3

Implementatieplan

Aanbeveling	Tijdspad voor implementatie: < 1 jaar, 1 tot 3 jaar of > 3 jaar	Verwacht effect op kosten	Randvoorwaarden voor implementatie (binnen aangegeven tijdspad)	Mogelijke barrières voor implementatie[1]	Te ondernemen acties voor implementatie[2]	Verantwoordelijken voor acties[3]	Overige opmerkingen
1e Verricht bij patiënten met een klein mondholtecarcinoom en een klinisch en/of bij beeldvorming negatieve hals een schildwachtklierprocedure of een electieve halsklierdissectie	<1 jaar	Geen	Geen	Geen	Gangbare disseminatie	Geen acties	Geen

[1] barrières kunnen zich bevinden op het niveau van de professional, op het niveau van de organisatie (het ziekenhuis) of op het niveau van het systeem (buiten het ziekenhuis). Denk bijvoorbeeld aan onenigheid in het land met betrekking tot de aanbeveling, onvoldoende motivatie of kennis bij de specialist, onvoldoende faciliteiten of personeel, nodige concentratie van zorg, kosten, slechte samenwerking tussen disciplines, nodige taakherschikking, et cetera.
[2] Denk aan acties die noodzakelijk zijn voor implementatie, maar ook acties die mogelijk zijn om de implementatie te bevorderen. Denk bijvoorbeeld aan controleren aanbeveling tijdens kwaliteitsvisitatie, publicatie van de richtlijn, ontwikkelen van implementatietools, informeren van ziekenhuisbestuurders, regelen van goede vergoeding voor een bepaald type behandeling, maken van samenwerkingsafspraken.
[3] Wie de verantwoordelijkheden draagt voor implementatie van de aanbevelingen, zal tevens afhankelijk zijn van het niveau waarop zich barrières bevinden. Barrières op het niveau van de professional zullen vaak opgelost moeten worden door de beroepsvereniging. Barrières op het niveau van de organisatie zullen vaak onder verantwoordelijkheid van de ziekenhuisbestuurders vallen. Bij het oplossen van barrières op het niveau van het systeem zijn ook andere partijen, zoals de NZA en zorgverzekeraars, van belang.

Evidence tables

Evidence table for intervention studies (randomized controlled trials and non-randomized *observational* studies (cohort studies, case-control studies, case series))[1]

This table is also suitable for diagnostic studies (screening studies) that compare the effectiveness of two or more tests. This only applies if the test is included as part of a test-and-treat strategy -otherwise the evidence table for studies of diagnostic test accuracy should be used.

Research question:

Study reference	Study characteristics	Patient characteristics [2]	Intervention (I)	Comparison / control (C) [3]	Follow-up	Outcome measures and effect size [4]	Comments
Hasegawa 2021	Type of study: Multicenter RCT Setting and country: Japan Funding and conflicts of interest: AH received research funding (Raiho Pharmaceutical, Ono Pharmaceutical, Eidai Co Ltd, Eisai Co Ltd) AS received honoraria (Kyorin, Mitsubishi Tanabe Pharma) and research funding (Taiho Pharmaceutical, Shionogi, Mitubishi Tanabe Pharma, Daiichi Sankyo/UCB Japan, Teijin Pharma, Takeda) YY had a consulting/advisory role (MSD KK, Chugai Pharma, AstraZeneca, Novartis,	Inclusion criteria: T1-2N0M0 oral cavity squamous cell carcinoma (TNM 7), No lymph nodes on contrast enhanced CT of the head/neck, no prior treatment, ≥18 years old, written consent Exclusion criteria: T1 tumors with ≤4mm depth of invasion, recurrence after definitive treatment (e.g. surgery or radiotherapy), history of radiation to the neck, planned or	Describe intervention (treatment/procedure/test): SLN identification was performed with ^{99m}Tc phytate, which was administered the day before surgery in the peritumoral mucosa (27 gauge needle). On the day of surgery, a gamma probe was used (lymphoscinigraphy with or withoutsingle-photon emission CT) to identify the SLN. During surgery frozen section analysis was performed (2mm blocks). When negative, the blocks were paraffin embedded for detailed staining analysis (hematoxylin en eosin, and cytokeratin immunostaining) on 4um sections. Isolated	Describe control (treatment/procedure/test): Neck dissection was performed (supraomohyoid).	Length of follow-up: Median 3.1 years. (3-year for endpoint overall survival) Loss-to-follow-up: Intervention: N=3 (3/137, 2.2%) Reasons: 1 declined treatment, 2 did not fulfil eligibility criteria Control: N=1 (1/138, 0.7%) Reasons: 1 did not fulfil eligibility criteria Incomplete outcome data: No reasons described. Missing data on QoL subscales and arm abduction test.	Outcome measures and effect size (include 95%CI and p-value if available): Regional recurrence, n (%): I: 15 (15/134, 11.2%) C: 13 (13/137, 9.5%) RR = 1.18 (95%CI: 0.58-2.38), calculated from the reported data. 3-Year overall survival: I: 87.9% (95%CI one-	Clinical negative neck status was assessed with CT and supplemented by US when necessary. MRI and PET/CT were added at the discretion of the study center. Patients with extracapsular spread of the lymph node metastasis received adjuvant therapy: radiotherapy within 6 weeks of surgery. Concomittant

	Amgen, Archer, Takeda, Daiichi Sankyo/UCB Japan) and speakers' bureau (MSD KK, Chugai Pharma, AstraZeneca, Novartis, Amgen, Archer, Pfizer, Ventana Medical Systems, Agilent, Thermo Fisher Scientific)	current pregnancy or lactation, other disqualifying reasons as judged by the attending physician. <u>N total at baseline</u>: Intervention: 137 Control: 138 <u>Important prognostic factors[2]</u>: *Median age (range):* *I: 63 (21-90)* *C: 63 (28-85)* *Sex (% males):* *I: 66.4% M* *C: 65.7% M* Tumor location, n: I: Tongue (109), FOM (13), lower gingiva (7), buccal mucosa (n=5) C: Tongue (114), FOM (14), lower gingiva (6), buccal mucosa (3). T-stage, n:	tumor cells were treated as metastatis-positive. Tumor resection was performed. Persons with positive SLN on frozen section immediately underwent neck dissection (level I-IV or I-V). If the pathologic specimen was positive the neck dissection was performed within 6 weeks of the initial surgery. When no metastasis was detected in the SLN and if the resection of the primary site required pull-through resection, a supraomohyoid neck dissection was performed. Patients with a negative SLN on the contralateral side of the neck received a SLN basin dissection.		<u>Quality of life (stiffness), missing I / C (%):</u> 1 month: 6.7% / 8% 3 months: 6.7% / 4.4% 6 months: 8.2 % / 6.6% 12 months: 19.4% / 12.4% <u>Quality of life (constriction), missing I / C (%):</u> 1 month: 6.7% / 8.8% 3 months: 6.7% / 3.4% 6 months: 8.2% / 6.6% 12 months: 19.4% . 12.4% <u>Quality of life (pain), missing I / C (%):</u> 1 month: 6.7% / 8% 3 months: 6.7% / 5.1 % 6 months: 8.2% / 6.6% 12 months: 19.4% / 12.4% <u>Quality of life (numbness), missing I / C (%):</u> 1 month: 7.4% / 8%	sided lower limit: 82.4%) C: 86.6% (95%CI one-sided lower limit: 80.9%) P<0.001. <u>Quality of life (stiffness), median score, 1 month/ 3 months / 6 months / 12 months:</u> I: 4 / 4 / 4 / 4 C: 3 / 3 / 4 / 4 P-value: <0.001 / <0.001 / 0,00105 / 0.00108 Alpha = 0.0125 <u>Quality of life (constriction), mean score 1 month/ 3 months / 6 months / 12 months:</u> I: 4 / 5 / 5 / 5 C: 3 / 3 / 4 / 4 P-value: <0.001 / <0.001 /	chemotherapy was left at the discretion of each study center. Patients with positive margins had: reoperation or radiation therapy with or without chemotherapy at the discretion of each study center. Border of clinical equivalence was set at 12% for 3-year overall survival. Medians for QoL scales were calculated from the reported frequency tables

		I: T1 (26), T2 (108) C: T1 (25), T2 (112) pN-status, n: I: pN- (86), pN+ (46), pNx (2) C: pN- (99), pN+ (34), pNx (4) Postoperative therapy: I: none (130), radiation and/or chemo (4) C: none (131), radiation and/or chemo (3) Median follow-up, months: I: 37 (IQR: 36-39) C: 37 (IQR: 36-38) Groups comparable at baseline? Yes			3 months: 6.7% / 4.4% 6 months: 8.2% / 6.5% 12 months: 19.4% / 12.4% <u>Quality of life (shoulder drop), missing I / C (%):</u> 1 month: 6.7% / 8% 3 months: 6.7% / 4.4% 6 months: 8.2 / 6.6% 12 months: 19.4% / 13.1% <u>Quality of life (reach above), missing I / C (%):</u> 1 month: 7.4% / 8% 3 months: 6.7% / 5.1% 6 months: 8.2% / 6.6% 12 months: 19.4% / 12.4% <u>Quality of life (neck appearance), missing I / C (%):</u> 1 month: 6.7% / 8.8% 3 months: 6.7% / 4.4% 6 months: 8.2% / 6.6%	<0.001 / 0.00133 Alpha = 0.0125 <u>Quality of life (pain), mean score 1 month/ 3 months / 6 months / 12 months:</u> I: 4 / 5 / 5 / 5 C: 4 / 4 / 4 / 4 P-value: 0.00117 / 0.00086 / 0.01272 / 0.06394 (NS) Alpha = 0.0125 <u>Quality of life (numbness), mean score 1 month/ 3 months / 6 months / 12 months:</u> I: 4 / 5 / 5 / 5 C: 4 / 4 / 4 / 4 P-value: 0.01345 (NS) / <0.001 / 0.00077 / <0.001 Alpha = 0.0125	

					12 months: 19.4% / 12.4% Arm abduction test), missing I / C (%): 1 month: 71.6% / 50.3% 3 months: 75.4% / 46.7% 6 months: 80.6% / 70.1% 12 months: 85.8% / 77.3%	Quality of life (shoulder drop), mean score 1 month/ 3 months / 6 months / 12 months: I: 5 / 5 / 5 / 5 C: 4 / 4 / 5 / 5 P-value: <0.001 / <0.001 / 0.004 / 0.04873 (NS) Alpha = 0.0125 Quality of life (reach above), mean score 1 month/ 3 months / 6 months / 12 months: I: 5 / 5 / 5 / 5 C: 4 / 4 / 5 / 4.5 P-value: <0.001 / <0.001 / 0.04327 (NS) / 0.09578 (NS) Alpha = 0.0125 Quality of life (neck appearance), mean score 1	

						month/ 3 months / 6 months / 12 months: I: 5 / 5 / 5 / 5 C: 3 / 4 / 4 / 4 P-value: <0.001 / <0.001 / 0.01852 (NS) / 0.04795 (NS) Alpha = 0.0125 Arm Abduction Test (ordinal), mean score 1 month/ 3 months / 6 months / 12 months: I: 3 / 4 / 4 / 4 C: 4 / 3 / 4 / 5 P-value: <0.001 / <0.001 / 0.06219 (NS) / 0.099 (NS) Alpha = 0.0125	
Garrel 2020	Type of study: Multi-center, open-label RCT Setting and country: Hospital, France	Inclusion criteria: >18 years old, with health insurance, signed informed consent, not participating in	Describe intervention (treatment/procedure/test): Preoperative cN0 status was checked by contrast enhanced CT or by MRI (when	Describe control (treatment/procedure/test): Preoperative cN0 status was checked by contrast enhanced CT or by MRI	Length of follow-up: 5 year follow-up schedule. Mean follow-up: 4.95 (SD: 2.45) years. Loss-to-follow-up:	Outcome measures and effect size (include 95%CI and p-value if available):	After randomization some exclusion were made. The sample thereafter size was:

	Funding and conflicts of interest: Manuscript states that disclosures are found at https://doi.org/10.1200/JCO.20.01661	another trial, primary oral or oropharyngeal SCC diagnosed by biopsy with histopathologic analysis in last month before inclusion, operable tumor, T1-2N0M0 tumors, Exclusion criteria: Treatment of other cancer, non-invasive tumor (high-grade dysplasia, in situ carcinoma), inadequate tumor excision, contraindication to SLNB / lymph node dissection / radiotherapy / medical imaging, allery or intolerance to contrast product, pregnancy, refusal to accept full treatment, follow-up not possible, refusal	there were contraindications for CT). Preoperative SLN identification by radiotracer injection, followed by lymphoscintigraphy the day prior or on the same day prior to the surgical intervention. A portable gamma probe was used to identify the SLN during surgery. Intraoperative histopathologic analysis was performed by imprint cytology or frozen section examination (depending on the pathologist's choice). Tumor invasion in the SLN was defined as at least one micrometastasis (tumor tissue 200 micrometer-2mm) or one macrometastasis (tumor tissue >2mm). A neck dissection was advocated in the case of positive SLN. Isolated tumor cells (<200 micrometer) were not considered to be nodal invasion. Is positive SLNs were detected after surgery, neck dissection was performed during a second surgical procedure.	(when there were contraindications for CT). Tumor surgery and neck dissection (homolateral, or bilateral in case the tumor approached the median line). Pathologic lymph node assessment was performed thereafter. Adjuvant radiotherapy was planned if two or ore lymph nodes (including the SL, if applicable) were positive. Concomitant adjuvant chemotherapy was proposed in case of poor prognostic factors (vascular, perineural, muscular invasion). Follow-up was performed by the surgeon every 2 months (first year), every 4 months (second year), and once yearly (up to the fifth year). Every visit had a clinical examination. Neck-tocax CT was performed at year 1 and year 2 post-surgery. Functional follow-up was performed at month 2, 4, 6, 12, 24 post-surgery.	Excluded after randomization: Intervention: N=15 (9.7%) Reasons (describe): In situ carcinoma (n=5), refusal for random assignment (n=1), withdrawal of consent (n=1), radiotherapy decision by oncologist (n=1), R1 margin without tumor surgery completion (n=1), history of surgery/radiotherapy (n=2), high-grade dysplasia (n=1) Control: N=13 (8.6%) Reasons (describe): in situ carcinoma (n=5), neck dissection despite isolated tumor cells only (n=1), refusal for random assignment (n=3), urgent carotis surgery (n=1), synchronous lung tumor (n=1), high grade dysplasia (n=1), T4 tumor (n=1), investigator's decision (n=1).	Neck recurrence during follow-up (without relapse of the primary tumor), n: I: 13/140 (9.3%) C: 14/139 (10.1%) No statistically significant difference between groups (p=0.82, chi squared test) RR = 0.92 (95%CI: 0.45-1.89) 2-year disease-specific survival rate: I: 93.0% (95%CI: 87-96) C: 95.5% (95%CI: 90-98) 5-year disease-specific survival rate: I: 87.1% (95%CI: 79-92) C: 88.6 (95%CI: 82-93)	I: 140 C: 139 In de SLNB-arm, 8 persons underwent ND because of SLNB failure (total 21 ND's in the SLNB-arm (21/140)) ND was performed in a second surgery in 12 patients in the SLNB-arm where the initial intraoperative histopathology analysis was negative. Relative risk was calculated from the reported data. Shoulder function questionnaire and abduction test were not performed at baseline.

		to accept follow-up and/or provide necessary information for the study, patients already treated for the tumor (with the exception of excision biopsy), chemotherapy or immunotherapy for another cancer in the last 6 months, history of neck surgery and/or radiotherapy. <u>N total at baseline</u>: Intervention: 155 (140 after exclusions) Control: 152 (139 after exclusions) <u>Important prognostic factors[2]</u>: *For example age ± SD:* *I: 60.8 (12)* *C:59.1 (10.9)* *Sex:* *I:) 88 M (62.8%)*	Adjuvant radiotherapy was planned if two or ore lymph nodes (including the SL, if applicable) were positive. Concomitant adjuvant chemotherapy was proposed in case of poor prognostic factors (vascular, perineural, muscular invasion). Follow-up was performed by the surgeon every 2 months (first year), every 4 months (second year), and once yearly (up to the fifth year). Every visit had a clinical examination. Neck-thorax CT was performed at year 1 and year 2 post-surgery. Functional follow-up was performed at month 2, 4, 6, 12, 24 post-surgery.		<u>Incomplete outcome data</u>: Intervention: N=1 (0.7%) for tumor location data Reasons (describe): not provided Control: N=1 (0.7%) for pN-stage invasion data Reasons (describe): not provided	No statistically significant difference between groups for disease-specific survival (p=0.68) <u>2-year overall survival rate:</u> I: 88.7% (95%CI: 82-93 C: 92.6 (95%CI: 87-96) <u>5-year overall survival rate:</u> I: 82.2% (95%CI: 74-88) C: 81.8% (95%CI: 74-88) No statistically significant difference between groups for overall survival (p=0.42) Scores from the neck-	

		C: 101 M (72.7%) *Tumor location, n, I / C:* *Oral cavity: 124 / 119* *Oropharynx: 15 / 20* Missing: 1 / 0 cT stage (TNM7), n, I / C: cT1: 88 / 91 cT2: 52 / 48 pN-stage, n, I / C: not invaded: 105 / 109 invaded with extranodal extension: 11 / 9 invaded without extranodal extension: 24 / 20 Missing: 0 / 1 Adjuvant treatment, n, I / C: No adjuvant treatment: 107 / 105 Radiotherapy alone: 17 / 24 CRT: 10 / 6 Brachytherapy: 6 / 4				shoulder impairment self-report questionnaire were reported in a figure and can only be approximated. <u>Neck-shoulder impairment self-report questionnaire at 2 months:</u> Shoulder stiffness: p<0.01 (favouring SLNB) Shoulder pain: NS Constriction of the neck: NS Limited ability to reach above head: p<0.01 (favouring SLNB) Neck numbness: NS Shoulder drop: NS Bothered by appearance of neck: NS Difficulty dressing: NS	

		Groups comparable at baseline? Yes				Difficulty combing hair: NS Limited in ability to do work: p<0.01 (favouring SLNB) Limited in ability to do leisure: p=0.01 (favouring SLNB) <u>Neck-shoulder impairment self-report questionnaire at 4 months:</u> Shoulder stiffness: p<0.01 (favouring SLNB) Shoulder pain: NS Constriction of the neck: NS Limited ability to reach above head: NS Neck numbness: NS Shoulder drop: NS	

						Bothered by appearance of neck: NS Difficulty dressing: NS Difficulty combing hair: NS Limited in ability to do work: NS Limited in ability to do leisure: p=0.05 (favouring SLNB) <u>Neck-shoulder impairment self-report questionnaire at 6 months:</u> Shoulder stiffness: p<0.01 (favouring SLNB) Shoulder pain: NS Constriction of the neck: p<0.01 (favouring SLNB) Limited ability to reach above head: p=0.03	

						(favouring SLNB) Neck numbness: NS Shoulder drop: NS Bothered by appearance of neck: NS Difficulty dressing: NS Difficulty combing hair: NS Limited in ability to do work: NS Limited in ability to do leisure: p=0.03 (favouring SLNB) <u>Neck-shoulder impairment self-report questionnaire at 12 months:</u> Shoulder stiffness: NS Shoulder pain: NS Constriction of the neck: NS Limited ability to reach above head: NS	

						Neck numbness: NS Shoulder drop: NS Bothered by appearance of neck: p=0.04 (favouring SLNB) Difficulty dressing: NS Difficulty combing hair: NS Limited in ability to do work: NS Limited in ability to do leisure: NS <u>Shoulder abduction test, % of group reaching 180 degrees abduction without pain or effort) at 2 months:</u> I: 71.03% C: 50.51% Statistically different between groups (p<0.01)	

						Shoulder abduction test, % reaching 108 degrees abduction without pain or effort) at 4 months: I: 74.29% C: 57.89% Statistically different between groups (p=0.01) Shoulder abduction test, % reaching 108 degrees abduction without pain or effort) at 6 months: I: 76.29% C: 60.23% Statistically different between groups (p=0.03) Shoulder abduction test, % reaching 108 degrees	

						abduction without pain or effort) at 12 months: I: 84.95% C: 76.92% No statistically significant difference between groups (p=0.18) Shoulder abduction test, % reaching 108 degrees abduction without pain or effort) at 24 months: I: 87.8% C: 78.38% No statistically significant difference between groups (p=0.11)	

Notes:

1. **Prognostic balance between treatment groups is usually guaranteed in randomized studies, but non-randomized (observational) studies require matching of patients between treatment groups (case-control studies) or multivariate adjustment for prognostic factors (confounders) (cohort studies); the evidence table should contain sufficient details on these procedures.**
2. **Provide data per treatment group on the most important prognostic factors ((potential) confounders).**
3. **For case-control studies, provide sufficient detail on the procedure used to match cases and controls.**
4. **For cohort studies, provide sufficient detail on the (multivariate) analyses used to adjust for (potential) confounders.**

Risk of bias table for intervention studies (randomized controlled trials)

Study reference (first author, publication year)	Describe method of randomisation[1]	Bias due to inadequate concealment of allocation?[2] (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation?[3] (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation?[3] (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation?[3] (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results?[4] (unlikely/likely/unclear)	Bias due to loss to follow-up?[5] (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis?[6] (unlikely/likely/unclear)
Hasegawa 2021	Random assignment (stratification by T-stage an primary subsite). Randomization was performed by a statistical researcher.	Unclear Reason: not enough procedures explained. Allocation was performed through a web enrolment system in a data center. It was unclear who had (no) access to the allocation scheme.	Likely (QoL, functional) Reason: patients were probably aware of the type of treatment. No mentioning of blinding.	Likely (QoL, functional) Reason: healthcare providers were probably aware of the type of treatment. No mentioning of blinding.	Likely (QoL, functional) Reason: outcome assessors were probably aware of the type of treatment. No mentioning of blinding.	Unlikely Reason: endpoint in the protocol are reported manuscript	Likely (QoL at 12 months/shoulder abduction) Reason: Loss to follow-up / missing data at 12 months is large.	Unlikely Reason: Seems like ITT was followed. Four cases that eventually did not meet the eligibility criteria were excluded.
			Unlikely (recurrence, survival data) Reasons: blinding probably does not affect survival and recurrence data	Unlikely (recurrence, survival data) Reasons: blinding probably does not affect survival and recurrence data	Unlikely (recurrence, survival data) Reasons: blinding probably does not affect survival and recurrence data		Unlikely (QoL/ until 6 months, survival, and recurrence) Reason: survival/recurrence only have n=4 loss to follow-up. Up to 6 months the missing data is somewhat acceptable, although no reasons were provided.	
Garrell 2020	Random assignment by small balanced	Unclear	Likely (functional outcomes)	Likely (other outcomes)	Likely (other outcomes)	Likely	Unlikely	Unlikely

	blocks per center with a 1:1 ratio. Unclear block size. Random sequence generation procedures not decribed.	Reason: procedures not provided	Reason: patients were aware of the type of treatment	Reason: open label RCT	Reason: open label RCT	Reason: protocol states that quality of life was an endpoint. Shoulder impairment was supposed to be measured at 24 months (stated in methods) but only reported up to 12 months.	Reason: persons were somewhat equally excluded in both groups after randomization (most of them meeting exclusion criteria).	Reason: protocol states that ITT was performed.
			Unlikely (recurrence, survival data) Reasons: blinding patients probably does not affect survival data	Unlikely (overall survival) Reason: blinding does not affect overall survival	Unlikely (overall survival) Reason: blinding does not affect overall survival			

1. **Randomisation: generation of allocation sequences have to be unpredictable, for example computer generated random-numbers or drawing lots or envelopes. Examples of inadequate procedures are generation of allocation sequences** by **alternation, according to case record number, date of birth or date of admission.**
2. **Allocation concealment: refers to the protection (blinding) of the randomisation process. Concealment of allocation sequences is adequate if patients and enrolling investigators cannot foresee assignment, for example central randomisation (performed at a site remote from trial location) or sequentially numbered, sealed, opaque envelopes. Inadequate procedures are all procedures based on inadequate randomisation procedures or open allocation schedules.**
3. **Blinding: neither the patient nor the care provider (attending physician) knows which patient is getting the special treatment. Blinding is sometimes impossible, for example when comparing surgical with non-surgical treatments. The outcome assessor records the study results. Blinding of those assessing outcomes prevents that the knowledge of patient assignement influences the proces of outcome assessment (detection or information bias). If a study has hard (objective) outcome measures, like death, blinding of outcome assessment is not necessary. If a study has "soft" (subjective) outcome measures, like the assessment of an X-ray, blinding of outcome assessment is necessary.**
4. **Results of all predefined outcome measures should be reported; if the protocol is available, then outcomes in the protocol and published report can be compared; if not, then outcomes listed in the methods section of an article can be compared with those whose results are reported.**
5. **If the percentage of patients lost to follow-up is large, or differs between treatment groups, or the reasons for loss to follow-up differ between treatment groups, bias is likely. If the number of patients lost to follow-up, or the reasons why, are not reported, the risk of bias is unclear**
6. **Participants included in the analysis are exactly those who were randomized into the trial. If the numbers randomized into each intervention group are not clearly reported, the risk of bias is unclear; an ITT analysis implies that (a) participants are kept in the intervention groups to which they were randomized, regardless of the intervention they actually received, (b) outcome data are measured on all participants, and (c) all randomized participants are included in the analysis.**

Table of excluded studies

Author and year	Reason for exclusion
Benateau 2005	SR in French
Govers 2013	SR concerns accuracy
Kim 2020	SR concerns accuracy
Liu 2017	SR concerns accuracy
Thompson 2013	SR concerns accuracy
Kim 2020	Concerns accuracy outcomes
Loxha 2020	Concerns accuracy outcomes
Cramer 2019	Includes c-ND in SLNB and compares this to END
Loree 2019	Does not report the data for the comparison of interest
Molstrom 2019	Concerns accuracy outcomes
Marttila 2020	Concerns accuracy outcomes
Garau 2019	Concerns procedures, standards, and advances
Rathod 2020	No comparison to END
De Kerangal 2021	Nonrandomized study
Den Toom 2019	Concerns accuracy outcomes
Den Toom 2020	Nonrandomized study
McDonald 2019	Not the comparison of interest
Crocetta 2020	Included non-randomized studies
Hinhsammer 2019	Non-randomized study
Vigili 2020	Non-randomized study
Seferin 2021	Nonrandomized study
Sundaram 2019	The reported composite outcome (nodal/distant recurrence) cannot be discerned for the outcome of interest (neck recurrence), the study also included patients with cT3 tumors.

Literature search strategy

Algemene informatie

Richtlijn: HHT	
Uitgangsvraag: UV 11.4 Wat zijn (on)gunstige effecten van een schildwachtklierprocedure vergeleken met electieve halsklierdissectie bij patiënten met een crT1-2N0 mondholtecarcinoom, PICO2	
Database(s): Ovid/Medline, Embase	Datum: 16-7-2020, 1-7-2021
Periode: 2000-	Talen: niet van toepassing
Literatuurspecialist: Ingeborg van Dusseldorp	
Toelichting en opmerkingen: 1-7-2021 Update gedraaid in een nieuwe Rayyan omgeving gezet. HHT: SLNB versus END - Update 2021 De twee sleutelartikelen worden gevonden	

16-7-2020
PICO 2: schildwachtklierprocedure versus electieve halsklierdissectie

Het sleutelartikel van Cramer, 2018 wordt gevonden. Het artikel van den Toom 2020 wordt niet gevonden omdat het nog niet in de databases is toegevoegd. Op basis van de titelwoorden kan met zekerheid worden gesteld dat het artikel wordt gevonden zodra het aan de database is toegevoegd.

Zoekopbrengst

	EMBASE	Embase 2021	OVID/MEDLINE	Ovid/Medline 2021	Ontdubbeld + update 2021
SRs	13	22	7	7	13 + 7
RCTs	76	82	40	44	98 + 9
Observationele studies	61	68	90	95	90 + 9
Overig					
Totaal					201+25

Zoekverantwoording

Ovid/Medline

1 (meta-analysis/ or meta-analysis as topic/ or (meta adj analy$).tw. or (systematic*or literature adj2 review$1).tw. or (systematic adj overview$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (295283)

2 (exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (2004168)

3 Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or consecutive*.tw. or Cross sectional.tw. or Cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/ (Onder exp cohort studies vallen ook longitudinale, prospectieve en retrospectieve studies) (3476010)

4 exp Tongue neoplasms/ or exp Mouth neoplasms/ or ((mouth or oral or intraoral or tongue or lingual) adj3 (cancer or tumor* or tumour* or malignan* or neoplasm* or carcinoma*)).ti,ab,kf. (82540)

5 exp sentinel lymph node biopsy/ or ((sentinel node or sentinal lymph*) adj3 (procedure* or assessment* or biop*)).ti,ab,kf. (12216)

6 exp Neck dissection/ or neck dissection.ti,ab,kf. or neck radical dissection.ti,ab,kf. (12274)

7 4 and 5 and 6 (219)

8 7 not ((exp animals/ or exp models, animal/) not humans/) not (letter/ or comment/ or editorial/) (210)

9 1 and 8 (7) SR

10 2 and 8 (42)

11 3 and 8 (116)

12 10 not 9 (40), RCT

13 11 not 10 not 9 (90), Observationeel

Embase

No.	Query	Results
#13	**#11 NOT #10 NOT #9, Observationeel**	**61**
#12	**#10 NOT #9, RCT**	**76**
#11	#7 AND #8	**125**
#10	#6 AND #8	**82**

#9	**#5 AND #8, SR**	**13**
#8	#4 AND (1-1-2000)/sd NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	**269**
#7	'major clinical study'/de OR 'clinical study'/de OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR 'prospective study'/de OR 'cohort analysis'/de OR ((cohort NEAR/1 (study OR studies)):ab,ti) OR (('case control' NEAR/1 (study OR studies)):ab,ti) OR (('follow up' NEAR/1 (study OR studies)):ab,ti) OR (observational NEAR/1 (study OR studies)) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti)	**5321407**
#6	('clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti) NOT 'conference abstract':it	**2340458**
#5	('meta analysis'/de OR cochrane:ab OR embase:ab OR psycinfo:ab OR cinahl:ab OR medline:ab OR ((systematic NEAR/1 (review OR overview)):ab,ti) OR ((meta NEAR/1 analy*):ab,ti) OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/de) NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	**473856**
#4	#1 AND #2 AND #3	**351**
#3	'neck dissection'/exp OR 'neck dissection':ti,ab,kw OR 'neck radical dissection':ti,ab,kw	**18795**
#2	'sentinel lymph node biopsy'/exp OR ((('sentinel node' OR 'sentinal lymph*') NEAR/3 (procedure* OR assessment* OR biop*)):ti,ab,kw)	**20548**
#1	'tongue cancer'/exp OR 'mouth cancer'/exp OR (((mouth OR oral OR intraoral OR tongue OR lingual) NEAR/3 (cancer OR tumor* OR tumour* OR malignan* OR neoplasm* OR carcinoma*)):ti,ab,kw)	**86742**

11.4 Voor de praktijk

Ten aanzien van het beleid van de klinisch negatieve hals bestaan van oudsher twee opties: electieve halsklierdissectie en watchful waiting. In het algemeen heeft een electieve halsklierdissectie de voorkeur. Factoren die bij de keuze een rol kunnen spelen zijn invasiediepte van de primaire tumor en andere tumor- en patiëntfactoren. Bij een tumor met een zeer geringe invasiediepte kan eventueel gekozen worden voor watchful waiting. Mocht gekozen worden voor een watchful waiting beleid dan wordt echografie van de hals met eventueel cytologische punctie tijdens de follow-up geadviseerd, bijvoorbeeld 3 tot 4 keer in het eerste jaar. Door een verbeterde diagnostiek van lymfekliermetastasen kan de noodzaak tot electieve halsklierdissectie verminderd worden. Hiervoor is de schildwachtklierprocedure het meest geschikt.

De aanbevelingen samengevat:
Verricht bij patiënten met een klein mondholtecarcinoom (cT1-T2) en een klinisch negatieve hals (cN0) bij voorkeur een electieve halsklierdissectie tenzij specifieke patiëntfactoren (b.v. co-morbiditeit), tumorfactoren (b.v. zeer geringe invasiediepte) of aanvullende diagnostiek (b.v. negatieve schildwachtklierprocedure) aanleiding geven tot een ‘watchful waiting’ strategie.

Module 13.1 Behandeling T1-T2N0 hypofarynxcarcinoom

Uitgangsvraag

Wat is de optimale behandeling van de primaire tumor van T1-T2N0 hypofarynxcarcinomen?

Inleiding

Hypofarynxcarcinomen komen relatief weinig voor: ze vormen 7% van alle hoofd-halstumoren. Elk jaar worden ongeveer 190 nieuwe patiënten gediagnosticeerd in Nederland (Parkin, 2002). Vanwege verborgen tekenen van ziekte en symptomen had meer dan 80% van de patiënten een vergevorderd tumorstadium op het moment van diagnose (Kuo, 2014). Sinds de jaren '90 worden T1-T2N0 kleine hypofarynxcarcinomen behandeld met radiotherapie van de primaire tumor en electieve radiotherapie van de bilaterale nek. Recent worden echter ook Transoral laser micro Surgery (TLM) en minimaal invasieve Transoral Robotic Surgery (TORS) gebruikt voor de behandeling van farynx- en larynxtumoren (Meulemans, 2019). Een primaire behandeling met TORS zonder adjuvante radiotherapie zou kunnen zorgen dat (chemo)radiotherapie bewaard kan blijven als behandeloptie bij een mogelijke secundaire primaire tumor of een recidief. Het is niet duidelijk welke behandeling de beste resultaten oplevert in termen van overleving, morbiditeit en functionele uitkomsten. Behandelopties voor een primaire tumor van een klein hypofarynxcarcinoom (T1-T2, N0) zijn radiotherapie of chirurgie. Het is onduidelijk wat de beste keuze is.

Search and select

A systematic review of the literature was performed to answer the following question: what are the effects of radiation versus surgery for patients with a primary tumor of small hypopharyngeal carcinomas (T1-T2, N0) on predefined outcomes?

P	(Patients)	= Patients with a primary T1-T2N0 hypopharyngeal carcinoma
I	(Intervention)	= Radiation
C	(Comparison)	= Surgery (TLM or TORS)
O	(Outcomes)	= Overall survival (3 to 5 years), disease-free survival, morbidity, functional outcomes, quality of life, head-neck specific quality of life, EORTC QLQ-C30, EORTC QLQ-H&N35, H&N43

<u>Relevant outcome measures</u>

The working group considered survival (3 to 5 years), disease free survival, morbidity and functional outcomes as critical outcome measures for decision making; and quality of life, head-neck specific quality of life, EORTC QLQ-C30, EORTC QLQ-H&N35, H&N43 as important outcome measures for decision making.

Clinically relevant difference

The working group defined a minimal clinically relevant difference at a minimum of a median follow-up period of three years) *(in line with "NVMO-commissie ter Beoordeling van Oncologische Middelen (BOM)")* of:

- Overall survival: > 5% difference, or > 3% and HR< 0.7.
- Relapse-free survival: HR< 0.7.

And, in case of absence of a clinically relevant difference in overall survival or relapse-free *survival:*

- Quality of life: A minimal clinically important 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.
- Complications/adverse events: Statistically significant less complications/adverse events.

Search and select (Methods)
The databases MEDLINE (via OVID) and Embase (via Embase.com) were searched with relevant search terms until July 15th, 2020. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 64 hits.

Studies were selected based on the following criteria: included patients with a primary tumor of small hypopharyngeal carcinomas (T1-T2, N0), compared radiation with surgery, reported at least one of the outcomes of interest, the study design was a systematic review (SR) or randomized controlled trial (RCT), and were written in English.

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

Results
None of the studies retrieved from the search compared the two interventions of interest in a randomized or observational design, therefore no studies were included.

Summary of literature
No studies reported on the crucial and important outcome measures.

Conclusions
No studies reported on the crucial and important outcome measures. Therefore, GRADE assessment could not be applied. As a result, no literature conclusions can be drawn about the effect of radiotherapy compared to surgery, on the pre-specified outcome measures.

Overwegingen – van bewijs naar aanbeveling

Voor- en nadelen van de interventie en de kwaliteit van het bewijs
Er zijn geen gerandomiseerde studies of kwalitatief goede vergelijkende observationele studies gevonden naar het effect van radiotherapie in vergelijking met chirurgie bij patiënten met een primaire tumor van kleine hypofarynxcarcinomen. Er kunnen daarom geen aanbevelingen worden gedaan op basis van de wetenschappelijke literatuur.

De chirurgische behandeling voor T1- of T2-hypofarynxcarcinomen kan bestaan uit Transoral Laser Microsurgery (TLM) of Transoral Robotic Laser Surgery (TORS). Het doel is om lokale controle te bereiken en tegelijkertijd orgaansparend te werk te gaan.

In een case series uit 2008 werd bij 172 patiënten met een T1-T4 hypofarynxcarcinoom de tumor gereseceerd met een CO_2 laser (Martin, 2008). Slechts 15% van de patiëntenpopulatie had een T1- of T2 tumor. De onderzoekers rapporteerden een 5-jaars lokale controle van 84% voor de T1-tumoren en 70% voor de T2-tumoren. Recidief-vrije overleving was 73% voor stadium I en II. De algehele 5-jaarsoverleving van patiënten met een T1- of T2-tumor was 68%. De onderzoekers concludeerden dat het mogelijk is om een oncologische resectie te verrichten met goede functionele uitkomsten. De functionele uitkomsten werden echter

niet gerapporteerd per tumorstadium. De onderzoekers benadrukten dat er maximaal één arytenoïd mag worden geresecteerd om de larynxfunctie te behouden.

Een prospectieve studie uit 2002 met 29 patiënten met hypofarynxtumoren die allen behandeld werden met TLM, toonde in 24% van deze patiënten een complicatie (Vilaseca-González, 2003). Het artikel bestudeert zowel patiënten met hypofarynx- als laryxntumoren in meerdere stadia (275 patiënten totaal, waarvan 94,7% man en gemiddelde leeftijd van 62.6 ± 10.4), en noemt voor alle soorten tumoren de volgende postoperatieve complicaties: lokale infectie, emfyseem en cervicale fistel, kortademigheid, postoperatieve bloeding en longontsteking. Als intra-operatieve complicatie wordt bij één patiënt ontbranding van de plakstrips voor de katheter gerapporteerd. Er wordt niet vermeld welke complicaties bij welk stadium of welke tumorsoort voorkomen. Er werd voor geen van de patiënten met een T1 tumor complicaties gerapporteerd, terwijl voor 17,6% van de patiënten met een T2 tumor een complicatie werd gerapporteerd.

Een recentere chirurgische benadering is de TORS, uitgevoerd met de Da Vinci robot. TORS wordt al vaker gebruikt bij patiënten met orofarynxcarcinomen, maar wordt de laatste tijd ook ingezet bij patiënten met hypofarynx- en larynxtumoren. TORS lijkt een haalbare en veilige behandelmodaliteit te zijn, maar data met betrekking tot overleving en functionele uitkomsten ontbreken (Durmus, 2015).

Een groot voordeel van TLM en TORS is dat radiotherapie achter de hand gehouden kan worden indien er een recidief of een tweede primaire tumor optreedt, mits er sprake is van adequate oncologische controle van de primaire tumor zonder adjuvante radiotherapie. Een goede patiëntselectie is hierbij van groot belang en de chirurg moet uitgebreide ervaring hebben met deze modaliteiten.
Met de juiste patiëntenselectie, informatie over eventuele uitbreiding van de tumor en een ervaren chirurg kunnen TLM of TORS goede behandelopties zijn voor patiënten met een T1- of T2-hypofarynxcarcinoom.

Naast behandeling van de primaire tumor is er ook een indicatie voor electieve behandeling van de hals. In een studie met 93 oppervlakkige hypofarynxtumoren behandeld met excisie (Takayuki, 2019) werd in 19.3% een positieve halsklier gevonden. Er was een relatie met de tumordikte van de primaire tumor. Behalve voor zeer oppervlakkige tumoren zal bij een T1-2 hypofarynxcarcinoom electieve behandeling plaats moeten vinden van op zijn minst de ipsilaterale hals, of door het uitvoeren van een electieve halsklierdissectie (met eventuele postoperatieve (chemo) radiatie afhankelijk van d pathologische bevindingen) of electieve bestraling. Het nadeel van TLM of TORS is dat de operatie moet worden uitgebreid, of er moet postoperatieve bestraling van de hals volgen.

<u>Waarden en voorkeuren van patiënten (en evt. hun verzorgers)</u>
Naast lokale controle en ziektevrije overleving is het aannemelijk dat kwaliteit van leven en functie van de larynx van belang is voor patiënten. Het doel van de behandeling van T1-T2 hypofarynxtumoren is naast oncologische controle dan ook om orgaansparend te werk te gaan. Er zijn geen studies gevonden waarin (chemo-)radiotherapie versus chirurgie (TLM of TORS) wordt onderzocht met betrekking tot de kwaliteit van leven en larynxfunctie.

Het streven is om een patiënt met zo min mogelijk verschillende modaliteiten te hoeven behandelen. Op basis van het resultaat van het histopathologisch onderzoek van het resectiepreparaat kan er een indicatie ontstaan voor adjuvante radiotherapie met of zonder chemotherapie. De noodzaak hiertoe is afhankelijk van een goede patiëntselectie voor TLM

en TORS. De frequentie van het gebruik van twee of drie in plaats van één behandelingsmodaliteit kan afhankelijk van de patiëntselectie aanzienlijk zijn. Mogelijk dat de radiotherapie dosis bij adjuvante radiotherapie wel lager kan zijn dan bij primaire radiotherapie.

Kosten (middelenbeslag)
Een case series met 10 patiënten toonde aan dat de gemiddelde operatietijd met TORS 62,4 minuten was en er 17,4 minuten nodig waren om het systeem in te stellen (Park, 2010). Een andere case series met 5 patiënten vond een gemiddelde opnameduur van 4-6 dagen (uitersten 4-5 dagen) (Durmus, 2015). Verwacht mag worden dat de operatietijd met TLM vergelijkbaar is. Patiënten zullen doorgaans 6 weken lang 5 keer per week poliklinisch bestraald worden.

Aanvaardbaarheid, haalbaarheid en implementatie
Radiotherapie is een behandeling die routinematig in alle hoofd-halscentra wordt toegepast. TLM wordt in alle hoofd-halscentra routinematig toegepast bij de behandeling van (kleine) larynxcarcinomen. In sommige centra worden ook andere tumoren met TLM behandeld. TORS wordt nog niet in alle centra toegepast. De ervaring met TORS voor de behandeling van hypofarynxcarcinomen is nog beperkt.

Aanbevelingen
Aanbeveling-1
Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies
De werkgroep is van mening dat radiotherapie de standaardbehandeling van patiënten met T1-2N0-1 hypopharynxcarcinoom blijft. Het gebrek aan studies waarin radiotherapie direct met TORS en/of TLM wordt vergeleken geeft vooralsnog geen richting om TORS of TLM als standaardbehandeling boven radiotherapie te verkiezen. De resultaten van de lopende gerandomiseerde studies dienen afgewacht te worden. Een goede patiëntselectie lijkt cruciaal te zijn.

De werkgroep is van mening dat patiënten door de verschillende complicatie- en toxiciteitspatronen die ontstaan wegens de aard van beide interventies een voorkeur voor één van beide interventies kunnen hebben. De werkgroep acht het daarom belangrijk dat de voor- en nadelen van beide interventies besproken moeten worden, maar ook dat aangegeven wordt dat radiotherapie vooralsnog de huidige standaardzorg is.

Vanwege het ontbreken van vergelijkende studies én het feit dat radiotherapie op dit moment al reguliere zorg is, dient een behandeling middels TLM of TORS alléén te geschieden bij een patiëntvoorkeur voor een chirurgische behandeling, in centra én wanneer TLM of TORS als adequaat alternatief kan worden gezien voor de patiënt.

Gebruik radiotherapie als standaardbehandeling.

TLM en TORS kunnen met de patiënt besproken worden indien:
- TLM en/of TORS technisch mogelijk zijn;
- er geen contra-indicaties zijn voor chirurgie;

Ondersteun de patiënt bij het maken van een behandelkeuze waarbij de individuele patiëntkarakteristieken dienen te worden afgewogen.

En bespreek de volgende belangrijke voor- en nadelen van de interventies indien van toepassing op de patiënt:

- **Behandelduur:**
  De duur van de behandelingen zonder complicaties bij TLM or TORS is één ingreep met een opnameduur van enkele dagen. Voor radiotherapie is de behandelduur zes tot zeven weken en behandeling omvat meerdere bezoeken. Voor beide behandelingen is een korte poliklinische voorbereiding nodig.
- **Procedures:**
  TLM en TORS worden onder narcose op een operatiekamer verricht. Radiotherapie wordt poliklinisch in 30 tot 35 korte sessies verricht. Radiotherapie zal volgens een behandelschema verlopen en vraagt om tandheelkundig focusvrij maken voorafgaand aan de radiotherapie.
- **Korte en lange termijn complicaties en toxiciteit:**
  Bij TLM en TORS kunnen bloedingen, pijnklachten en ontstekingen optreden. Bij radiotherapie kan smaakverlies, een droge mond en slikklachten optreden. Ook kunnen hypothyroïdie, versnelling van artherosclerose en, met een zeer gering risico, secundaire tumoren ontstaan ten gevolge van radiotherapie.
- **Kans op adjuvante behandeling:**
  Er bestaat afhankelijk van de patiëntselectie voor TLM en TORS een grote kans op een adjuvante behandeling met (chemo-)radiatie. In een beperkt aantal patiënten zal na radiotherapie bij residu of recidief tumor salvage chirurgie nodig zijn.

Literatuur

Durmus, K., Kucur, C., Uysal, I. O., Dziegielewski, P. T., & Ozer, E. (2015). Feasibility and clinical outcomes of transoral robotic surgery and transoral robot-assisted carbon dioxide laser for hypopharyngeal carcinoma. Journal of Craniofacial Surgery, 26(1), 235-237.

Kuo, P., Chen, M. M., Decker, R. H., Yarbrough, W. G., & Judson, B. L. (2014). Hypopharyngeal cancer incidence, treatment, and survival: temporal trends in the United States. The Laryngoscope, 124(9), 2064-2069.

Martin, A., Jäckel, M. C., Christiansen, H., Mahmoodzada, M., Kron, M., & Steiner, W. (2008). Organ preserving transoral laser microsurgery for cancer of the hypopharynx. The Laryngoscope, 118(3), 398-402.

Meulemans, J., Delaere, P., & Vander Poorten, V. (2019). Primary treatment of T1–T2 hypopharyngeal cancer: changing paradigms. Hypopharyngeal Cancer, 83, 54-65.

Park, Y. M., Kim, W. S., Byeon, H. K., De Virgilio, A., Jung, J. S., & Kim, S. H. (2010). Feasiblity of transoral robotic hypopharyngectomy for early-stage hypopharyngeal carcinoma. Oral oncology, 46(8), 597-602.

Parkin, D. M., Whelan, S. L., Ferlay, J., Teppo, L., & Thomas, D. B. E. (2002). Cancer incidence in five continents Volume VIII. IARC scientific publication, (155).

Vilaseca-González, I., Bernal-Sprekelsen, M., Blanch-Alejandro, J. L., & Moragas-Lluis, M. (2003). Complications in transoral CO2 laser surgery for carcinoma of the larynx and hypopharynx. Head & Neck: Journal for the Sciences and Specialties of the Head and Neck, 25(5), 382-388.

Bijlagen bij module 13.1

Implementatieplan

Aanbeveling	Tijdspad voor implementatie: < 1 jaar, 1 tot 3 jaar of > 3 jaar	Verwacht effect op kosten	Randvoorwaarden voor implementatie (binnen aangegeven tijdspad)	Mogelijke barrières voor implementatie[1]	Te ondernemen acties voor implementatie[2]	Verantwoordelijken voor acties[3]	Overige opmerkingen
Module Behandeling T1-T2N0 hypofarynxcarcinoom	< 1 jaar	Geen	Geen	De werkgroep ziet geen belemmeringen voor implementatie en acht acties om mogelijke barrières voor implementatie op te lossen niet nodig.	Geen	n.v.t.	Geen

[1] Barrières kunnen zich bevinden op het niveau van de professional, op het niveau van de organisatie (het ziekenhuis) of op het niveau van het systeem (buiten het ziekenhuis). Denk bijvoorbeeld aan onenigheid in het land met betrekking tot de aanbeveling, onvoldoende motivatie of kennis bij de specialist, onvoldoende faciliteiten of personeel, nodige concentratie van zorg, kosten, slechte samenwerking tussen disciplines, nodige taakherschikking, et cetera.
[2] Denk aan acties die noodzakelijk zijn voor implementatie, maar ook acties die mogelijk zijn om de implementatie te bevorderen. Denk bijvoorbeeld aan controleren aanbeveling tijdens kwaliteitsvisitatie, publicatie van de richtlijn, ontwikkelen van implementatietools, informeren van ziekenhuisbestuurders, regelen van goede vergoeding voor een bepaald type behandeling, maken van samenwerkingsafspraken.
[3] Wie de verantwoordelijkheden draagt voor implementatie van de aanbevelingen, zal tevens afhankelijk zijn van het niveau waarop zich barrières bevinden. Barrières op het niveau van de professional zullen vaak opgelost moeten worden door de beroepsvereniging. Barrières op het niveau van de organisatie zullen vaak onder verantwoordelijkheid van de ziekenhuisbestuurders vallen. Bij het oplossen van barrières op het niveau van het systeem zijn ook andere partijen, zoals de NZA en zorgverzekeraars, van belang.

Evidence tables

Not applicable

Table of excluded studies

Author and year	Reason for exclusion
Corvo 2007	Not a systematic review. Next to that, only one database is used and dated evidence.
Che 2019	Wrong tumour type: both hypopharynx and larynx are studied together. Advanced tumour stadia are discussed. Both direct and indirect evidence is used.
De Virgilio 2019	Only single arm studies are included.
Yamazaki 2000	Wrong intervention, combined treatments are given. Also advance tumor stadia are included.

Nakamura 2006	Wrong intervention. Also not an RCT but overview of retrospective data.
Zackrisson 2011	Study includes both oropharynx, larynx, oral cavity and hypopharynx carcinoma. Next to that surgery is not studied, but two different forms of radiotherapy are compared.
Krstevska 2012	Article is a narrative review.
Miah 2012	Only chemotherapy and radiotherapy are given as treatment, not surgery. Next to that, patients with stage III and stage IV tumours are included.
Nakashima 2017	Patients with stage III and stage IV tumours are included. Next to that, chemotherapy is given as a treatment, not surgery.
Rosenthal 2017	Patients with stage III and stage IV tumours are included. Study includes both oropharynx, larynx, oral cavity and hypopharynx carcinoma. Next to that, different doses of postoperative radiotherapy are studied.
Xiang 2018	Patients with stage III and stage IV tumours are included. Study includes both oropharynx, larynx, oral cavity and hypopharynx carcinoma. Study compares radiotherapy with chemotherapy, surgery is not studied. Next to that, different doses of postoperative radiotherapy are studied.

Literature search strategy

Algemene informatie

Richtlijn: Hoofd-Halstumoren	
Uitgangsvraag: Wat is de juiste behandeling van de primaire tumor van kleine hypofarynxcarcinomen?	
Database(s): Ovid/Medline, Embase	Datum: 15-7-2020
Periode: 2000-	Talen: niet van toepassing
Literatuurspecialist: Ingeborg van Dusseldorp	
Toelichting en opmerkingen: In afstemming met de adviseur is voor deze zoekopdracht specifiek gezocht naar hypopharynxcarcinoom en zijn de termen: postcricoid area, arytenoid, Piriform sinus, pharyngoepiglottic fold, aryepiglottic fold, vallecula , niet meegenomen. Daarnaast is specifiek gezocht op early stage t1-N0. Als interventie is meegenomen: chemotherapie, radiotherapie, systemische therapie. De volgende termen zijn niet meegenomen in de interventie: laser surgery, surgery, treatment management. Er is niet gezocht op de comparison.	

Zoekopbrengst

	EMBASE	OVID/MEDLINE	Ontdubbeld
SRs	2	3	6
RCTs	15	49	60
Observationele studies			
Overig			
Totaal			64

Zoekverantwoording

Ovid/Medline

1 exp Hypopharyngeal neoplasms/ or ((hypopharyn* or hypofaryn*) adj3 (cancer or tumor* or tumour* or malignan* or neoplasm* or carcinoma*)).ti,ab,kf. (4567)

2 ((early adj3 (cancer or tumor* or tumour* or malignan* or neoplasm* or carcinoma* or stage or staging)) or (ct1 2n0 or t1?t2 or stage i?ii)).ti,ab,kf. (183643)

3 1 and 2 (399)

4 exp Antineoplastic Agents/ or exp Chemotherapy, Adjuvant/ or exp Taxoids/ or exp Anthracyclines/ or exp Cyclophosphamide/ or exp Immunosuppressive Agents/ or (chemotherapeutics:ti,ab or chemotherapy or anti cancer drug or anti neoplastic agent or anticancer agent or anticancer drug or anticancerogen or anticarcinogen or anticarcinogenic agents or antineoplastics or antitumor agent or antitumor drug or antitumour agent or antitumour drug or cancer inhibitor or carcinostatic drug or tumor inhibitor or tumour inhibitor or taxo* or anthracyclin or cyclophosphamid*).ti,ab,kf. (1523211)

5 exp Radiotherapy/ or (bioradiant therapy or bucky ray or bucky therap* or radio therap* or radio treatment or radiohypophysectomy or radiotherap* or roentgen therap* or roentgen treatment or rontgen therap* or therapeutic radiology or x radiotherapy or x ray therap* or x ray treatment or x-ray therapy or irradiati* or radiati*).ti,ab,kf. (698810)

6 exp Chemoradiotherapy/ or exp Combined Modality Therapy/ or (systemic therap* or systemic treatment or chemoradiati* or chemoradiotherap* or radiochemotherap* or targeted therap* or combined modality therap* or multimodal cancer therap* or multimodality cancer therap* or multiple modality cancer therap* or multiple modality treatment*).ti,ab,kf. (338743)

7 3 and (4 or 5 or 6) (279)

8 limit 7 to yr="2000 -Current" (216)

9 (meta-analysis/ or meta-analysis as topic/ or (meta adj analy$).tw. or (systematic*or literature adj2 review$1).tw. or (systematic adj overview$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (295283)

10 (exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (2004168)

11 8 and 9 (3), SR

12 8 and 10 (51)

13 12 not 11 (49), RCT

Embase

No.	Query	Results
#18	#12 AND #14	**534**
#17	#12 AND #13	**68**
#16	#11 AND #14	**15**
#15	#11 AND #13	**2**
#14	('clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti) NOT 'conference abstract':it	**2413022**
#13	('meta analysis'/de OR 'meta analysis (topic)'/exp OR cochrane:ab OR embase:ab OR psycinfo:ab OR cinahl:ab OR medline:ab OR ((systematic NEAR/1 (review OR overview)):ab,ti) OR ((meta NEAR/1 analy*):ab,ti) OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/de) NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	**527529**
#12	#10 AND (1-1-2000)/sd NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	**2752**
#11	#9 AND (1-1-2000)/sd NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	**133**

#10	#1 AND #8	**3966**
#9	#3 AND #8	**188**
#8	#5 OR #6 OR #7	**3763852**
#7	'systemic therapy'/exp OR 'systemic therapy':ti,ab,kw OR 'systemic treatment':ti,ab,kw OR 'chemoradiotherapy'/exp OR 'chemoradiati*':ti,ab,kw OR 'chemoradiotherap*':ti,ab,kw OR 'radiochemotherap*':ti,ab,kw OR 'targeted therapy'/exp OR 'targeted therap*':ti,ab,kw OR 'multimodality cancer therapy'/exp OR 'combined modality therap*':ti,ab,kw OR 'multimodal cancer therap*':ti,ab,kw OR 'multimodality cancer therap*':ti,ab,kw OR 'multiple modality cancer therap*':ti,ab,kw OR 'multiple modality treatment*':ti,ab,kw	**261759**
#6	'radiotherapy'/exp OR 'bioradiant therapy':ti,ab,kw OR 'bucky ray':ti,ab,kw OR 'bucky therapy':ti,ab,kw OR 'radio therapy':ti,ab,kw OR 'radio treatment':ti,ab,kw OR 'radiohypophysectomy':ti,ab,kw OR 'radiotherapy':ti,ab,kw OR 'roentgen therapy':ti,ab,kw OR 'roentgen treatment':ti,ab,kw OR 'rontgen therapy':ti,ab,kw OR 'therapeutic radiology':ti,ab,kw OR 'x radiotherapy':ti,ab,kw OR 'x ray therapy':ti,ab,kw OR 'x ray treatment':ti,ab,kw OR 'x-ray therapy':ti,ab,kw OR irradiati*:ti,ab,kw OR radiati*:ti,ab,kw	**1039848**
#5	'chemotherapy'/exp OR 'antineoplastic agent'/exp OR 'taxoid'/exp OR 'anthracycline'/exp OR 'cyclophosphamide'/exp OR 'immunosuppressive agent'/exp OR 'chemotherapeutics':ti,ab OR 'chemotherapy':ti,ab OR 'anti cancer drug':ti,ab,kw OR 'anti neoplastic agent':ti,ab,kw OR 'anticancer agent':ti,ab,kw OR 'anticancer drug':ti,ab,kw OR 'anticancerogen':ti,ab,kw OR 'anticarcinogen':ti,ab,kw OR 'anticarcinogenic agents':ti,ab,kw OR 'antineoplastics':ti,ab,kw OR 'antitumor agent':ti,ab,kw OR 'antitumor drug':ti,ab,kw OR 'antitumour agent':ti,ab,kw OR 'antitumour drug':ti,ab,kw OR 'cancer inhibitor':ti,ab,kw OR 'carcinostatic drug':ti,ab,kw OR 'tumor inhibitor':ti,ab,kw OR 'tumour inhibitor':ti,ab,kw OR 'taxo*':ti,ab,kw OR 'anthracyclin':ti,ab,kw OR cyclophosphamid*:ti,ab,kw OR cisplatin:ti,ab,kw	**2999848**
#4	'postcricoid area':ti	**4**
#3	#1 AND #2	**341**
#2	'early cancer'/exp OR ((early NEAR/3 (cancer OR tumor* OR tumour* OR malignan* OR neoplasm* OR carcinoma* OR stage OR staging)):ti,ab,kw) OR 'ct1 2n0':ti,ab,kw OR 't1/t2':ti,ab,kw OR 't1-t2':ti,ab,kw OR 'stage i/ii':ti,ab,kw	**239564**
#1	'hypopharynx cancer'/exp OR 'hypopharynx squamous cell carcinoma'/exp OR (((hypopharyn* OR hypofaryn*) NEAR/3 (cancer OR tumor* OR tumour* OR malignan* OR neoplasm* OR carcinoma*)):ti,ab,kw)	**7143**

Module 14.1 Behandeling Tis/T1 glottisch larynxcarcinoom

Uitgangsvraag

Hoe moeten Tis/T1 glottisch larynxcarcinomen worden behandeld: met radiotherapie of chirurgisch?

Inleiding

Glottische larynxcarcinomen ontstaan ~~vaak~~ in de stembanden. Mogelijke behandelingen zijn radiotherapie en chirurgische behandeling (open chirurgie of endolaryngeale/transorale chirurgie)~~, of een combinatie van deze twee interventies~~. Het is onduidelijk wat de optimale behandelstrategie is wat betreft totale overleving, ziektevrije overleving, stemkwaliteit, kwaliteit van leven en (werk)participatie.

Search and select

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

What are the effects of radiotherapy compared to surgical treatment (open surgery/endolaryngeal surgery) in patients with Tis/T1 glottic laryngeal carcinomas?

P: patients with Tis/T1 glottic laryngeal carcinomas;
I: open surgery/endolaryngeal or transoral surgery;
C: radiotherapy;
O: overall survival at five years, disease-free survival at five years, voice quality, quality of life, secondary treatment, (work)participation.

Relevant outcome measures

The guideline development group considered overall survival, relapse-free survival and functional outcomes (voice quality) as crucial outcome measures for decision making; and quality of life, secondary treatment, complications/adverse events, and (work)participation as important outcome measures for decision making.

The guideline development group defined the outcome measures as follows:

Overall survival	~~Overall survival (defined as t~~Time from randomisation to death from any cause,~~)~~ with a minimum follow-up of 5 years.
Relapse-free survival	~~Relapse-free survival (t~~Time during and after cancer treatment that the patient survives without any signs or symptoms of cancer recurrence~~)~~, with a minimum follow-up of 5 years.
Functional outcomes	Voice quality: self-rated (measured with an instrument such as the VHI-10), or expert-rated (measured with an instrument such as the GRBAS scale (grade, roughness, breathiness, asthenia, and strain)).
Larynx preservation	Laryngeal preservation rate.
Quality of life	Quality of life (overall or regarding a specific domain) as measured with a validated and reliable instrument such as the SF-36 or EORTC QLQ-C30.
Secondary treatment	Whether or not secondary (adjuvant) treatment is necessary.
Complications/adverse events	All negative effects related to the treatment (lethal, acute/serious, chronic).
(Work)participation:	Participation in school, work and/or informal care.

Clinically relevant difference
The guideline development group defined a minimal clinically relevant difference at a minimum of a median follow-up period of three years) *(in line with "NVMO-commissie ter Beoordeling van Oncologische Middelen (BOM)")* of:

- Overall survival: > 5% difference, or > 3% and HR< 0.7.
- Relapse-free survival: HR< 0.7.

And, in case of absence of a clinically relevant difference in overall survival or relapse-free survival:

- Quality of life: a minimal clinically important 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.
- Complications/adverse events: statistically significant less complications/adverse events.
- Functional outcomes: statistically significant better functional outcomes.
- (Work)participation: statistically significant better (work)participation.

Search and select (Methods)
The guideline development group decided that the Cochrane review from Warner (2014) could be used as a base. After a more detailed investigation of the included study in this Cochrane review, the guideline development group decided that the interventions studied by Ogol'tsova (1990) were not relevant anno 2020, and therefore this study was excluded from the body of evidence. Literature was searched for studies published after the search date of Warner (September 2014). The databases Medline (via OVID) and Embase (via Embase.com) were searched for SRs and RCTs with relevant search term until July 10th, 2019. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 1967 hits.

Studies were selected based on the following criteria: included patients with Tis/T1 glottic larynx carcinoma, compared radiotherapy with open or endolaryngeal surgery, reported at least one of the outcomes of interest, the study design was a systematic review (SR) or randomized controlled trial (RCT), and written in English language.

Eight studies were initially selected based on title and abstract screening. After reading the full texts and thorough assessment of the included studies, seven studies were excluded (see the table with reasons for exclusion under the tab Methods). Through the SR of Huang (2017) one RCT (Aaltonen, 2014) was included. No other, more recent, RCTs were found. Therefore, in addition to this RCT, the guideline development group decided to select the most recent SR of observational studies that could answer the PICO (Ding, 2019). The comparative observational studies described in this SR were added to the body of evidence and described in the summary of literature.

Data-synthesis
Results from RCTs and observational studies were described and synthesized (preferably by meta-analysis) separately. A priori, the guideline development group decided that observational studies should be of sufficient quality to allow a useful GRADE assessment and to allow conclusions that can guide the recommendations. The guideline development group used the following criteria for eligible observational studies of sufficient quality:

- Compared at least two interventions.
- Included at least 50 patients.
- Corrected for at least one plausible confounder, for example by matching cases and controls, stratification, or statistical correction by performing a multivariable analysis.

Results
One RCT (Aaltonen, 2014) and seven comparative observational studies were included in the analysis of the literature. They all compared laser surgery with radiation therapy (RT). 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 table. No studies were found that compared open surgery with radiotherapy.

Summary of literature
Description of studies
Randomised controlled trials
The RCT performed by **Aaltonen (2014)** included male patients with histologically confirmed squamous cell carcinoma, limited to one mobile vocal cord, staged as T1aN0M0. Transoral laser surgery (TLS, tumour excision with a CO_2 laser) was compared with external beam radiation therapy (RT). The outcome was voice quality, which was assessed at baseline and 6 and 24 months after treatment and was measured in three ways: an expert-rated quality of voice, self-rated quality of voice, and videolaryngostroboscopic findings. In the study, 60 male patients were randomized to TLS (n=32, of which 31 were evaluated) or radiation therapy (n=28, of which 25 were evaluated). The follow-up period was 24 months. The median age was 69 years in the TLS group and 61 years in the RT group.

Observational studies
The systematic review by **Ding (2019)** included 18 studies in their analysis. Of them, seven were published after 2010 and met our PICO criteria. Since none of these observational studies corrected for confounding, these results do not contribute to the body of evidence and were not graded, but only described for informative purposes.

Overall survival at five years follow-up was reported in four studies and ranged from 86 % to 97% in the laser surgery group, and from 70% to 96% in the radiotherapy group. Relapse was reported in two studies (one study reported disease-free survival and one study reported local and regional recurrence). Functional outcomes were reported in six studies (three studies acoustic parameters, four studies voice handicap index, and one study Grade, Roughness, Breathiness, Asthenia, and Strain scale), and most studies reported worse functional outcomes in laser surgery patients, compared to radiotherapy patients. The results are summarized in the evidence table.

The retrospective cohort study by **Low (2016)** included patients with T1aN0 glottic squamous cell carcinoma (SCC) and was performed in Australia. Transoral laser microsurgery (TLM) was compared with RT on oncologic outcomes (overall survival and relapse-free survival). In total, 105 patients were included, of whom 53 were treated with TLM and 52 with RT. The mean age was 65.4 (sd 13.0) and 70.6 (sd 11.0) years, and 42/53 (79%) and 44/52 (85%) were men in the TLM and RT group, respectively. The mean follow-up was 3.58 (sd 2.41) years in the TLM group and 4.55 (sd 3.17) years in the RT group. They concluded that patients with T1aN0 glottic SCC treated with RT or TLM have similar survival outcomes.

The retrospective cohort study by **Kono (2016)** included patients with T1aN0M0 glottic cancer and was performed in Japan. Laser surgery (LS) was compared with RT, on functional outcomes (acoustic parameters, voice handicap index, and auditory-perceptual evaluation). Until July 2010, the laser was used in super pulse continuous mode with 4 to 5 W power (vaporization with defocused mode using laser surgery (LS-Vap)), and from August 2010, the laser was used in super pulse continuous mode with 1 W power in focus (LS-Ex). In total 64 patients were included, of whom 37 were treated with LS and 27 with RT. The mean age was

69 (sd 9.8) and 69 (sd 9.8) years, and 33/37 (89%) and 22/27 (81%) were men in the TLM and RT group, respectively. The median follow-up period was 37 months. They concluded that early glottic cancer could be successfully treated by either RT or LS-Ex with equivalent posttherapeutic laryngeal function and quality of life.

The prospective cohort study by **Taylor (2013)** included patients with T1b squamous cell carcinoma (SCC) of the glottic larynx and was performed in Canada. TLS was compared with RT, on the oncologic outcomes (overall survival and disease-free survival), and functional outcomes (voice handicap index). In total, 63 patients were included, of whom 21 were treated with TLS and 42 with RT. The mean age was 64 and 69 years, and 18/21 (86%) and 39/42 (93%) were men in the TLM and RT group, respectively. Median follow-up was 34 months in both groups. They concluded that among patients with stage T1b SCC of the glottis oncological outcomes after TLM were at least equivalent to RT, and that voice quality was similar between the two groups.

The retrospective cohort study by **Remmelts (2013)** included patients with early stage (Tis-T2) glottic laryngeal carcinoma and was performed in the Netherlands. LS was compared with RT, on oncologic outcomes (overall survival), and functional outcomes (voice handicap index). In total, 248 patients were included, of whom 89 were treated with LS and 159 with RT. The mean age was 67 and 64 years, and 78/88 (88%) and 138/159 (87%) were men in the LS and RT group, respectively. The mean follow-up was 44 months in the LS group, and 48 months in the RT group. They concluded that oncological outcomes of both LS and RT are similar in T1a laryngeal cancer, and that numbers in this study were too small to allow any conclusions on oncological outcomes in stage T1b laryngeal cancer. According to subjective voice analysis outcomes were comparable in T1a lesions. For T1b lesions patients treated with LS had a statistically significantly higher percentage of voice deficiency (see details in the evidence tables).

The prospective cohort study by **Milovanovic (2013)** included patients with Tis and T1a glottic carcinoma and was performed in Serbia. TLM was compared with RT, on functional outcomes (acoustic parameters), and oncologic outcomes (overall survival). In total, 146 patients were included, of whom 72 were treated with TLM and 74 with RT. Mean age was 59.5 and 62.9 years, and 65/72 (90%) and 67/74 (91%) were men in the TLM and RT group, respectively. The follow-up ranged from 38 to 107 months. They concluded that, given that choice of treatment was also influenced by other factors, TLM was highly efficient and preferred choice of treatment for early glottic carcinoma in Serbia.

The prospective cohort study by **Van Gogh (2012)** included patients with T1aN0M0 glottic cancer and was performed in the Netherlands. Endoscopic laser surgery (LS) was compared with RT on functional outcomes (acoustic parameters). In total, 106 patients were included of whom 67 were treated with LS and 39 with RT. Mean age was 66 and 65 years, and 67/67 (100%) and 39/39 (100%) was men in the LS group and RT group, respectively. Median time of follow-up was comparable for patients in both groups and was maximum 24 months. They concluded that LS is the first treatment of choice in the treatment of selected cases of T1a glottic carcinomas with good functional and oncological results.

The retrospective cohort study by **Kerr (2012)** included patients with stage 1 or 2 glottic carcinoma and was performed in Canada. TLM was compared with RT, on oncologic outcomes (overall survival), and functional outcomes (voice handicap index). In total, 243 patients were included of whom 143 were treated with TLM, and 91 with RT. Median age was 67 in both groups, and 123/143 (86%) and 82/91 (90%) were men in the TLM and RT

group, respectively. Median follow-up was 28 months in the TLM and 32 months in the RT group. They concluded that TLM patients had poorer voice quality than RT patients (see details in the evidence tables). However, the authors argued that advantages of TLM in most patients outweighed the degree of voice handicap.

Results

None of the observational studies corrected for confounding and therefore their results did not contribute to the conclusions.

Overall survival at five years (crucial)

None of the studies reported on overall survival after a minimum follow-up duration of five years.

Relapse-free survival at five years (crucial)

None of the studies reported on relapse-free survival after a minimum follow-up duration of five years.

Functional outcomes (crucial)

1. Expert-rated quality of voice

Aaltonen (2014): The mean scores in expert-rated overall voice quality (G), voice roughness (R), and strain (S) remained similar between the groups during follow-up, but patients treated with TLS had a more breathy voice (B) than those who received radiation therapy (score 1.52 versus 0.28 (on a scale from 0 (normal) to 3 (extremely abnormal) 2 years after treatment, P<0.001). A statistically significant difference emerged also in asthenia (A) (0.74 versus 0.11; P=0.003), but in both groups the absolute value was under 1, suggesting limited clinical relevance of this finding. Breathiness and asthenia improved significantly with time in the radiation therapy group (from 1.17 at baseline to 0.28 2 years after treatment, P=0.001; and from 0.56 to 0.11, P=0.001, respectively) but not in the TLS group.

The degree of voice breathiness varied between groups. In the TLS group, 5/27 (19%) had no voice breathiness (score 0), the majority (20/27, 74%) had mildly or moderately breathy voice (score 1 or 2), and 2/27 (7%) had extremely breathy voice (score 3). In the RT group, the majority of patients (14/20, 70%) had no voice breathiness (score 0), 6/20 (30%) had mildly or moderately breathy voice (score 1 or 2), and none of the patients had extremely breathy voice (score 3).

2. Self-rated quality of voice

Aaltonen (2014): Self-rated hoarseness was judged similar between the groups (P=0.144). The self-reported quality of voice improved significantly from the baseline quality during follow-up in both groups (in the TLS group, the VAS-score decreased from 59.0 to 43.1, P=0.040; and in the RT group, from 53.1 to 35.4, P=0.026). Patients assigned to RT reported less impact of hoarseness on their daily living activities than did patients assigned to TLS (P=0.007).

3. Videolaryngostroboscopic findings

Aaltonen (2014): In comparison with the RT group, patients assigned to TLS had less sufficient glottal function at videolaryngostroboscopy performed two years after study entry. They had higher scores for irregular glottal closure (P=0.025), oval closure (P=0.005), and incomplete glottal closure (P=0.018).

Larynx preservation (important)
None of the studies reported on larynx preservation.

Quality of life (important)
None of the studies reported on quality of life.

Secondary treatment (important)
None of the studies reported on secondary treatment.

Complications/adverse events (important)
None of the studies reported on complications or adverse events.

(Work)participation (important)
None of the studies reported on (work)participation.

Certainty of the evidence
None of the observational studies corrected for confounding and therefore their results could not contribute to the conclusions. GRADE was applied to assess the certainty of the evidence originating from the RCT of Aaltonen (2014).

Crucial outcome measures
Overall survival and relapse-free survival at five years
None of the studies reported on the crucial outcome measures overall survival and relapse-free survival at five years, and therefore GRADE could not be applied, and no conclusions could be drawn.

Functional outcomes (voice quality)
The certainty of the evidence regarding functional outcomes started high as the evidence originated from an RCT, and was downgraded by three levels because of study limitations: one level for risk of bias (patients and assessors were not blinded); and two levels for very serious imprecision (only one study was included, with a very small sample size). Therefore, the certainty of the evidence was very low.

Important outcome measures
None of the studies reported on any of the important outcome measures (quality of life, secondary treatment, complications/adverse events, and (work)participation) and therefore GRADE could not be applied, and no conclusions could be drawn.

Conclusions
Crucial outcome measures
Overall survival

- **GRADE**	No conclusion can be drawn about the effect of treatment with laser surgery versus radiotherapy on overall survival on overall survival.

Relapse-free survival

- **GRADE**	No conclusion can be drawn about the effect of treatment with laser surgery versus radiotherapy on relapse-free survival on relapse-free survival.

Functional outcomes

Very low GRADE	*Expert-rated quality of voice* Laser surgery may increase voice breathiness and asthenia, and have no effect on overall voice quality, voice roughness and strain when compared with radiotherapy, but the evidence is very uncertain. *Self-rated quality of voice* Laser surgery may have no effect on self-rated hoarseness and may increase the impact of hoarseness on patients daily living activities two years after treatment, when compared with radiotherapy, but the evidence is very uncertain. *Videolaryngostroboscopic findings* Laser surgery may reduce sufficient glottal function at videolaryngostroboscopy performed two years after treatment, when compared with radiotherapy, but the evidence is very uncertain. *Sources: (Aaltonen, 2014)*

Important outcome measures

Larynx preservation, quality of life, secondary treatment, complications/adverse events, (work)participation

- GRADE	No conclusion can be drawn about the effect of treatment with laser surgery versus radiotherapy on larynx preservation, quality of life, secondary treatment, complications/adverse events, (work)participation

Overwegingen - van bewijs naar aanbeveling

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

Eén RCT vergeleek laserchirurgie en radiotherapie, maar alleen op functionele uitkomsten (stemkwaliteit). De bewijskracht van deze studie is zeer laag. We zijn daarom onzeker of na de behandeling met radiotherapie de stemkwaliteit beter is, dan na laserchirurgie. Er werden geen studies gevonden waarin men verschillende typen chirurgische behandeling vergeleek. Omdat er bij deze vraag geen trials waren die de cruciale uitkomstmaten totale overleving of relapse-free survival onderzochten, is er gekeken naar geaggregeerd observationeel onderzoek (Ding, 2019). De individuele studies in deze review (die zijn gepubliceerd vanaf 2010) zijn beoordeeld (zie Evidence table). In geen van deze observationele studies corrigeerden de auteurs voor confounders, waardoor een verband tussen de interventies en uitkomsten zwakker of juist sterker kan zijn. Deze studies konden daarom niet bijdragen aan het formuleren van conclusies die dienen als basis voor richtlijnaanbevelingen.

Voor de cruciale uitkomstmaten *overall survival* en *relapse-free survival* zijn geen data beschikbaar uit RCT's. De reden voor de zeer lage bewijskracht van de functionele uitkomstmaat is dat er slechts één RCT met een klein aantal patiënten is gevonden. De overall bewijskracht is daarom zeer laag. Ook op de belangrijke uitkomsten is er geen data beschikbaar uit RCT's of observationeel onderzoek.

Mogelijke bijwerkingen van laserchirurgie zijn nabloeding of benauwdheid. De mogelijke bijwerkingen van radiotherapie zijn huid- en slijmvliesreacties, slikklachten en vermoeidheid. Bij beide behandelingen kan tijdens of kort na de behandeling heesheid tijdelijk toenemen. De kans op het optreden van complicaties erg klein. Er is een subgroep van patiënten (eigen

dentitie en retrognathie, beperkte mondopening) bij wie laser chirurgie niet haalbaar is. Voor deze groep zal radiotherapie de enige goede behandeling zijn.

Belangrijk is verder te realiseren dat de techniek en het type laserbehandeling in de gepubliceerde studies kan verschillen en vaak niet goed omschreven is. Om dit in toekomstige studies te ondervangen is door European Laryngological Society een classificatie voor endoscopische chordectomie voorgesteld (Remacle, 2000; Remacle 2007).

RCT's die deze behandelmodaliteiten hebben getracht te vergelijken zijn gefaald omdat de behandelingen niet volledig gelijkwaardig zijn, de artsen gebiased zijn en de patiënten voorkeur hebben. Zij willen dus niet zomaar gerandomiseerd worden. Zie ook het artikel van Hamilton over de EaStER-trial (Hamilton, 2013).

Waarden en voorkeuren van patiënten (en eventueel hun verzorgers)
~~Voor de patiënten zijn een~~Een goed oncologisch resultaat met een goede functionele uitkomst zijn belangrijk. De belasting voor de patiënt is wel verschillend. Grofweg kan gesteld worden dat laserchirurgie een behandeling van 1 uur is in dagopname of met een opname van 1 nacht. Radiotherapie is een behandeling waarbij de patiënt 16 tot 33 keer behandeld zal worden en daarvoor naar het ziekenhuis moet komen.

Het is aannemelijk dat de kans op langdurigere en uiteindelijke preservatie van de larynx groter is als in eerste instantie behandeld wordt met laserchirurgie. Bij een recidief of 2^{e} primaire tumor is het immers dan nog mogelijk om te behandelen met een nieuwe laserbehandeling of radiotherapie en is een laryngectomie niet de enige overgebleven optie (Schrijvers, 2009; Van Gogh, 2012).

Kosten (middelenbeslag)
Er zijn geen studies gevonden over kosteneffectiviteit van laserchirurgie versus radiotherapie. Goor (2007) lieten zien dat radiotherapie duurder is dan laserchirurgie, als de kosten voor de behandeling van mogelijke terugkeer van kanker worden meegenomen, terwijl de effecten voor beide behandelopties gelijk zijn. De werkgroep verwacht daarom dat deze aanbeveling wel een impact op de zorgkosten kan hebben.

Aanvaardbaarheid, haalbaarheid en implementatie
Beide behandelingen worden al langer toegepast in Nederland en zijn in de behandelprotocollen van de diverse hoofd-halscentra opgenomen. De beschikbaarheid van beide behandelingen is wijd verspreid in Nederland.

Aanbeveling
Aanbeveling-1
Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies
De behandeling van Tis-T1 glottisch larynxcarcinoom kan met radiotherapie of laserchirurgie. Uit de literatuur zijn er geen verschillen in overleving of functieverlies gevonden tussen de beide behandelmogelijkheden. Behandeling met laserchirurgie is wel goedkoper en heeft waarschijnlijk meer kans op langduriger behoud van de larynx.

De behandeling van Tis-T1 larynxcarcinoom kan op twee manieren: laserchirurgie en radiotherapie. De werkgroep kan geen aanbevelingen geven over voorkeur voor radiotherapie of laserchirurgie omdat geen verschil is gevonden in oncologische en functionele uitkomsten.

Bespreek beide opties en ondersteun de patiënt bij het maken van een behandelkeuze waarbij de individuele patiëntkarakteristieken afgewogen dienen te worden.

Bespreek de volgende belangrijke voor- en nadelen van de interventies indien van toepassing op de patiënt:

- *Behandelduur:*
  Laserchirurgie: De duur van de behandelingen zonder complicaties is één ingreep met een opname van één of twee dagen.
  Radiotherapie: De behandelduur varieert van 16 tot 33 behandelingen.
- *Procedures:*
  Laserchirurgie: opname en narcose.
  Radiotherapie: wordt poliklinisch verricht gedurende enkele weken.
- *Korte en lange termijn complicaties en toxiciteit:*
  Laserchirurgie: Er kunnen bloedingen, pijnklachten, tijdelijke heesheid en ontstekingen optreden.
  Radiotherapie: Er kunnen vermoeidheid, huid- en slijmvliesreactie, tijdelijk heesheid en slikklachten optreden.
- *Kans op adjuvante behandeling:* geen. ~~Welk kan peroperatief blijken dat therapeutische laserchirurgie niet haalbaar is.~~

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Bijlagen bij module 14.1

Implementatieplan

Aanbeveling	Tijdspad voor implementatie: < 1 jaar, 1 tot 3 jaar of > 3 jaar	Verwacht effect op kosten	Randvoorwaarden voor implementatie (binnen aangegeven tijdspad)	Mogelijke barrières voor implementatie[1]	Te ondernemen acties voor implementatie[2]	Verantwoordelijken voor acties[3]	Overige opmerkingen
Behandeling Tis/T1 glottisch larynxcarcinoom~~1~~	< 1 jaar	Geen	Geen	Er worden geen barrières verwacht die de implementatie in de weg staan.	Geen	n.v.t.	Geen

[1] Barrières kunnen zich bevinden op het niveau van de professional, op het niveau van de organisatie (het ziekenhuis) of op het niveau van het systeem (buiten het ziekenhuis). Denk bijvoorbeeld aan onenigheid in het land met betrekking tot de aanbeveling, onvoldoende motivatie of kennis bij de specialist, onvoldoende faciliteiten of personeel, nodige concentratie van zorg, kosten, slechte samenwerking tussen disciplines, nodige taakherschikking, et cetera.
[2] Denk aan acties die noodzakelijk zijn voor implementatie, maar ook acties die mogelijk zijn om de implementatie te bevorderen. Denk bijvoorbeeld aan controleren aanbeveling tijdens kwaliteitsvisitatie, publicatie van de richtlijn, ontwikkelen van implementatietools, informeren van ziekenhuisbestuurders, regelen van goede vergoeding voor een bepaald type behandeling, maken van samenwerkingsafspraken.
[3] Wie de verantwoordelijkheden draagt voor implementatie van de aanbevelingen, zal tevens afhankelijk zijn van het niveau waarop zich barrières bevinden. Barrières op het niveau van de professional zullen vaak opgelost moeten worden door de beroepsvereniging. Barrières op het niveau van de organisatie zullen vaak onder verantwoordelijkheid van de ziekenhuisbestuurders vallen. Bij het oplossen van barrières op het niveau van het systeem zijn ook andere partijen, zoals de NZA en zorgverzekeraars, van belang.

Evidence tables

Randomised controlled trial

Study reference	Study characteristics	Patient characteristics [2]	Intervention (I)	Comparison / control (C) [3]	Follow-up	Outcome measures and effect size [4]	Comments
Aaltonen, 2014	Type of study: RCT Setting and country: Three largest university hospitals in Finland Funding and conflicts of interest: None reported	Inclusion criteria: Patients with previously untreated, histologically confirmed squamous cell carcinoma limited to 1 mobile vocal cord, staged as T1aN0M0 Exclusion criteria: Females N total at baseline: Intervention: 28 included, 25 analysed (radiation therapy) Control: 32 included, 31 analysed (Transoral Laser Surgery or TLS) Important prognostic factors[2]:	**Radiation therapy** Patients allocated to radiation therapy had their treatments started within 6 weeks after randomization. The larynx was irradiated with 6-MeV photons from 2 opposing 4.5 x 4.5 to 5 x 5 cm wedge fields to a total cumulative dose of 66 Gy in 2-Gy daily fractions over 6.5 weeks with a linear accelerator. When necessary an anterior bolus was added to achieve the desired dose at the anterior commissure. The uniformity criteria within the planned target volume were defined according to the International Commission on Radiation Units and Measurements Report 50. The clinical target volume encompassed the larynx with no attempt to irradiate the regional lymphatics.	**Laser surgery** Patients assigned to TLS had the tumour excised under general anaesthesia within 6 weeks from randomization by use of a CO2 laser. The operations were performed as described elsewhere (8, 9) by only 7 experienced senior surgeons. In short, the tumours were first split, and tumour tissue was removed down to a macroscopically healthy muscle layer. After tumour excision, small biopsy specimens were taken to ensure complete (R0) removal.	Length of follow-up: 24 months Loss-to-follow-up: Intervention: 1 (4%) Reasons: not mentioned Control: 0 (0%) Incomplete outcome data: None mentioned In total, 1 participant was excluded because she was female and 3 participants withdrew consent.	Expert rated quality of voice The mean scores in expert-rated overall voice quality (G) , voice roughness (R), and strain (S) remained similar between the groups during follow-up, but patients treated with TLS had a more breathy voice than those who received radiation therapy (score 1.52 versus 0.28 (on a scale from 0 (normal) to 3 (extremely abnormal) 2 years after treatment, P<0.001). A statistically significant difference emerged also in asthenia (0.74 versus 0.11; P=0.003), but in both groups the absolute value was under 1, suggesting limited clinical relevance of this finding. Breathiness and asthenia improved significantly with time in the radiation therapy group (from 1.17 at baseline to 0.28 2 years after treatment, P=0.001; and from 0.56 to 0.11, P=0.001, respectively) but not in the TLS group. The degree of voice breathiness varied between groups. In the TLS group, 5/27 (19%) had no voice breathiness (score 0), 20/27 (74%) had mildly or moderately breathy voice (score 1 or 2), 2/27 (7%) had extremely breathy voice (score 3), and in the radiation therapy group,	Sixty patients entered the study between June 1998 and October 2008.

		age ± SD: *I: 61.0* *C: 69.0* *Sex:* *I: 100% M* *C: 100% M* *Groups comparable at baseline?* Yes				14/20 (70%) had no voice breathiness (score 0), 6/20 (30%) had mildly or moderately breathy voice (score 1 or 2), 0/20 (0%) had extremely breathy voice (score 3). <u>Self-rated quality of voice</u> Self-rated hoarseness was judged similar between the groups (P=0.144). The self-reported quality of voice improved significantly from the baseline quality during follow-up in both groups (in the TLS group, the VAS score decreased from 59.0 to 43.1, P=0.040; and in the radiation therapy group, from 53.1 to 35.4, P=0.026). Patients assigned to radiation therapy reported less impact of hoarseness on their daily living activities than did patients assigned to TLS (P=0.007). <u>Videolaryngostroboscopic findings</u> In comparison with the radiation therapy group, patients assigned to TLS had less sufficient glottal function at videolaryngostroboscopy performed 2 years after study entry. They had higher scores for irregular glottal closure (P=0.025), oval closure (P=0.005), and incomplete glottal closure (P=0.018).	

Observational studies

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Ding (2019)	SR and meta-analysis of observational studies *Literature search up to 04/2017.* *18 studies were included in the SR, of which 7 studies were published after 2010 and met our PICO criteria* **A**: Low, 2016 **B**: Kono, 2016 **C**: Taylor, 2013 **D**: Remmelts, 2013 **E**: Milovanovic, 2013 **F**: Van Gogh, 2012 **G**: Kerr, 2012 Study design: **A:** retrospective cohort **B:** retrospective cohort **C:** prospective cohort	**Inclusion criteria SR:** (1) patients with glottic cancer; (2) intervention was LS compared with RT; (3) outcomes data reported; and (4) article type was original research. **Exclusion criteria SR:** (1) Reviews, letters (2) Irrelevant (3) Not glottic cancer (4) No usable outcomes data **Important patient characteristics at baseline:** N, total and per group (LS/RT)	**Laser surgery (LS)** **A**: Transoral laser microsurgery (TLM) **B**: *LS-Vap*: vaporization with defocused mode using laser surgery *LS-Ex*: type II subligamental cordectomy procedure using the advantages of the laser device and our proficiency in phonosurgical microflap technique **C**: Transoral laser Microsurgery (TLM) **D**: Direct microlaryngoscopy with complete resection of the lesion with CO2 laser surgery (LS) **E**: Transoral laser microsurgery (TLM) **F**: Endoscopic laser surgery	**Radiotherapy (RT)** **A**: Conventional two-field techniques RT (prior to 2009) / Intensity-modulated radiation therapy (IMRT) (after 2009) **B**: Conventional RT **C**: Curative dose of radiation **D**: Radiotherapy with photon linear accelerator **E**: Radiotherapy **F**: Radiotherapy **G**: Radiotherapy	End-point of follow-up: **A:** mean: 3.58 (sd 2.41) (LS) versus 4.55 (sd 3.17) (RT) years, max 60 months. **B:** median 37 (range 10-70) months. **C:** median 34 (range 5-102) months **D:** mean 44 (range 3-89) (LS) versus 48 (2-108) (RT) months. **E:** range 38-107 months. **F:** max 24 months. **G:** median 28 (LS) versus 32 (RT) months, max 60 months. For how many participants were no complete outcome data available? **A:** unclear **B:** unclear **C:** voice outcomes not available for 40 patients	Overall survival at 5 years **A:** TLM: 86%, RT: 85% P=0.887 **B:** *not reported* **C:** *not reported* **D:** LS: 80/89 (90%), RT: 125/159 (70%) P=0.106 **E:** TLM: 97.2% RT: 95.9% P>0.05 **F:** *not reported* **G:** LS: 91 ± 3%, RT: 90 ± 4% P = not significant. No differences were found in the matched stage and substage analyses. Diasease-free survival at 5 years	Author's conclusion (on 18 studies) Early stage glottic carcinoma patients who underwent LS had increased larynx preservation and overall survival, especially in T1a stage patients compared to RT patients. LS and RT had comparable local control, disease-specific survival, and recurrence. This indicates that LS may be a better option for glottic cancer treatment. When doctors and patients choosing treatment modality for glottic carcinoma, they should take survival, local control, laryngeal preservation, voice function, and complications of treatment into account. Studies show that LS is a safe and effective treatment modality that can be used for treating glottic carcinoma. However, large-scale and well-designed RCTs are required before a conclusive statement

	D: retrospective cohort **E:** prospective cohort **F:** prospective cohort **G:** retrospective cohort <u>Setting and Country</u>: **A:** Australia **B:** Japan **C:** Canada **D:** the Netherlands **E:** Serbia **F:** the Netherlands **G:** Canada <u>Source of funding and conflicts of interest:</u> **Ding (2019):** not reported **A:** The authors had no funding, financial relationships, or conflicts of interest to disclose.	A: 105, 53/52 B: 64, 37/27 C: 63, 21/42 D: 248, 89/159 E: 146, 72/74 F: 106, 67/39 G: 243, 143/91 <u>Mean age in years (LS versus RT)</u> A: 65.4 versus 70.6 B: 64 versus 69 C: 64.3 versus 68.6 D: 67 versus 64 E:59.5 versus 62.9 F: 66 versus 65 G: 67 versus 67 <u>Sex (% men, LS versus RT)</u>: A: 79 versus 85 B: 81 versus 89 C: 86 versus 93 D: 88 versus 87 E: 90.3 versus 90.5 F: 100 versus 100 G: 86 versus 90 <u>Stage</u> **A:** T1a **B:** T1a	**G**: Transoral laser Microsurgery (TLM)		(11/21 LS and 29/42 RT), other outcomes: unclear **D:** quality of voice not available for 106 patients (30/89 LS, 76/159 RT), other outcomes: unclear **E:** unclear **F:** unclear **G:** voice quality data not available for 111 patients (94/ 143 LS, 8/91 RT)	(Defined as) **A:** (Disease-free survival) LS: 69%, RT: 78% p=0.151 **B:** *not reported* **C:** *not reported* **D**: (Local recurrence) LS: 17/89 (19%) RT: 18/159 (11%) P=0.0091 (Regional recurrence) L: 2/89 (2%) RT: 2/159 (1%) P=0.62 **E**: *not reported* **F**: *not reported* **G**: *not reported* <u>Larynx preservation</u> **A:** (laryngectomy-free survival at 5-year follow-up) TLM: 65% RT: 77% P=0.20	could be made regarding the efficacy of laser surgery and radiotherapy for glottic carcinoma. <u>Personal remarks on study quality</u> - None of the studies corrected for confounding - Only 7 of the 18 studies met out inclusion criteria (published after 2010 and met PICO criteria)

	B: *not reported.* **C:** The authors declare that they have no competing interests. Funding not *reported.* **D:** The authors have no conflict of interest. Funding *not reported*. **E:** Conflict of interest: none. Funding *not reported.* **F:** *not reported.* **G:** Financial disclosure of authors and reviewers: None reported. Conflict of interest: *not reported.*	**C:** T1b **D:** Tis, T1a, T1b, T2 **E:** Tis, T1a **F:** T1a **G:** T1, T2 *Groups comparable at baseline?* **A:** significant difference in age between groups **B:** unclear **C:** yes **D:** significant difference in age and primary tumour stage between groups **E:** significant difference in age between groups **F:** unclear **G:** unclear, there seems to be a difference in tumour stage between groups **H:** unclear, there seems to be a difference in tumour stage between groups				**B:** *not reported* **C:** (laryngeal preservation rate at 2-year follow-up) LS: 100% RT: 85.9% **D:** (larynx preservation rate at 5-year follow-up) LS: 87/89 (93%) RT: 142/159 (83%) P=0.049 **E:** *not reported* **F:** (larynx preservation at 2-year follow-up) LS: 67/67 (100%) RT: 37/39 (95%) **G:** (laryngeal preservation rate at 2-year follow-up) *Stage 1* TLM: 100% RT: 92 ± 4% P=0.004 <u>Voice quality / Voice preservation</u> (measured with) **A:** *not reported* **B:** (GRASB scale) At the time point of 12 months after treatment,	

						perceptual scores of grade and breathiness were significantly higher in the LS group compared with those in the RT group. Scores of roughness, asthenia, and strain were similar in both groups. According to the acoustic analysis, significant differences were not observed in fundamental frequency between these 2 groups. However, other acoustic parameters, including jitter, shimmer, and NHR, as well as aerodynamic MPT, were significantly better in the RT group than in the LS group. (VHI) LS: 29.3 ± 4.9 RT: 12.6 ± 3.2 p=0.012 **C:** (VHI) During the last work up VHI-10 ranged from 0 to 11 (median 6) in the laser group and 0 to 34 (median 7) in the radiation group. **D:** (VHI)	

						LS: 12.4 ± 8.9 RT: 8.3 ± 7.7 p=0.005 For the VHI median scores were 8.3 and 12.4 respectively for the patients treated with radiotherapy or laser surgery, with a higher score reflecting a worse outcome (p value < 0.05). If split between T1a and T1b, only for the T1b subgroup these results were of significance. **E:** (vocal analysis) There was a highly significant change in values of F0, MPT, jitter and shimmer in all three groups of patients (p < 0.01). F0, jitter and shimmer increased significantly, and MPT decreased significantly for all three groups. HNR significantly increased for TLM and RT group, but no statistically significant changes were detected in SC group. The differences between mean values of acoustic and aerodynamic parameters among different groups were	

						compared, using Bonferroni multiple comparison, and shown in the Table 6. There is a highly significant difference in values of F0, shimmer and HNR between all groups ($p < 0.01$) before and six months after the treatment. There was little difference in mean values of MPT among TLM and RT group before had after the treatment, and in mean values of jitter between TLM and RT group six months after the treatment ($p > 0.05$). **F:** (vocal analysis) Three months after treatment there was a significant difference between the two treatment modalities with better scores for patients treated with laser surgery regarding jitter and shimmer ($t = -2.9$, $p = 0.007$ and $t = -3.1$, $p = 0.004$ respectively) and higher fundamental frequency for patients treated with laser	

						surgery (t = 3.8, p = 0.000). At 6, 12 and 24 months there were no significant differences any longer between the two treatment modalities except for the fundamental frequency. Voices of patients treated with laser surgery were significantly higher pitched compared to patients treated by radiotherapy at 12 and 24 months after treatment (t = 2.3, p = 0.027 and t = 2.4, p = 0.018 respectively). **G:** (VHI) Median VHI-10 scores were worse for laser patients at all three time intervals despite a stage bias in favour of TLM (range of median VHI score over time intervals: TLM = 9.5 to 12, RT = 3.5 to 8; p = .01–.08).	

Risk of bias table

Randomised controlled trial

Study reference	Describe method of randomisation[1]	Bias due to inadequate	Bias due to inadequate blinding of participants to	Bias due to inadequate blinding of care providers to	Bias due to inadequate blinding of outcome	Bias due to selective outcome	Bias due to loss to follow-up?[5]	Bias due to violation of

		concealment of allocation?[2]	treatment allocation?[3]	treatment allocation?[3]	assessors to treatment allocation?[3]	reporting on basis of the results?[4]		intention to treat analysis?[6]
Aaltonen, 2014	Study participants were randomized to the treatments at a 1:1 ratio by means of a computer program with random digits weighted according to the proportions of past randomizations to yield a roughly balanced number of randomizations between the groups in a concealed fashion. Randomization was carried out by a hospital staff member who was independent of the study. Tumour site in the vocal cord was used as a stratification factor at randomization. The result of randomization was communicated to the centres by phone.	**Unlikely**	**Likely** Note: patients were not blinded	**Likely** Note: care providers were not blinded	**Likely** Note: the self-rated quality of voice may have bias, as patients knew to which arm they were randomized. It was not reported whether other assessors (expert-rated and videolaryngostrobos copic findings) were blinded.	**Unlikely**	**Unclear** Note: loss to follow-up was not reported	**Unlikely**

Table of excluded studies

Author and year	Reason for exclusion
Che, 2019	Population does not match with PICO.
Ding, 2019	SR of observational studies. Most recent SR, and observational studies which met our PICO and were published after 2010 were described.
Guimarães, 2018	SR of observational studies.
Lee, 2018	SR of observational studies.
Huang, 2017	SR of observational studies and one RCT. The RCT is included in the analysis.
Gioacchini, 2017	SR of observational studies.
Waghmare, 2017	Narrative review.
Mo, 2016	SR of observational studies.

Literature search strategy

Study type	PubMed and Embase	De-duplicated
SR	970	680
RCT	1588	1287
Total	2558	1967

PubMed

Search	Query	Items found
#48	Search #35 AND #47	1
#47	Search warner 2014	696
#35	Search #33 AND #34	198
#36	Search randomized controlled trial(pt) OR controlled clinical trial(pt) OR randomized(tiab) OR placebo(tiab) OR drug therapy(sh) OR randomly(tiab) OR trial(tiab) OR groups(tiab)	4540413
#37	Search #33 AND #36	1088
#34	Search ("Meta-Analysis as Topic"(Mesh) OR “Meta-Analysis”(Publication Type) OR metaanaly*(tiab) OR metanaly*(tiab) OR meta-analy*(tiab) OR meta synthes*(tiab) OR metasynthes*(tiab) OR meta ethnograph*(tiab) OR metaethnograph*(tiab) OR meta summar*(tiab) OR metasummar*(tiab) OR meta-aggregation(tiab) OR metareview(tiab) OR meta-review(tiab) OR overview of reviews(tiab) OR ((systematic*(ti) OR scoping(ti) OR umbrella(ti) OR meta-narrative(ti) OR metanarrative(ti) OR evidence based(ti)) AND (review*(ti) OR overview*(ti))) OR ((evidence(ti) OR narrative(ti) OR metanarrative(ti) OR qualitative(ti)) AND synthesis(ti)) OR systematic review(pt) OR prisma(tiab) OR preferred reporting items(tiab) OR quadas*(tiab)) NOT ("Comment" (Publication Type) OR "Letter" (Publication Type)) NOT (“Animals”(Mesh) NOT “Humans”(Mesh))	250838
#33	Search #3 AND #31 Filters: Publication date from 2014/01/01	5515
#32	Search #3 AND #31	27083
#31	Search #14 OR #26 OR #30	4419727
#30	Search surgery (tiab) OR surgical* (tiab) OR (laryn* (tiab) AND preserv* (tiab)) OR laryngectom* (tiab) OR hemilaryngectom* (tiab) OR “excision biopsy” (tiab) OR endoscop* (tiab) OR endolaryngeal (tiab) OR transoral* (tiab) OR “trans oral” (tiab) OR (neck (tiab) AND incision* (tiab)) OR cordectom* (tiab) OR (vocal (tiab) AND cord (tiab) AND stripping (tiab))	1909425
#26	Search "Surgical Procedures, Operative"(Mesh) OR "Otorhinolaryngologic Surgical Procedures"(Mesh) OR "Minimally Invasive Surgical Procedures"(Mesh) OR “Microsurgery” (Mesh) OR "laser surgery"(Mesh)	2996203
#14	Search #7 OR #13	704302
#13	Search "radiotherapy" (Subheading)	185017
#7	Search “Radiotherapy” (Mesh) OR irradiat* (tiab) OR radiotherap* (tiab) OR radiation (tiab)	670142

#6	Search #3 OR #5	46632
#5	Search "Laryngeal Neoplasms"(Mesh)	26901
#3	Search #1 AND #2	46632
#2	Search “Larynx” (Mesh) OR “LARYNGEAL DISEASES” (Mesh) OR laryn* (tiab) OR “vocal cord*” (tiab) OR cordal (tiab) OR glott* (tiab) OR throat (tiab) OR “voice box” (tiab) OR subglotti* (tiab) OR supra- glotti* (tiab)	134821
#1	Search “Neoplasms” (Mesh) OR (cancer* (tiab) OR malignan* (tiab) OR premalignan* (tiab) OR neoplasm* (tiab) OR carcinoma* (tiab) OR dysplasia (tiab) OR tumor* (tiab) OR tumour* (tiab) OR precancer* (tiab)	4114090

Embase

No.	Query	Results
#17	#11 AND #15	**500**
#16	#10 AND #15	**574**
#15	#14 NOT 'conference abstract'/it	**6217**
#14	#13 AND (1-1-2014)/sd	**8694**
#13	#7 AND #12	**28656**
#12	#8 OR #9	**5347273**
#11	random* OR factorial* OR crossover* OR (cross NEXT/1 over*) OR placebo* OR (doubl* AND blind*) OR (singl* AND blind*) OR assign* OR allocat*OR volunteer* OR 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'randomized controlled trial'/exp OR 'single blind procedure'/exp	**2427134**
#10	('meta analysis'/exp OR 'systematic review'/exp OR ((meta NEAR/3 analy*):ab,ti) OR metaanaly*:ab,ti OR review*:ti OR overview*:ti OR ((synthes*NEAR/3 (literature* OR research* OR studies OR data)):ab,ti) OR (pooled AND analys*:ab,ti) OR (((data NEAR/2 pool*):ab,ti) AND studies:ab,ti) OR medline:ab,ti OR medlars:ab,ti OR embase:ab,ti OR cinahl:ab,ti OR scisearch:ab,ti OR psychinfo:ab,ti OR psycinfo:ab,ti OR psychlit:ab,ti OR psyclit:ab,ti OR cinhal:ab,ti OR cancerlit:ab,ti OR cochrane:ab,ti OR bids:ab,ti OR pubmed:ab,ti OR ovid:ab,ti OR (((hand OR manual OR database*OR computer*) NEAR/2 search*):ab,ti) OR ((electronic NEAR/2 (database* OR 'data base' OR 'data bases')):ab,ti) OR bibliograph*:ab OR 'relevant journals':ab OR (((review* OR overview*) NEAR/10 (systematic* OR methodologic* OR quantitativ* OR research* OR literature* OR studies OR trial* OR effective*)):ab)) NOT ((((retrospective* OR record* OR case* OR patient*) NEAR/2 review*):ab,ti) OR (((patient* OR review*) NEAR/2 chart*):ab,ti)) NOT ('editorial'/exp OR 'erratum'/de OR 'letter'/exp)	**1201293**
#9	'surgery'/exp OR 'ear nose throat surgery'/exp OR 'larynx surgery'/exp OR 'dissection'/exp OR 'endoscopic surgery'/exp OR 'laser surgery'/exp OR 'microsurgery'/exp OR 'excision'/exp	**4969914**

	OR surgery:ti OR surgical*:ti OR (laryn*:ti AND preserv*:ti) OR laryngectom*:ti OR hemilaryngectom*:ti OR 'excision biops*':ti OR endoscop*:ti OR endolaryngeal:ti OR transoral*:ti OR 'trans oral':ti OR (neck:ti AND incision*:ti) OR cordectom*:ti OR (vocal:ti AND cord:ti AND stripping:ti)	
#8	'radiotherapy'/exp OR irradiat:ti OR radiotherap*:ti OR radiation:ti	**619001**
#7	#5 OR #6	**53858**
#6	'larynx tumor'/exp	**35623**
#5	#1 AND #4	**53858**
#4	#2 OR #3	**133499**
#3	'larynx disorder'/exp	**81751**
#2	'larynx'/exp OR laryn*:ti OR ((vocal NEAR/2 cord*):ti) OR cordal:ti OR glott*:ti OR throat:ti OR ((voice NEAR/2 box):ti) OR subglotti*:ti OR supraglottic*:ti	**94417**
#1	'neoplasm'/exp OR cancer*:ti OR malignan*:ti OR premalignan*:ti OR neoplasm*:ti OR carcinoma*:ti OR dysplasia:ti OR tumor*:ti OR tumour*:ti OR precancer*:ti	**4901117**

Module 14.2 Behandeling van Tis/T1 supraglottische larynxcarcinomen

Uitgangsvraag

Op welke wijze dienen Tis/T1 supraglottisch larynxcarcinomen behandeld te worden?

Inleiding

In de literatuur worden drie verschillende behandelingsopties als geaccepteerde behandeling voor het T1 supraglottisch larynxcarcinoom besproken: radiotherapie, endoscopische behandeling (meestal met CO_2 laser) en horizontale supraglottische laryngectomie. Welke van deze opties, of combinatie van opties, de beste kans op herstel of minste kans op recidief geeft is niet duidelijk.

Search and select

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

What are the effects of horizontal supraglottic laryngectomy versus endoscopic treatment or radiotherapy for patients with a Tis/T1 supraglottic laryngeal carcinoma?

P: Patients with a Tis/T1 supraglottic laryngeal carcinoma;
I: Horizontal supraglottic laryngectomy;
C: Radiotherapy or endoscopic treatment;
O: 5-year survival, 5-year recurrence of disease, dysphagia (SwalQoL and swallowing tests: video-based swallowing research, assessing penetration scores), eating and drinking, voice quality, breathing (dyspnea), feeding tube, tracheotomy.

Relevant outcome measures

The guideline development group considered recurrence free (local and regional) survival and dysphagia as critical outcome measures for decision making; and disease free survival and permanent feeding tube, eating and drinking, voice quality, breathing (dyspnea) and tracheotomy 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.

Clinically relevant difference

The guideline development group defined a minimal clinically relevant difference at a minimum of a median follow-up period of three years *(in line with "NVMO-commissie ter Beoordeling van Oncologische Middelen (BOM)")* of:

- Overall survival: > 5% difference, or > 3% and HR< 0.7
- Relapse-free survival: HR< 0.7

And, in case of absence of a clinically relevant difference in overall survival or relapse-free survival:

- Quality of life: A minimal clinically important 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.
- Complications/adverse events: Statistically significant less complications/adverse events.

Search and select (Methods)

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms for RCTs and systematic reviews until March 11th, 2020. The detailed

search strategy is depicted under the tab Methods. The systematic literature search resulted in 660 hits.

Studies were selected based on the following criteria:
- the study design was a systematic review (SR) or randomized controlled trial (RCT);
- written in English language;
- included patients with a Tis/T1 supraglottic laryngeal carcinoma;
- compared horizontal supraglottic laryngectomy with radiotherapy or endoscopic treatment;
- reported at least one of the outcomes of interest.

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

Results
No studies were included in the analysis of the literature.

Summary of literature
No studies were found that reported on the crucial and important outcome measures.

Conclusions
No studies were selected that reported on the crucial and important outcome measures. Therefore, GRADE could not be applied, and no conclusions about the three treatment options for patients with Tis/T1 supraglottic laryngeal carcinomas could be drawn.

Overwegingen – van bewijs naar aanbeveling

Voor- en nadelen van de interventie en de kwaliteit van het bewijs
Er zijn geen gerandomiseerde studies of kwalitatief goede vergelijkende observationele studies gevonden die de effecten hebben onderzocht van horizontale supraglottische laryngectomie in vergelijking met endoscopische behandeling of radiotherapie, voor patiënten met een Tis/T1 supraglottisch larynxcarcinoom.

De meest uitgebreide review is van Van der Woerd (2018). Deze review werd gevonden in de search maar voldeed niet aan alle criteria. Het gaat om een systematische review naar functionele uitkomsten bij patiënten met een T1 (43%) of T2 (57%) supraglottische tumor, die radiotherapie (n=320) of orgaansparende chirurgie (n=320) ondergingen. Onder de tien geïncludeerde studies waren zes retrospectieve cohort studies en vier case series, in veel gevallen ging het om data van meer dan tien jaar oud. Wegens heterogeniteit en onvolledige rapportage van functionele uitkomsten voor de verschillende behandelopties kon geen voorkeur voor één van beide modaliteiten worden uitgesproken. Er kunnen daarom geen conclusies worden getrokken op basis van de wetenschappelijke literatuur ter onderbouwing van een aanbeveling.

Expert opinion: In de meeste instituten in Nederland en Noord-Europa worden patiënten met een Tis / T1 supraglottisch carcinoom behandeld met primaire radiotherapie met een lokale controle > 90% en goed functioneel resultaat. In een systematische review van Sanabria (2020) werd de incidentie van occulte lymfekliermetastasen per tumorlocatie en tumorstadium gerapporteerd. In 19 studies werd data gerapporteerd voor supraglottische tumoren. In een subgroepanalyse van studies met daarin tenminste 75% van de patiënten

met een T1/T2 tumor werd een incidentie van 18,4% (95%BI 11,8% tot 25,0%) occulte metastasen gerapporteerd. Er was aanzienlijke variatie; de hoogst gerapporteerde incidentie was 48,2% terwijl drie studies een incidentie lager dan 12% rapporteerden. Deze variatie kon niet goed worden verklaard. Het advies van de auteurs van de review luidt om bij T1-T2 cNO supraglottische tumor level IIa-III bilateraal te bestralen.

Mutlu (2014) voerde een retrospectieve studie uit onder 118 patiënten die een chirurgische behandeling met daarbij een nek dissectie hadden ondergaan. Bij 11 van de 38 patiënten (28,9%) met een supraglottische tumor (tumorstadium niet gespecificeerd) werden occulte lymfeklier metastasen aangetroffen. Bij twee van de 19 patiënten (10,5%) met een T1 tumor (supraglottisch, glottisch of transglottisch) werden occulte metastasen aangetroffen.
Bij primaire tumor > 4 cm is deze kans verhoogd. Het lijkt daarom aan te bevelen electieve bestraling van de halsklierstations level IIA-III af te laten hangen van het tumor volume, op basis van de literatuur zijn geen exacte maten aan te geven.

Transorale laser chirurgie dan wel horizontale supraglottische laryngectomie via een externe benadering is een alternatief in geselecteerde casus. Selectiecriteria betreffen o.a. voldoende marge naar de stembanden en een goede longfunctie. Bij endoscopische chirurgie moet de tumor goed bereikbaar zijn. Dit hangt onder andere af van de mondopening, dentitie en lokale anatomie.

Bij deze tumoren dient zoveel mogelijk gestreefd te worden naar een behandeling met één modaliteit, chirurgie of radiotherapie. Indien het risico op adjuvante radiotherapie hoog is kan het beste gekozen worden voor primaire radiotherapie. Tevens moet afhankelijk van lokalisatie, grootte en uitbreiding ingeschat worden met welke behandeling het slikken, spreken en ademen zonder tracheotomie zo goed mogelijk behouden kunnen blijven. Patiënten dienen dus goed geselecteerd te worden voor één van deze behandelingen. De behandeling zal dan dus ook geïndividualiseerd zijn.

Samengevat is primaire chirurgie een alternatief bij kleine craniaal gelegen epiglottische tumoren bij patiënten met een goede long- en slikfunctie waarbij het risico op adjuvante radiotherapie laag is en voldoende behoud van functies mogelijk lijkt te zijn. Deze voor- en nadelen moeten worden besproken met de individuele patiënt en afgewogen worden bij het gezamenlijk nemen van een beslissing over de in te zetten behandeling.

<u>Waarden en voorkeuren van patiënten (en evt. hun verzorgers)</u>
Er wordt gestreefd naar een hoge kans op locoregionale genezing van de tumor (bij Tis/ T1 supraglottisch larynxcarcinoom > 90%) met een goed functioneel resultaat, goede slikfunctie en spraak. Radiotherapie wordt poliklinisch toegepast in 25-35 fracties in 5-7 weken. De meeste klachten betreffen slikklachten en heesheid en ontstaan tijdens de radiotherapie en voorbijgaand in de periode 6 weken na de bestraling. Chirurgie is een eenmalige ingreep met een paar dagen ziekenhuis opname. Bij chirurgie is de duur van behandeling zonder complicaties één tot enkele dagen. Bij chirurgie kunnen bloedingen, pijnklachten en ontstekingen optreden. Als lange termijn effect kunnen slikklachten ontstaan waarvoor in ernstige gevallen logopedische sliktraining of een blijvende gastrostomie nodig kan zijn. Bij een deel van de patiënten zal nog postoperatieve radiotherapie volgen; in een retrospectieve studie van Dyckhoff (2021) kregen 7 van de 31 patiënten (22,6%) met een T1 supraglottisch larynxcarcinoom adjuvante radiotherapie na transorale laser chirurgie. De kans op lange termijncomplicaties, met name slikklachten zal hierdoor toenemen (expert opinion). Goede selectie van patiënten is dan ook noodzakelijk.

Bij radiotherapie kunnen er klachten van vermoeidheid, huid- en slijmvliesreactie en slikklachten optreden

Kosten (middelenbeslag)
Er bestaan geen studies over een kostenvergelijking tussen de therapeutische opties.
Wat betreft de primaire behandeling is de vergelijking tussen een kortdurende klinische opname met een operatie onder narcose (chirurgie) versus een poliklinische behandeling 5 dagen per week gedurende 5 tot 7 weken. Daarnaast zullen na alle behandelingen nog kosten gemaakt worden voor revalidatie vanwege klachten van slikken en spreken.

Aanvaardbaarheid, haalbaarheid en implementatie
Behandeling van Tis/ T1 supraglottische carcinomen is voorbehouden aan de bij de NWHHT aangesloten HH centra. Een horizontale supraglottische laryngectomie wordt ook binnen de NWHHT centra in Nederland maar beperkt toegepast. Het kan een reden zijn om deze patiënten te verwijzen naar een centrum met expertise op dit gebied.

Aanbeveling(en)
Aanbeveling-1
Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies
Er is onvoldoende wetenschappelijke literatuur om conclusies te kunnen trekken over de rol van horizontale supraglottische laryngectomie in vergelijking met endoscopische behandeling of radiotherapie voor patiënten met een Tis/T1 supraglottisch larynxcarcinoom. In de meeste instituten worden deze patiënten behandeld met primaire radiotherapie, met goed resultaat. Op basis van expert opinie wordt aanbevolen om patiënten bij voorkeur met radiotherapie te behandelen, waarbij transorale laser chirurgie of horizontale supraglottische laryngectomie in geselecteerde gevallen overwogen kunnen worden.

Behandel patiënten met Tis/T1 supraglottisch larynxcarcinoom bij voorkeur met radiotherapie. Overweeg een horizontale laryngectomie of een endoscopische behandeling indien:
- de kans op adjuvante radiotherapie laag is;
- de tumor goed bereikbaar is;
- voldoende behoud van functies mogelijk lijkt te zijn.

Aanbeveling-2
Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies
Er zijn geen vergelijkende studies wat betreft het effect van chirurgische behandeling en behandeling met radiotherapie op locoregionale genezing en functionele uitkomsten. Indien chirurgische behandeling overwogen wordt, bespreek de verschillende behandelopties en de voor- en nadelen van deze opties met de patiënt en beslis samen welke behandeling het meest geschikt is voor de patiënt.

Ondersteun patiënten die in aanmerking komen voor zowel radiotherapie als chirurgie bij het maken van een behandelkeuze waarbij de individuele patiënt- en tumorkarakteristieken dienen te worden afgewogen.

Bespreek de volgende belangrijke voor- en nadelen van de interventies indien van toepassing op de patiënt:

- **Behandelduur:**

De duur van de behandelingen zonder complicaties is bij chirurgie één tot enkele dagen.
Voor RT is de behandeling poliklinisch en de behandelduur vijf tot zeven weken.

- **Overblijvende behandelopties:**
  Na radiotherapie is doorgaans geen radiotherapie meer mogelijk voor een recidief of tweede primaire tumor in het bestraalde gebied.
  Na chirurgie is radiotherapie en soms ook nog hernieuwde chirurgie mogelijk.

- **Procedures:**
  Een dergelijke operatie wordt onder narcose verricht.
- **Korte en lange termijn complicaties en toxiciteit:**
  Bij chirurgie kunnen bloedingen, pijnklachten en ontstekingen optreden. Als lange termijn effect kunnen slikklachten ontstaan waarvoor in ernstige gevallen logopedische sliktraining of een blijvende gastrostomie nodig kan zijn.
  Bij radiotherapie kunnen heesheid en slikklachten optreden. Zes weken na radiotherapie verdwijnen deze klachten in het algemeen. De kans op radionecrose of een secundaire tumor door de radiotherapie is zeer klein.
- ***Voor primaire chirurgie bestaat een kans op een adjuvante behandeling met radiotherapie. Wanneer dit nodig is, is de kans op lange termijn complicaties groter, met name slikklachten.***

- ***De kans op genezing is bij beide behandelopties gelijk.***

Literatuur

Dyckhoff G, Warta R, Herold-Mende C, Rudolph E, Plinkert PK, Ramroth H. An Observational Cohort Study on 194 Supraglottic Cancer Patients: Implications for Laser Surgery and Adjuvant Treatment. Cancers (Basel). 2021 Feb 2;13(3):568. doi: 10.3390/cancers13030568. PMID: 33540592; PMCID: PMC7867201.

van der Woerd B, Patel KB, Nichols AC, Fung K, Yoo J, MacNeil SD. Functional outcomes in early (T1/T2) supraglottic cancer: a systematic review. J Otolaryngol Head Neck Surg. 2018 Dec 18;47(1):76. doi: 10.1186/s40463-018-0321-8. PMID: 30563567; PMCID: PMC6299571.

Sanabria A, Shah JP, Medina JE, Olsen KD, Robbins KT, Silver CE, Rodrigo JP, Suárez C, Coca-Pelaz A, Shaha AR, Mäkitie AA, Rinaldo A, de Bree R, Strojan P, Hamoir M, Takes RP, Sjögren EV, Cannon T, Kowalski LP, Ferlito A. Incidence of Occult Lymph Node Metastasis in Primary Larynx Squamous Cell Carcinoma, by Subsite, T Classification and Neck Level: A Systematic Review. Cancers (Basel). 2020 Apr 24;12(4):1059. doi: 10.3390/cancers12041059. PMID: 32344717; PMCID: PMC7225965.

Mutlu V, Ucuncu H, Altas E, Aktan B. The Relationship between the Localization, Size, Stage and Histopathology of the Primary Laryngeal Tumor with Neck Metastasis. Eurasian J Med. 2014 Feb;46(1):1-7. doi: 10.5152/eajm.2014.01. PMID: 25610286; PMCID: PMC4261447.

Bijlagen bij module 14.2

Implementatieplan

Aanbeveling	Tijdspad voor implementatie: < 1 jaar, 1 tot 3 jaar of > 3 jaar	Verwacht effect op kosten	Randvoorwaarden voor implementatie (binnen aangegeven tijdspad)	Mogelijke barrières voor implementatie[1]	Te ondernemen acties voor implementatie[2]	Verantwoordelijken voor acties[3]	Overige opmerkingen
Module Behandeling Tis-T1 supraglottsiche laryncarcinomen	< 1 jaar	Geen	Geen	De werkgroep ziet geen belemmeringen voor implementatie en acht acties om mogelijke barrières voor implementatie op te lossen niet nodig.	Geen	n.v.t.	In Nederland is de expertise met een uitwendige partiele laryngectomie beperkt

[1] Barrières kunnen zich bevinden op het niveau van de professional, op het niveau van de organisatie (het ziekenhuis) of op het niveau van het systeem (buiten het ziekenhuis). Denk bijvoorbeeld aan onenigheid in het land met betrekking tot de aanbeveling, onvoldoende motivatie of kennis bij de specialist, onvoldoende faciliteiten of personeel, nodige concentratie van zorg, kosten, slechte samenwerking tussen disciplines, nodige taakherschikking, et cetera.
[2] Denk aan acties die noodzakelijk zijn voor implementatie, maar ook acties die mogelijk zijn om de implementatie te bevorderen. Denk bijvoorbeeld aan controleren aanbeveling tijdens kwaliteitsvisitatie, publicatie van de richtlijn, ontwikkelen van implementatietools, informeren van ziekenhuisbestuurders, regelen van goede vergoeding voor een bepaald type behandeling, maken van samenwerkingsafspraken.
[3] Wie de verantwoordelijkheden draagt voor implementatie van de aanbevelingen, zal tevens afhankelijk zijn van het niveau waarop zich barrières bevinden. Barrières op het niveau van de professional zullen vaak opgelost moeten worden door de beroepsvereniging. Barrières op het niveau van de organisatie zullen vaak onder verantwoordelijkheid van de ziekenhuisbestuurders vallen. Bij het oplossen van barrières op het niveau van het systeem zijn ook andere partijen, zoals de NZA en zorgverzekeraars, van belang.

Evidence tables

Not applicable

Table of excluded studies

Author and year	Reason for exclusion
Eksteen (2003)	Wrong intervention
Rigby (2011)	Wrong study design (narrative review not a systematic review)
Swanson (2017)	Wrong intervention
Bussu (2009)	Wrong study design (no randomisation)
Holsinger (2010)	Wrong study design (narrative review)
Zhong (2015)	Wrong population (recurrent carcinoma)
Van der Woerd (2018)	Review including only retrospective single arm (mostly outdated) studies among patients with a T1/T2 supraglottic carcinoma

Literature search strategy

Algemene informatie

Uitgangsvraag: Op welke wijze dienen Tis/T1 supraglottisch larynxcarcinomen behandeld te worden?	
Database(s): PubMed, Embase	Datum: 11-3-2020
Periode: 2000-	Talen: niet van toepassing
Toelichting: Met vriendelijke groet, Ingeborg van Dusseldorp	

Zoekopbrengst

	Inclusief dubbele referenties	Ontdubbeld
SR	133	105
RCT	630	555
Observationeel		
Totaal		660

Zoekverantwoording

PubMed

Search	Query	Items found
#14	Search #9 AND #11	416
#13	Search #9 AND #12	57
#12	Search ("Meta-Analysis as Topic"(Mesh) OR “Meta-Analysis”(Publication Type) OR metaanaly*(tiab) OR metanaly*(tiab) OR meta-analy*(tiab) OR meta synthes*(tiab) OR metasynthes*(tiab) OR meta ethnograph*(tiab) OR metaethnograph*(tiab) OR meta summar*(tiab) OR metasummar*(tiab) OR meta-aggregation(tiab) OR metareview(tiab) OR meta-review(tiab) OR overview of reviews(tiab) OR ((systematic*(ti) OR scoping(ti) OR umbrella(ti) OR meta-narrative(ti) OR metanarrative(ti) OR evidence based(ti)) AND (review*(ti) OR overview*(ti))) OR ((evidence(ti) OR narrative(ti) OR metanarrative(ti) OR qualitative(ti)) AND synthesis(ti)) OR systematic review(pt) OR prisma(tiab) OR preferred reporting items(tiab) OR quadas*(tiab) OR systematic review*(tiab) OR systematic literature(tiab) OR structured literature search(tiab) OR systematic overview*(tiab) OR scoping review*(tiab) OR umbrella review*(tiab) OR mapping review*(tiab) OR systematic mapping(tiab) OR evidence synthes*(tiab) OR narrative synthesis(tiab) OR metanarrative synthesis(tiab) OR research synthesis(tiab) OR qualitative synthesis(tiab) OR realist synthesis(tiab) OR realist review(tiab) OR realist evaluation(tiab) OR systematic qualitative review(tiab) OR mixed studies review(tiab) OR mixed methods synthesis(tiab) OR mixed research synthesis(tiab) OR quantitative literature review(tiab) OR systematic evidence review(tiab) OR evidence-based review(tiab) OR comprehensive literature search(tiab) OR integrated review*(tiab) OR integrated literature review(tiab) OR integrative review*(tiab) OR integrative literature review*(tiab) OR structured literature review*(tiab) OR systematic search and review(tiab) OR meta-narrative review*(tiab) OR metanarrative review(tiab) OR systematic narrative review(tiab) OR systemic review(tiab) OR systematized review(tiab) OR systematic research synthesis(tiab) OR bibliographic*(tiab) OR hand-search*(tiab) OR handsearch*(tiab) OR manual search*(tiab) OR searched manually(tiab) OR manually searched(tiab) OR journal database*(tiab) OR review authors independently(tiab) OR reviewers independently(tiab) OR independent reviewers(tiab) OR independent review authors(tiab) OR electronic database search*(tiab) OR (study selection(tiab) AND data extraction(tiab)) OR (selection criteria(tiab) AND data collection(tiab)) OR (selection criteria(tiab) AND data analysis(tiab)) OR (evidence acquisition(tiab) AND evidence synthesis(tiab)) OR (pubmed(tiab) AND embase(tiab)) OR (medline(tiab) AND embase(tiab)) OR (pubmed(tiab) AND cochrane(tiab)) OR (medline(tiab) AND cochrane(tiab)) OR (embase(tiab) AND cochrane(tiab)) OR (pubmed(tiab) AND psycinfo(tiab)) OR (medline(tiab) AND psycinfo(tiab)) OR (embase(tiab) AND psycinfo(tiab)) OR (cochrane(tiab) AND psycinfo(tiab)) OR (pubmed(tiab) AND web of science(tiab)) OR (medline(tiab) AND web of science(tiab)) OR (embase(tiab) AND web of science(tiab)) OR (psycinfo(tiab) AND web of science(tiab)) OR (cochrane(tiab) AND web of science(tiab)) OR ((literature(ti) OR qualitative(ti) OR quantitative(ti) OR integrated(ti) OR integrative(tiab) OR rapid(ti) OR short(ti) OR critical*(ti) OR mixed stud*(ti) OR mixed method*(ti) OR focused(ti) OR	335882

	focussed(ti) OR structured(ti) OR comparative(ti) OR comparitive(ti) OR evidence(ti) OR comprehensive(ti) OR realist(ti)) AND (review*(ti) OR overview*(ti)) AND (literature search(tiab) OR structured search(tiab) OR electronic search(tiab) OR search strategy(tiab) OR gray literature(tiab) OR grey literature(tiab) OR Review criteria(tiab) OR eligibility criteria(tiab) OR inclusion criteria(tiab) OR exclusion criteria(tiab) OR predetermined criteria(tiab) OR included studies(tiab) OR identified studies(tiab) OR (systematic search(tiab) AND literature(tiab)) OR strength of evidence(tiab) OR citation*(tiab) OR references(tiab) OR database search*(tiab) OR electronic database*(tiab) OR data base search*(tiab) OR electronic data-base*(tiab) OR search criteria(tiab) OR study selection(tiab) OR data extraction(tiab) OR methodological quality(tiab) OR methodological characteristics(tiab) OR methodologic quality(tiab) OR methodologic characteristics(tiab))) OR ((literature review(tiab) OR literature search*(tiab)) AND (structured search(tiab) OR electronic search(tiab) OR Search strategy(tiab) OR gray literature(tiab) OR grey literature(tiab) OR review criteria(tiab) OR eligibility criteria(tiab) OR inclusion criteria(tiab) OR exclusion criteria(tiab) OR predetermined criteria(tiab) OR included studies(tiab) OR identified studies(tiab) OR (systematic search(tiab) AND literature(tiab)) OR strength of evidence(tiab) OR citation*(tiab) OR references(tiab) OR database search*(tiab) OR electronic database*(tiab) OR data base search*(tiab) OR electronic data-base*(tiab) OR search criteria(tiab) OR study selection(tiab) OR data extraction(tiab) OR methodological quality(tiab) OR methodological characteristics(tiab) OR methodologic quality(tiab) OR methodologic characteristics(tiab)))) NOT ("Comment" (Publication Type) OR "Letter" (Publication Type)) NOT (“Animals”(Mesh) NOT “Humans”(Mesh))	
#11	Search Search randomized controlled trial(pt) OR controlled clinical trial(pt) OR randomized(tiab) OR placebo(tiab) OR drug therapy(sh) OR randomly(tiab) OR trial(tiab) OR groups(tiab)	4711359
#9	Search #3 AND #7 Filters: Publication date from 2000/01/01	1811
#8	Search #3 AND #7	3191
#7	Search #4 OR #5 OR #6	741277
#6	Search "Lasers, Gas"(Mesh) OR acupulse(tiab) OR co2 laser(tiab) OR "pixel perfect"(tiab)) OR smartxide(tiab) OR "ultrapulse encore"(tiab)) OR "ultrapulse surgitouch"(tiab)) OR carbon dioxide laser(tiab) OR co 2 laser(tiab) OR continuous wave carbon dioxide laser(tiab) OR eco2(tiab) OR gas laser(tiab)	10203
#5	Search "Low-Level Light Therapy"(Mesh) OR endoscopic laser therapy(tiab) OR laser biostimulation(tiab) OR laser therapy(tiab) OR laser treatment(tiab) OR low energy laser therapy(tiab) OR low energy laser treatment(tiab) OR low intensity laser therapy(tiab) OR low intensity laser treatment(tiab) OR low level laser therapy(tiab) OR low level laser treatment(tiab) OR low level light therapy(tiab) OR low power laser therapy(tiab) OR low power laser treatment(tiab) OR low-level light therapy(tiab)	19800
#4	Search "Radiotherapy"(Mesh) OR "radiotherapy"(Subheading) OR "Radiosurgery"(Mesh) OR radiotherap*(tiab) OR radiati*(tiab) OR radiosurg*(tiab) OR irradiati*(tiab) OR "x ray therapy" (tiab) OR "x ray therapies" (tiab) OR radioimmunotherap*(tiab) OR immunoradiotherap*(tiab)	720564
#3	Search #1 AND #2	7906
#2	Search (“Neoplasms” (Mesh) OR (cancer* (tiab) OR malignan* (tiab) OR premalignan* (tiab) OR neoplasm* (tiab) OR carcinoma* (tiab) OR dysplasia (tiab) OR tumor* (tiab) OR tumour* (tiab) OR precancer* (tiab)) AND (“Larynx” (Mesh) OR “LARYNGEAL DISEASES” (Mesh) OR laryn* (tiab) OR “vocal cord*” (tiab) OR cordal (tiab) OR glott* (tiab) OR throat (tiab) OR “voice box” (tiab) OR subglotti* (tiab) OR supra- glotti* (tiab))	47944
#1	Search "Laryngectomy"(Mesh) OR laryngectom*(tiab)	11651

Embase

No.	Query	Results
#21	#15 NOT #14	**214**
#20	#18 AND #19	**2**

#19	#14 OR #15	**290**
#18	#16 OR #17	**2**
#17	comparison AND of AND swallowing AND act AND videofluoroscopy AND after AND open A ND laser AND partial AND supraglottic AND laryngectomy AND bilic	**1**
#16	warner AND 2017 AND transoral AND laser AND microsurgery AND versus AND radiotherap y	**1**
#15	#11 AND #13	**239**
#14	#11 AND #12	**76**
#13	('clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti) NOT 'conference abstract':it	**2359711**
#12	('meta analysis'/de OR cochrane:ab OR embase:ab OR psycinfo:ab OR cinahl:ab OR medline:ab OR ((systematic NEAR/1 (review OR overview)):ab,ti) OR ((meta NEAR/1 analy*):ab,ti) OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/de) NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	**481200**
#11	#10 AND (2000-2020)/py NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	**1844**
#10	#3 AND #9	**3051**
#9	#6 OR #7 OR #8	**822884**
#8	'carbon dioxide laser'/exp OR 'acupulse':ti,ab,kw OR 'co2 laser':ti,ab,kw OR 'ds-40u':ti,ab,kw OR 'juvia':ti,ab,kw OR 'gas laser':ti,ab,kw OR 'lasertronics paragon 50':ti,ab,kw OR 'mosaic co2':ti,ab,kw OR 'opelaser-03 s':ti,ab,kw OR 'pixel perfect':ti,ab,kw OR 'scx10 carbon dioxide slab laser':ti,ab,kw OR 'smartxide':ti,ab,kw OR 'um-l30':ti,ab,kw OR 'ultrapulse encore':ti,ab,kw OR 'ultrapulse surgitouch':ti,ab,kw OR 'carbon dioxide laser':ti,ab,kw OR 'co 2 laser':ti,ab,kw OR 'continuous wave carbon dioxide laser':ti,ab,kw OR 'eco2':ti,ab,kw	**14044**
#7	'low level laser therapy'/exp OR 'endoscopic laser therapy':ti,ab,kw OR 'laser biostimulation':ti,ab,kw OR 'laser therapy':ti,ab,kw OR 'laser treatment':ti,ab,kw OR 'low energy laser therapy':ti,ab,kw OR 'low energy laser treatment':ti,ab,kw OR 'low intensity laser therapy':ti,ab,kw OR 'low intensity laser treatment':ti,ab,kw OR 'low level laser therapy':ti,ab,kw OR 'low level laser treatment':ti,ab,kw OR 'low level light therapy':ti,ab,kw OR 'low power laser therapy':ti,ab,kw OR 'low power laser treatment':ti,ab,kw OR 'low-level light therapy':ti,ab,kw	**34724**
#6	'radiotherapy'/exp OR 'irradiation':ti,ab,kw OR 'radiation therap*':ti,ab,kw OR 'radio therap*':ti,ab,kw OR 'radiotherapy':ti,ab,kw OR 'radiotreatment':ti,ab,kw OR 'roentgen therapy':ti,ab,kw OR 'x ray therapy':ti,ab,kw OR 'x ray treatment':ti,ab,kw	**783765**
#5	#3 AND #4	**1**

#4	warner AND 2017 AND transoral AND laser AND microsurgery AND versus AND radiotherapy	**1**
#3	#1 AND #2	**6058**
#2	'supraglottic laryngectomy'/exp OR 'larynx surgery'/exp OR laryngectom*:ti,ab,kw	**18273**
#1	'larynx cancer'/exp OR 'glottic squamous cell carcinoma'/exp OR (((glottic OR epiglott* OR glottis OR laryn* OR subglot* OR supraglot* OR 'vocal cord*') NEAR/3 (squamous OR carcinoma)):ti,ab,kw)	**25005**

Module 16.1 Endoscopische chirurgie maligne neus(bij)holtetumoren

Uitgangsvraag

Wat is de rol van endoscopische chirurgie bij patiënten met maligne tumoren van neusholte of neus~~(~~bij~~)~~holte?

Inleiding

Tot eind jaren 90 was de standaard behandeling van maligne neusbijholtetumoren een externe benadering middels sublabiale incisie, laterale rhinotomie, midfacial degloving of vergelijkbare technieken. Vervolgens werd een deel van maxilla (en eventueel andere benige structuren van de neusbijholten) verwijderd. In de laatste twee decennia met de vooruitgang van de endoscopische technieken wordt vaker een tumorresectie uitgevoerd op een 'piecemeal' manier. Deze techniek is patiëntvriendelijker. De vraag is of de endoscopische 'piecemeal' resectie van maligne neusbijholtetumoren dezelfde oncologische resultaten geeft als een externe chirurgische benadering.

Search and select

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

P: Patients with nasal cavity and paranasal sinus carcinoma;
I: Endoscopic surgery;
C: External surgery;
O: Overall survival, disease-free survival, complications/adverse events, quality of life.

Relevant outcome measures

The guideline development group considered overall survival and disease-free survival as a critical outcome measure for decision making; and complications/adverse events, quality of life as an important outcome measure for decision making.

The guideline development group defined the outcome measures as follows:

Overall survival	Time from randomisation to death from any cause, with a minimum follow-up of 5 years
Disease-free survival	Time during and after cancer treatment that the patient survives without any signs or symptoms of cancer recurrence, with a minimum follow-up of 5 years
Complications/adverse events	All negative effects related to the treatment (lethal, acute/serious, chronic)
Quality of life (QoL)	Overall QoL or regarding a specific domain, measured with an ~~validated and reliable~~ instrument~~,~~ such as the SF-36 or EORTC QLQ-C30 or EORTC QLQ-HN35/43.

Clinically relevant difference

The guideline development group defined a minimal clinically relevant difference at a minimum of a median follow-up period of three years) *(in line with "NVMO-commissie ter Beoordeling van Oncologische Middelen (BOM)")* of:

- Overall survival: > 5% difference, or > 3% and HR< 0.7.
- Relapse-free survival: HR< 0.7.

And, in case of absence of a clinically relevant difference in overall survival or relapse-free survival:

- Quality of life: A minimal clinically important 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.
- Complications/adverse events: Statistically significant less complications/adverse events.

Search and select (Methods)
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until July 6th, 2020. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 241 hits.

Studies were selected based on the following criteria: included with nasal cavity and paranasal sinus carcinoma, compared endoscopic surgery with external surgery, reported at least one of the outcomes of interest, the study design was a systematic review (SR), randomized controlled trial (RCT) or observational study, and were written in English language.

Fifty-six studies were initially selected based on title and abstract screening. After reading the full text, ~~51~~ 53 studies were excluded (see the table with reasons for exclusion under the tab Methods), and 3 studies were included.

Data-synthesis
Results from RCTs and observational studies were described and synthesized (preferably by meta-analysis) separately. A priori, the guideline development group decided that observational studies should be of sufficient quality to allow a useful GRADE assessment and to allow conclusions that can guide the recommendations. The guideline development group used the following criteria for eligible observational studies of sufficient quality:
- Compared at least two interventions.
- Included at least 50 patients.
- Corrected for at least one plausible confounder, for example by matching cases and controls, stratification, or statistical correction by performing a multivariable analysis.

Results
Three 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
Systematic reviews
Hur (2019) performed a systematic review and meta-analysis comparing endoscopic resections with open resection in patients with sinonasal mucosal melanoma (SNM). They searched scientific literature up to May 2018. Inclusion criteria were: (1) participants: patients diagnosed with SNM; (2) intervention: endoscopic resection (ER) of SNM; (3) comparison: open resection (OR) or combined resection (endoscopic and open) of SNM; (4) outcomes: overall survival (OS) or disease-free survival (DFS). Exclusion criteria were: studies which did not report survival rates or no comparison was performed between endoscopic and open approaches. In total, 9 studies were included. Nine studies were included in the qualitative synthesis, and 7 studies were included in quantitative synthesis (meta-analysis). Eight studies were retrospective cohort studies, and one study was a prospective cohort study. The studies included a total of 485 participants. Two hundred thirty-two participants

received endoscopic resection and 253 participants received open resection. Follow-up ranged from a median of 0.6 years to a mean of 40.9 months across studies. The following relevant outcome measures were reported: overall survival and disease-free survival.

Lu (2019) performed a systematic review and meta-analysis comparing endoscopic resections with open resections in patients with uncommon sinonasal malignancies ~~(SNM)~~. They searched scientific literature up to April 2019. Inclusion criteria were: (1) histopathological primary malignancies involving the sinonasal cavity; (2) in comparative cohorts managed by both endoscopic resection and open resection approaches; (3) with reported at least one surgical outcome; and (4) in patients aged 18 years or older. Exclusion criteria were: (1) mucosal melanoma histology as that represents a distinctly different tumor type; (2) tumors that are not deemed malignant, for example, angiofibroma and papilloma; (3) recurrent pathologies; (4) hybrid cranioendoscopic approaches to resection; and (5) case series/reports with no comparative cohort. In total, 10 studies were included in the quantitative synthesis (meta-analysis). All 10 studies were retrospective observational cohort studies. The studies included a total of 900 participants. Three hundred ninety-nine participants received endoscopic resection and 501 participants received open resection. Follow-up ranged from a median of 21.0 months to a median of 79.2 months across studies. The following relevant outcome measure was reported: overall survival.

Observational studies
Kiliç (2018) performed a propensity score-matched analysis comparing endoscopic resections with open resection in cases with sinonasal squamous cell carcinoma (SNSCC) without cervical or distant metastases. Cases of SNSCC diagnosed between January 1, 2010 and December 31, 2014 were used. The selection was further limited to cases that received definitive primary site surgery, with a known surgical approach. Exclusion criteria were: (1) preoperative chemotherapy and/or radiotherapy > 180 days after surgery; (2) any N stage other than N0 (which would necessitate neck dissection); (3) M1/stage IVC; (4) unknown vital status or follow-up time. A total of 1483 cases were included in the study. Three hundred fifty-three cases underwent endoscopic resection and 1130 patients underwent open resection. Propensity score-matched analyses were performed with 652 patients: 326 with endoscopic resection and 326 matching patients with open resections. The mean length of follow-up was not reported. The following relevant outcome measures were reported: 5-year overall survival.

<u>Results</u>
Overall survival
Overall survival was reported in three studies (Hur, 2019; Lu, 2019; Kiliç, 2018).

In the systematic review of Hur (2019), seven studies (Cao, 2017; Ledderose, 2015; Lund, 2012; Meng, 2014; Miglani, 2017; Swegal, 2014; Won, 2015) reported the hazard-ratio (HR) for five-year overall survival. Intervention group = endoscopic resection, control group: open resection.

- Cao (2017): HR = 1.43 (95% CI= 0.09 to 23.64), in favour of open resection.
- Ledderose (2015): HR = 0.96 (95% CI= 0.09 to 10.71), in favour of endoscopic resection.
- Lund (2012): HR = 0.52 (95% CI= 0.30 to 0.92), in favour of the intervention group.
- Meng (2014): HR = 1.21 (95% CI= 0.61 to 2.40), in favour of open resection.
- Miglani (2017): HR = 0.06 (95% CI= 0.00 to 31.88), in favour of endoscopic resection.
- Swegal (2014): HR = 1.01 (95% CI= 0.15 to 6.76), in favour of endoscopic resection.
  Won (2015): HR = 0.58 (95% CI= 0.34 to 0.99), in favour of endoscopic resection.

In the systematic review of Lu (2019), four studies (Hagemann, 2019; Huang, 2018; Farquhar, 2016; Saedi, 2014) reported overall survival outcomes. The studies reported different statistical outcome measures and follow-up lengths. Hagemann (2019) reported the five-year overall survival rate (%). Huang, 2018) reported the mean overall survival in months. Farquhar (2016) reported the three-year overall survival rate (%). Saedi (2014) reported the median overall survival in months.

- Hagemann (2019): The five-year overall survival rate was 76% in the endoscopic resection group and 59% in the open resection group.
- Huang (2018): The mean overall survival was 80 months in the endoscopic resection group and 65 months in the open resection group.
- Farquhar (2016): The three-year overall survival rate was 91% in the endoscopic resection group and 76% in the open resection group.
- Saedi (2014): The median overall survival was 24 months in the endoscopic resection group and 28 months in the open resection group.

The study of Kılıç (2018) reported the five-year overall survival rate.

- The five-year overall survival rate after propensity matching was 50.8% (95% CI= 37.7% to 63.5%) in the intervention group and 56.53% (95% CI= 46.5% to 66.5%) in the control group (p=0.850).

Disease-free survival
Disease-free survival was reported in one systematic review (Hur, 2019).

In the systematic review of Hur (2019), five studies (Cao, 2017; Ledderose, 2015; Lee, 2015; Miglani, 2017; Swegal, 2014) reported the hazard-ratio (HR) for five-year disease-free survival. The definition of disease-free survival was not explicitly reported in the study. Since the study reported five-year overall survival, it is assumed that the study also used five-year disease-free survival a study outcome.

- Cao (2017): HR = 1.36 (95% CI= 0.35 to 5.38), in favour of open resection.
- Ledderose (2015): HR = 0.38 (95% CI= 0.03 to 5.34), in favour of endoscopic resection.
- Lee (2015): HR = 0.35 (95% CI= 0.10 to 1.20), in favour of endoscopic resection.
- Miglani (2017): HR = 0.49 (95% CI= 0.06 to 3.74), in favour of endoscopic resection.
- Swegal (2014): HR = 0.60 (95% CI= 0.06 to 5.72), in favour of endoscopic resection.

Complications
Complications were reported in one systematic review (Lu, 2019).

In the systematic review of Lu (2019), five studies (Hagemann, 2019; Huang, 2018; Fu, 2017; Farquhar, 2016; Mortuaire, 2016) reported the risk-ratio (RR) for complications.

- Hagemann (2019): RR= -4.75 (95% CI= -5.27 to -4.23), in favour of endoscopic resection.
- Huang (2018): RR= -3.50 (95% CI= -5.57 to 1.43), in favour of endoscopic resection.
- Fu (2017): RR= -0.70 (95% CI= -1.30 to -0.11), in favour of endoscopic resection.
- Farquher (2016): RR= -2.90 (95% CI= -3.95 to -1.85), in favour of endoscopic resection.
- Mortuaire (2016): RR= -2.60 (95% CI= -3.45 to -1.75), in favour of endoscopic resection.

Quality of life
None of the included studies reported quality of life as an outcome measure.

Level of evidence of the literature

Overall survival

The certainty of the evidence regarding **overall survival** started low, as the evidence originated from observational studies, and was downgraded by one level because of the small number of patients in the studies (imprecision). The level of evidence was graded as *very low*.

Disease-free survival

The certainty of the evidence regarding **disease-free survival** started low, as the evidence originated from observational studies, and was downgraded by one level because of the small number of patients in the studies (imprecision). The level of evidence was graded as very low.

Complications

The certainty of the evidence regarding **complications** started low, as the evidence originated from observational studies, and was downgraded by one level because of the small number of patients in the studies (imprecision). The level of evidence was graded as very low.

Quality of life

The level of evidence was not graded because no studies reported **quality of life**.

Conclusions

Overall survival

Very low GRADE	It is uncertain whether treatment with endoscopic resection results in higher overall survival compared with treatment with open resection in patients with sinonasal malignancies~~SNM/SNSCC~~. *Sources: (Cao, 2017; Ledderose, 2015; Lund, 2012; Meng, 2014; Miglani, 2017; Swegal, 2014; Won, 2015; Hagemann, 2019; Huang, 2018; Farquhar, 2016; Saedi, 2014; Kılıç, 2018)*

Disease-free survival

Very low GRADE	It is uncertain whether treatment with endoscopic resection results in higher disease-free survival compared with treatment with open resection in patients with sinonasal malignancies~~SNM/SNSCC.~~ *Sources: (Cao, 2017; Ledderose, 2015; Lee, 2015; Miglani, 2017; Swegal, 2014)*

Complications/adverse events

Very low GRADE	It is uncertain whether treatment with endoscopic resection results in less complications compared with treatment with open resection in patients with sinonasal malignancies~~SNM/SNSCC.~~. *Sources: (Hagemann, 2019; Huang, 2018; Fu, 2017; Farquhar, 2016; Mortuaire, 2016)*

Quality of life

- **GRADE**	None of the included studies reported quality of life.

Overwegingen - van bewijs naar aanbeveling

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

De geïncludeerde studies vergeleken een endoscopische resectie met een open resectie bij patiënten met een neusholte of neusbijholtecarcinoom. De systematische literatuuranalyse laat zien dat het onduidelijk is of behandeling met een endoscopische resectie positieve effecten heeft op algemene overleving, ziektevrije overleving en complicaties. Geen van de geïncludeerde studies rapporteerde over de uitkomstmaat kwaliteit van leven. Hierdoor is het niet mogelijk een uitspraak te doen over het effect van een endoscopische behandeling op kwaliteit van leven in vergelijking met een open resectie. De gerapporteerde duur van de opname is korter met endoscopische resecties. De overall bewijskracht van de literatuur werd gegradeerd als zeer laag. Dit heeft te maken met imprecisie van de bevindingen door het kleine aantal patiënten in de studiearmen, en beperkingen in de onderzoeksopzet. Het was daarnaast niet mogelijk een meta-analyse uit te voeren, vanwege de statistische heterogeniteit in de uitkomstmaten tussen de studies en wegens heterogeniteit in de patiëntpopulaties tussen de studies.

Waarden en voorkeuren van patiënten (en eventueel hun verzorgers)

Er is geen objectief bewijs dat de patiënten voorkeur hebben voor endoscopisch of open resecties. In het algemeen worden endoscopische resecties geaccepteerd als patiëntvriendelijker en leiden zij tot een kortere opnameduur. Verwacht mag worden dat indien oncologisch gelijkwaardig patiënten de endoscopische procedure prefereren gezien het minder invasieve karakter en het ontbreken van de noodzaak tot een litteken in het gelaat.

Kosten (middelenbeslag)

Er is geen bewijs voor een betere kosten(effectiviteit) van endoscopische resecties. In Nederland zijn er geen groepen die nadeel zou hebben van de kosten geassocieerd aan de behandelmethoden.

Aanvaardbaarheid, haalbaarheid en implementatie

Er is geen gestructureerd onderzoek gedaan in de vorm van procesevaluatie naar de haalbaarheid van endoscopische resecties en externe benaderingen, maar beide worden in Nederland reeds breed toegepast. Er is zeer laag bewijs dat endoscopische resectie dezelfde effectiviteit heeft als open resecties (externe benadering). Endoscopische of open resecties zijn beide complexe ingrepen die uitgevoerd moeten worden door daarvoor opgeleide chirurgen. Er is geen subgroep in Nederland die geen toegang kan krijgen naar de aanbevolen behandeling. De behandeling van neus(bij)holtetumoren ~~worden~~ wordt uitgevoerd in een aantal gespecialiseerde ziekenhuizen in Nederland. In al deze ziekenhuizen worden de ingrepen uitgevoerd door daarvoor opgeleide chirurgen. De haalbaarheidscriteria van endoscopisch of open chirurgie van de neusbijholten zijn vergelijkbaar. Specifiek expertise is vereist, maar deze is in centra voorhanden. Dit type chirurgie kan zonodig, afhankelijk van de lokale situatie, in samenwerking tussen hoofd-halschirurg en KNO-arts gespecialiseerd in neusbijholtechirurgie uitgevoerd worden.

Aanbeveling

Aanbeveling-1

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

Er is geen overtuigend bewijs dat endoscopische resectie van neus(bij)holtetumoren voordeliger of nadeliger is dan open resectie (via externe benadering) wat betreft de algemene overleving, ziekte specifieke overleving of kwaliteit van leven. De bestaande publicaties van retrospectieve data tonen vergelijkbare uitkomsten met endoscopische en

open resecties. De opname duur is korter met endoscopische resecties. Endoscopische technieken zijn nieuwer en in de afwezigheid van nadelen in de geaccumuleerde data kunnen deze worden uitgevoerd door daarvoor opgeleide chirurgen. Deze aanbeveling is niet sterk onderbouwd. Open resecties blijven een geldige optie.

Bespreek met de patiënt de twee chirurgische behandelopties van maligne neus(bij)holtetumoren, te weten een uitwendige open en een endoscopische benadering, en wijs daarbij op de voor- en nadelen van deze behandelmogelijkheden.

Endoscopische chirurgie vs. externe chirurgie:

- Vergelijkbare uitkomsten wat betreft overleving en kwaliteit van leven
- Voordelen: betere visualisatie aan lumen zijde, kortere operatieduur, kortere ziekenhuisopname, minder morbiditeit en afwezigheid uitwendige littekens.
- Nadelen: niet bij alle neus(bij)holtetumoren mogelijk en chirurgische ervaring en apparatuur nodig.

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Bijlagen bij module 16.1

Implementatieplan

Aanbeveling	Tijdspad voor implementatie: < 1 jaar, 1 tot 3 jaar of > 3 jaar	Verwacht effect op kosten	Randvoorwaarden voor implementatie (binnen aangegeven tijdspad)	Mogelijke barrières voor implementatie[1]	Te ondernemen acties voor implementatie[2]	Verantwoordelijken voor acties[3]	Overige opmerkingen
Endoscopische chirurgie maligne neus(bij)holtetumoren	< 1 jaar	Geen	In elk centrum moeten beide technieken (endoscopisch en uitwendig) beheerst worden.	Expertise oncologische neusbijholte chirurgie		NWHHT-centra	

[1] barrières kunnen zich bevinden op het niveau van de professional, op het niveau van de organisatie (het ziekenhuis) of op het niveau van het systeem (buiten het ziekenhuis). Denk bijvoorbeeld aan onenigheid in het land met betrekking tot de aanbeveling, onvoldoende motivatie of kennis bij de specialist, onvoldoende faciliteiten of personeel, nodige concentratie van zorg, kosten, slechte samenwerking tussen disciplines, nodige taakherschikking, et cetera.
[2] Denk aan acties die noodzakelijk zijn voor implementatie, maar ook acties die mogelijk zijn om de implementatie te bevorderen. Denk bijvoorbeeld aan controleren aanbeveling tijdens kwaliteitsvisitatie, publicatie van de richtlijn, ontwikkelen van implementatietools, informeren van ziekenhuisbestuurders, regelen van goede vergoeding voor een bepaald type behandeling, maken van samenwerkingsafspraken.
[3] Wie de verantwoordelijkheden draagt voor implementatie van de aanbevelingen, zal tevens afhankelijk zijn van het niveau waarop zich barrières bevinden. Barrières op het niveau van de professional zullen vaak opgelost moeten worden door de beroepsvereniging. Barrières op het niveau van de organisatie zullen vaak onder verantwoordelijkheid van de ziekenhuisbestuurders vallen. Bij het oplossen van barrières op het niveau van het systeem zijn ook andere partijen, zoals de NZA en zorgverzekeraars, van belang.

Evidence tables

Systematic reviews

Author	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Hur, 2019	*Literature search up to October 13, 2017 and updated on May 4, 2018* **A**: Cao (2017) **B**: Ledderose (2015) **C:** Lee (2015) **D**: Lombardi (2016) **E**: Lund (2012) **F**: Meng (2014) **G**: Miglani (2017) **H**: Swegal (2014) **I**: Won (2015) Origin of the study **A:** Yangzhou, China **B**: Munich, Germany **C**: Seoul, South Korea **D**: Varese and Brescia, Italy **E**: London, UK **F**: Shanghai, China **G**: Phoenix, Arizona, US **H**: Cleveland, Ohio, US **I**: South Korea Study design: SR and meta-analysis of 8 retrospective	Inclusion criteria SR: - Participants: patients diagnosed with sinonasal mucosal melanoma (SNM); - Intervention: ER of SNM; - Comparison: open resection (OR) or combined resection (endoscopic and open) of SNM; - Outcomes: overall survival or disease-free survival Exclusion criteria SR: - Studies which did not report survival rates or no comparison was performed between endoscopic and open approaches. *7 studies included* Important patient characteristics at baseline: Sample size (N)	Describe intervention: **A**: Endoscopic resection **B**: Endoscopic resection **C**: Endoscopic resection **D**: Endoscopic resection **E**: Endoscopic resection **F**: Endoscopic resection **G**: Endoscopic resection **H**: Endoscopic resection **I**: Endoscopic resection	Describe control: **A**: Open resection **B**: Open resection **C**: Open resection **D**: Open and endoscopic resection **E**: Open resection **F**: Open resection **G**: Open resection **H**: Open resection **I**: Open and endoscopic resection	End-point of follow-up: **A**: Median ER = 0.8 years, Median OR = 0.6 years **B**: Not reported in study **C**: Median = 9.0 months **D**: Median = 30 months **E**: Median = 37.5 months **F**: Mean = 34 months **G**: Median = 25 months **H**: Median ER = 1.4 years, Median OR = 2.0 years **I**: Mean = 40.9 months For how many participants were no complete outcome data available? (intervention/control) Not reported.	**Overal survival** Defined as 5-year survival Effect measure: Hazard ratio (95% CI): **A**: HR= 1.43 (95% CI= 0.09 to 23.64) favoring OR **B**: HR= 0.96 (95% CI= 0.09 to 10.71) favoring ER **E:** HR= 0.52 (95% CI= 0.30 to 0.92) favoring ER **F:** HR= 1.21 (95% CI= 0.61 to 2.40) favoring OR **G:** HR= 0.06 (95% CI= 0.00 to 31.88) favoring ER **H:** HR= 1.01 (95% CI= 0.15 to 6.76) favoring OR **I:** HR= 0.58 (95% CI= 0.34 to 0.99) favoring ER Pooled effect (random effects model): HR= 0.68 (95% CI= 0.49 to 0.95) favoring ER Heterogeneity (I^2): 0.0%; p=0.550 **Disease-free survival** Definition of disease-free survival is not explicitly	Author's conclusion: Based on the available literature, an endoscopic approach for SNM resection has improved OS and similar DFS compared to an open approach. Further multicenter trials or meta-analyses are necessary to assess oncologic outcomes, postoperative morbidity, and cost between the 2 approaches.

	cohort studies and 1 prospective cohort study <u>Setting and Country</u>: Caruso Department of Otolaryngology – Head and Neck Surgery, Keck School of Medicine, University of Southern California, Los Angeles, California. <u>Source of funding:</u> The author(s) received no financial support for the research, authorship, and/or publication of this article. <u>conflicts of interest:</u> The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.	(ER= endoscopic resection; OR=open resection) **A**: ER: N = 15 OR: N = 18 Total: 33 **B**: ER: N = 12 OR: N = 10 Total: 22 **C**: ER: N = 16 OR: N = 15 Total: 31 **D**: ER: N = 37 OR: N = 7 ER + OR: N = 14 Total: 58 **E**: ER: N = 31 OR: N = 86 Total: 117 **F**: ER: N = 41 OR: N = 28 Total: 69 **G**: ER: N = 9 OR: N = 13 Total: 22 **H**: ER: N = 12 OR: N = 13 Total: 25				<u>reported in the study. Since the study reported 5-year overall survival it is assumed that the study also used 5-year disease-free survival as an outcome of the study.</u> **A:** HR= 1.36 (95% CI= 0.35 to 5.38) favoring OR **B:** HR= 0.38 (95% CI= 0.03 to 5.34) favoring ER **C:** HR= 0.35 (95% CI= 0.10 to 1.20) favoring ER **G:** HR= 0.49 (95% CI= 0.06 to 3.74) favoring ER **H:** HR= 0.60 (95% CI= 0.06 to 5.72) favoring ER Pooled effect (random effects model): HR= 0.59 (95% CI= 0.28 to 1.25) favoring ER Heterogeneity (I^2): 0.0%; p=0.668	

		I: ER: N = 59 OR: N = 63 ER + OR: N = 11 Total: 133 Groups comparable at baseline? Not reported					
Lu, 2019	SR and meta-analysis of retrospective cohort studies *Literature search up to April 2019* **A**: Hagemann (2019) **B**: Huang (2018) **C**: Fu (2017) **D**: Farquhar (2016) **E**: Mortuaire (2016) **F**: Naunheim (2016) **G**: Bhayani (2014) **H**: Guo (2014) **I**: Saedi (2014) **J:** Arnold (2012) Origin of the study **A:** Mainz, Germany **B**: Guangdong, China **C**: Toronto, Canada **D**: Philadelphia, US **E**: Lille, France **F**: Boston, US **G**: Houston, US **H**: Shanghai, China **I**: Tehran, Iran	Inclusion criteria SR: - Histopathological primary malignancies involving the sinonasal cavity; - In comparative cohorts managed by both ER and OR approaches; - With reported at least one surgical outcome; - In patients > 18 years. Exclusion criteria SR: - Mucosal melanoma (MM) histology as that represents a distinctly different tymor type; - Tumors that are not deemed malignant, for example, angiofibroma and papilloma; - Reuccrent pathologies; - Hybrid cranioendoscopic	Describe intervention: **A**: Endoscopic resection **B**: Endoscopic resection **C**: Endoscopic resection **D**: Endoscopic resection **E**: Endoscopic resection **F**: Endo- and cranioendoscopic resection **G**: Endoscopic resection **H**: Endoscopic resection **I**: Endoscopic resection **J:** Endoscopic resection	Describe control: **A**: Open resection **B**: Open resection **C**: Open resection **D**: Open resection **E**: Open resection **F**: Open resection **G**: Open resection **H**: Open resection **I**: Open resection **J:** Open resection	Median follow-up: **A**: 45.5 months **B**: 73.6 months **C**: Not reported **D**: 40.1 months **E**: 79.2 months **F**: 27.4 months **G**: 55.3 months **H**: 67 months **I**: 21 months **J:** 36.3 months	**Overall survival** **A:** ER: 5-year OS rate = 76% OR: 5-year OS rate = 59% P=0.36 **B:** ER: mean OS = 80 months OR: mean OS = 65 months P=0.14 **D:** ER: 3-year OS rate = 91% OR: 3-year OS rate = 76% P=0.02 **I:** ER: median OS = 24 months OR: median OS = 28 months P=0.13 The data were not robust enough for meta-analysis	**Conclusion** Current pooled evidence suggested that when compared to OR, ER is a comparable surgical approach for SNMs based on direct data in the literature in terms of many surgical outcomes, tempering superiority assumptions implied by indirect comparisons. Outcomes which will improve our understanding of approach significance in the future include long-term OS outcomes as well as longer term recurrence control. It is likely that particular patients and presentations will benefit more from one of the approaches versus the other; however, greater research is required to identify these potential surgical

	J: Berne, Switzerland Study design: SR and meta-analysis of 10 retrospective observational cohort studies. Setting and Country: Prince of Wales Clinical School, University of New South Wales, Sydney, Australia Source of funding The author(s) received no financial support for the research, authorship, and/or publication of this article. Conflicts of interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.	approaches to resection; - Case series/reports with no comparative cohort. *10 studies included* Important patient characteristics at baseline: Sample size, N (%) (ER= endoscopic resection; OR= open resection) **A**: ER: N = 123 (55%) OR: N = 102 (45%) **B**: ER: N= 27 (57%) OR: N= 20 (43%) **C**: ER: N = 15 (17%) OR: N = 72 (83%) **D**: ER: N = 82 (66%) OR: N = 42 (34%) **E**: ER: N = 20 (47%) OR: N = 23 (53%) **F**: ER: N = 10 (18%)				due to the different scales and timeframes **Complications** Effect measure: RR (95% CI) **A:** RR= 0.74 (95% CI= 0.50 to 1.10) favoring ER **C:** RR= 2.40 (95% CI= 0.67 to 8.54) favoring OR **D:** RR= 0.55 (95% CI= 0.29 to 1.03) favouring ER **E:** RR= 0.23 (95% CI= 0.01 to 4.50) favoring ER **F:** RR= 0.26 (95% CI= 0.04 to 1.76) favoring ER **J:** RR= 0.18 (95% CI= 0.01 to 3.07) favoring ER Pooled effect (random effects model): RR= 0.68 (95% CI= 0.42 to 1.10) favoring ER Heterogeneity (I^2): 27.2%; p=0.231 **Length of stay** Effect measure: RR (95% CI) **A:** RR= -4.75 (95% CI= -5.27 to -4.23) favoring ER **B:** RR= -3.50 (95% CI= -5.57 to -1.43) favoring ER **C:** RR= -0.70 (95% CI= -1.30 to -0.11) favoring ER	subgroups and overcome the selection bias concerns present in the current literature.

		OR: N = 45 (82%) **G**: ER: N = 14 (27%) OR: N = 38 (73%) **H**: ER: N = 8 (33%) OR: N = 16 (67%) **I**: ER: N = 72 (45%) OR: N = 88 (55%) **J:** ER: N = 28 (34%) OR: N = 55 (66%) Total: ER: N = 399 (44%) OR: N = 501 (56%) <u>Median age</u> **A**: Not reported **B**: Not reported **C**: 56 years **D**: 54 years **E**: 70 years **F**: 58 years **G**: 57 years **H**: 35 years **I**:47 years **J:** 63 years <u>Sex</u>: **A:** 60% male **B**: Not reported				**D:** RR= -2.90 (95% CI= -3.95 to -1.85) favoring ER **E:** RR= -2.60 (95% CI= -3.45 to -1.75) favoring ER Pooled effect (random effects model): RR= -2.87 (95% CI= -4.68 to -1.05) favoring ER Heterogeneity (I^2): 96.0%; p=0.000 **<u>Recurrence; RR (95% CI)</u>** Effect measure: RR (95% CI) **A:** RR= 0.91 (95% CI= 0.69 to 1.19) favoring ER **B:** RR= 0.12 (95% CI= 0.02 to 0.91) favoring ER **D:** RR= 0.63 (95% CI= 0.34 to 1.18) favoring ER **E:** RR= 0.57 (95% CI= 0.20 to 1.63) favoring ER **H:** RR= 0.81 (95% CI= 0.36 to 1.84) favoring ER **I:** RR= 1.24 (95% CI= 1.03 to 1.50) favoring OR Pooled effect (random effects model): RR= 0.84 (95% CI= 0.58 to 1.21) favoring ER Heterogeneity (I^2): 67.6%; p=0.009	

		C: 57% male **D**: 53% male **E**: 98% male **F**: 69% male **G**: 73% male **H**: 42% male **I**:70% male **J:** 67% male <u>Radiation therapy (%) / Chemotherapy (%)</u> **A:** 58% / 20% **B**: Not reported **C**: 77% / 15% **D**: 73% / 34% **E**: Not reported **F**: 82% / 62% **G**: Not reported **H**: Not reported **I**: 38% / 27% **J:** 65% / 23% <u>Groups comparable at baseline?</u> Not reported					

Observational studies

Author	Study characteristics	Patient characteristics [2]	Intervention (I)	Comparison / control (C) [3]	Follow-up	Outcome measures
Kılıç, 2018	<u>Type of study:</u> Observational study. <u>Setting and country:</u> Department of Otolaryngology–Head and Neck Surgery, Rutgers New	<u>Inclusion criteria</u>: - Cases of SNSCC diagnosed between January 1, 2010 and December 31, 2014; - Cases that received definitive primary site surgery, with a known surgical approach. <u>Exclusion criteria</u>: - Cases diagnosed before 2010;	<u>Describe intervention:</u> Endoscopic surgical approach	<u>Describe control:</u> Open surgical approach	<u>Length of follow-up</u>: Not reported. <u>Loss-to-follow-up</u>: Not reported.	**<u>5-year overall survival (BEFORE PROPENSITY SCORE-MATCHING); % (95% CI)</u>** I: 46.0% (95% CI= 33.2 to 58.8) C: 56.5% (95% CI= 51.3 to 61.6)

	Jersey Medical School, Newark, NJ, USA Funding None provided. Conflicts of interest: None provided.	- Cases that received preoperative chemotherapy and/or radiotherapy; - Cases that received postoperative chemotherapy and/or radiotherapy 180 days after surgery; - Cases coded as “stage 0” disease and those with unknown overall stage; - Cases with any N stage other than N0; - M1/stage IVC cases; - Cases with unknown vital status or follow-up time. N total at baseline: 1438 Intervention: N = 353 Control: N = 1130 Age <60; N (%): I: N = 135 (38.2%) C: N = 389 (34.4%) Total: N = 524 (35.3%) Age 60-70; N (%): I: N = 99 (28%) C: N = 376 (33.3%) Total: N = 475 (32%) Age >70; N (%): I: N = 119 (33.7%) C: N = 365 (32.3%) Total: N = 484 (32.6%) P=0.168 Sex: I: N = 218 (61.8%) M C: N = 745 (65.9%) M Total: N = 963 (64.9%) P=0.152			Incomplete outcome data: Not reported.	p=0.953 **5-year overall survival (AFTER PROPENSITY SCORE-MATCHED COHORT); % (95% CI)** I: 50.8% (95% CI= 37.7 to 63.5) C: 56.53% (95% CI= 46.5 to 66.5) P=0.850 **Length of stay (days) (BEFORE PROPENSITY SCORE MATCHING)** I: 2.50 days C: 4.67 days P<0.0001 **Length of stay (days) (AFTER PROPENSITY SCORE MATCHING)** I: 2.54 days C: 4.69 days P<0.0001 **Surgical approach; Univariate HR (95% CI)** I: HR= 1.00 (REF) C: HR= 1.01 (95% CI= 0.81 to 1.26) P=0.953 **Surgical approach; Multivariate HR (95% CI)** I: HR= 1.00 (REF)

		Groups comparable at baseline? The 2 groups did not differ in any demographic characteristics, but they did differ significantly in facility type, anatomic subsite, AJCC clinical stage group, tumor size, and histologic grade. Mortality at 30 days and 90 days did not significantly differ between the 2 groups (p = 0.901 and p = 0.307, respectively), suggesting that there is no significant difference in perioperative mortality.				C: HR= 1.01 (95% CI= 0.77 to 1.34) P=0.932 **Complications** Not reported due to a limited number of variables related to complications. **Quality of life** Not reported.

Quality assessment

Systematic reviews

Study **First author, year**	**Appropriate and clearly focused question?[1]** **Yes/no/unclear**	**Comprehensive and systematic literature search?** **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/notapplicable**	**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**
Hur (2019)	Yes *Aim* *This study aims to systematically review the current literature to*	Yes *Period* *Until October 13, 2017and updated on May 4, 2018* *Databases* *Pubmed, Embase, Cochrane library*	Yes *We obtained full-text articles for 56 titles in our review. Forty-seven articles were excluded either*	Yes *The studies gives a brief description of the sample size, follow-up period, design, interventions,*	Unclear	Yes *The Newcastle-Ottawa Quality Assessment Scale was used to review the quality of the*	Yes *Seven out of 9 studies had sufficient data to be included in the meta-analysis of OS. The 2 studies*	No *Publication bias may have prevented smaller case series or publications with negative*	Yes *The author(s) declared no potential conflicts of interest with respect to the research, authorship,*

	compare the survival outcomes of endoscopic versus nonendoscopic surgical resection in patients with SNM. *<u>Inclusion criteria</u>* *Studies were included if they met the following criteria: (1) participants: patients diagnosed with SNM; (2) intervention: ER of SNM; (3) comparison: open resection (OR) or combined resection (endoscopic and open) of SNM; (4) outcomes: OS or DFS.* *<u>Exclusion criteria</u>* *Exclusion criteria included*	*and Web of Science*	*because they did not compare an endoscopic versus an open approach for resection of SNM or they did not report OS or DFS.*	*disease stage etc. of the included studies.*		*included studies.*	*excluded either did not report OS or had missing data such as the absence of a Kaplan–Meier survival curve.*	*results to be published, leading our data set to have an inflated survival rate.*	*and/or publication of this article.*

	studies which did not report survival rates or no comparison was performed between endoscopic and open approaches.								
Lu (2019)	Yes *Aim* *the aim of this meta-analysis was to critically evaluate ER versus OR by pooling the current literature to identify and compare clinical outcomes between the 2 approaches in treating all primary sinonasal malignancies ~~SNMs~~ based on comparative studies only.* *Inclusion criteria* *(1) histopathological primary*	Yes *Period* *Up to April 2019.* *Databases* *Ovid Embase, Pubmed, Scopus and Cochrane*	No *Reasons for exclusion of the full-texts were not reported. After removal of 479 duplicate studies, inclusion and exclusion criteria were applied to titles and abstracts of the 521 articles. This yielded 26 studies that underwent full-text analysis. Ten individual retrospective cohort studies20–29 fulfilled the selection criteria and were included*	Yes *Overall, all included studies reported the survival prognosis of 900 sinonasal malignancy~~SNM~~ patients, with median age ranging from 35 to 70 years, and 42% to 98% were male. ER and OR were utilized in 399 (44%) and 501 (56%) cases, respectively (Table 1). Median follow-up of all patients ranged from 21 to 74 months across all studies.*	Yes *Meta-regression was performed to analyze potential effect modification by mean age, proportion male, median follow-up, radiation therapy use, and chemotherapy use on overall outcomes with 5 studies. These results were summarized by the slope, which identified the direction of the modification by the variable. All P values were 2-sided with significance set at P<.05.*	Yes *According to the Newcastle Ottawa Scale criteria, all studies were identified* to be of good quality.	No Three studies reported the incidence of positive margins. Although not robust enough for meta-analysis due to their heterogenous values, we describe their individual findings in turn.	Yes *Publication and small-study biases were assessed through the generation of a funnel plot and assessedfor asymmetry. Egger's linear regression test and Begg's correlation test were used to investigate suspect asymmetry.*	Yes *The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.*

	malignancies involving the sinonasal cavity, (2) in comparative cohorts managed by both ER and OR approaches, (3) with reported at least one surgical outcome, and (4) in patients>18 years. Surgical outcomes were positive margins, complications, and length of stay (LOS). *Exclusion criteria* *(1) mucosal melanoma (MM) histology as that represents a distinctly different tumor type, (2) tumors that are not deemed malignant, for example, angiofibroma*		*for quantitative analysis (Table 1).*	*Where reported, radiation therapy and chemotherapy were used in management in 38% to 82% and 15% to 62% of cases, respectively. When studies reported outcomes for multiple sinonasal malignancy~~SNM~~ histologies, SCC was the most common.*					

	and papilloma, (3) recurrent pathologies, (4) hybrid cranioendoscopic approaches to resection, and (5) case series/reports with no comparative cohort.								

Observational studies

Study reference (first author, year of publication)	**Bias due to a non-representative or ill-defined sample of patients?**[1] (unlikely/likely/unclear)	**Bias due to insufficiently long, or incomplete follow-up, or differences in follow-up between treatment groups?**[2] (unlikely/likely/unclear)	**Bias due to ill-defined or inadequately measured outcome ?**[3] (unlikely/likely/unclear)	**Bias due to inadequate adjustment for all important prognostic factors?**[4] (unlikely/likely/unclear)
Kılıç (2018)	Unlikely *The study applied specific eligibility criteria*	Unlikely *Patients with unknown follow-up time were excluded.*	Unlikely *The study investigates hard (objective) outcome measures (5 year overall survival).*	Unlikely *Multivariate binary logistic regression was used to identify factors associated with endoscopic surgical approach. Variables with p ≤ 0.1 on univariate analysis were included in the multivariate model. p<0.05 was considered significant for all other tests.*

Table of excluded studies

Author and year	Reason for exclusion
Antognoni 2015	Wrong study design
Arnold 2012	Included in Lu (2019)
Arnold 2020	Does not match PICO: wrong comparison
Boghani 2013	Does not match PICO: wrong population
Cao 2017	Included in Hur (2019)
Chang 2010	Wrong study design
Dagan 2016	Wrong study design
Duval 2013	Does not match PICO: wrong population
Farber 2019	Wrong study design
Fiani 2019	Background article
Fu 2017	Included in Lu (2019)
Gao 2020	Does not match PICO: wrong population
Gore 2018	Does not match PICO: no comparison between ER en external surgery
Gu 2014	Does not match PICO: wrong population
Hagemann 2019	Included in Lu (2019)
Harvey 2017	Does not match PICO: no comparison of intervention and control
Harvey 2017	Does not match PICO: no comparison of intervention and control
Huang 2018	Included in Lu (2019)
Husain 2019	Wrong study design
Kılıç 2018	Duplicate with included study of Kılıç (2018)
Kim 2017	Does not match PICO: wrong population
Lai 2020	Wrong study design
Lisan 2016	Does not match PICO: wrong population
Lundberg 2019	Wrong study design
Mays 2018	Wrong study design
Meccariello 2016	Does not match PICO
Miglani 2017	Included in Hur (2019)
Nicolai 2016	Wrong study design
Oker 2018	Wrong study design
Papacharalampous 2013	Background article
Peng 2019	Does not match PICO: wrong population
Perkins 2017	Wrong study design
Persky 2018	Does not match PICO: wrong population
Petruzzelli 2015	Wrong study design
Povolotskiy 2019	Wrong study design
Ran 2011	Wrong study design
Saedi 2014	Included in Lu (2019)
Soler 2012	Wrong publication type: letter to the editor
Su 2014	Narrative review
Su 2014	Duplicate with Su (2014)
Swegal 2014	Included in Hur (2019)
Torabi 2020	Duplicate with Torabi (2019)
Torabi 2019	Wrong study design
Van Gerven 2011	Wrong study design
Verillaud 2012	Wrong study design
Wang 2019	Does not match PICO: wrong publication and no comparison of intervention and control
Wang 2019	Does not match PICO: wrong publication and no comparison of intervention and control
Wertz 2018	Wrong study design
Won 2015	Included in Hur (2019)
Woods 2018	Wrong study design
Xiao 2019	Wrong study design
Yin 2019	Wrong study design
Zhang 2010	Wrong study design

Literature search strategy

Algemene informatie

Richtlijn: Hoofd- Halstumoren	
Uitgangsvraag: neus(bijholte)carcinoom en endoscopie versus open chirurgie	
Database(s): Ovid/Medline, Embase	Datum: 06-07-2020
Periode: 2010-	Talen: niet van toepassing
Literatuurspecialist: Ingeborg van Dusseldorp	

Zoekopbrengst

	EMBASE 11-6	Embase 6-7	OVID/MEDLINE	Som	Ontdubbeld	Ontdubbeld update + overige 6-7
SRs	17	18	7	24	21	1
RCTs	14	19	3	17	15	0
Observationele studies	76	93	38	115	86	2
Overig		126				116
Totaal				156	122	119

Zoekverantwoording

Embase 6 juli 2020, aanscherping van de vraag

No.	Query	Results
#31	#8 AND #30 **Nose tumor and endoscopic surgery and open surgery**	**235**
#30	#4 AND #29 **Nose tumor and endoscopic surgery**	**2714**
#29	#2 AND #28	**7196**
#28	'nose tumor'/exp OR 'nose cancer'/exp OR 'sinonasal cancer'/exp OR 'sinonasal malignancy'/exp OR 'sinonasal melanoma'/exp OR 'maxilla resection'/exp OR maxillectom*:ti,ab,kw OR ((sinonasal:ti,ab,kw OR nose:ti,ab,kw OR paranasal*:ti,ab,kw OR nasal:ti,ab,kw) AND (cancer*:ti,ab,kw OR neoplasm*:ti,ab,kw OR tumor*:ti,ab,kw OR tumour*:ti,ab,kw OR malignan*:ti,ab,kw OR carcinoma:ti,ab,kw))	**46526**
#27	#24 NOT #12	**1**
#26	#23 NOT #11	**1**
#25	#22 NOT #10	**1**
#24	#7 AND #21	**94**
#23	#6 AND #21	**20**
#22	#5 AND #21	**19**
#21	#20 AND (2010-2020)/py NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	**238**
#20	#8 AND #19	**453**
#19	#2 AND #18	**5485**
#18	#1 OR #17	**34120**
#17	#15 AND #16	**6339**
#16	'malignant neoplasm'/exp	**3723935**

#15	'nose'/exp	**73055**
#14	#12 NOT #11 NOT #10	**76**
#13	#11 NOT #10	**14**
#12	#7 AND #9	**93**
#11	#6 AND #9	**21**
#10	#5 AND #9	**19**
#9	#4 AND #8 **Nose tumor and endoscopic surgery and open surgey**	**235**
#8	'open surgery'/exp OR 'open surgery':ti,ab,kw OR 'open resect*':ti,ab,kw OR ('open':ti AND 'resect*':ti) OR 'external surgery':ti,ab,kw OR ((external NEAR/3 approach):ti,ab,kw) OR 'medial maxillectom*':ti,ab,kw OR 'midfacial degloving':ti,ab,kw OR 'weber ferguson':ti,ab,kw OR 'open versus endoscopic':ti,ab,kw OR 'endoscopic versus open':ti,ab,kw	**39034**
#7	'major clinical study'/de OR 'clinical study'/de OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR 'prospective study'/de OR 'comparative study'/de OR 'cohort analysis'/de OR ((cohort NEAR/1 (study OR studies)):ab,ti) OR (('case control' NEAR/1 (study OR studies)):ab,ti) OR (('follow up' NEAR/1 (study OR studies)):ab,ti) OR (observational NEAR/1 (study OR studies)) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti)	**5972509**
#6	('clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti) NOT 'conference abstract':it	**2400633**
#5	('meta analysis'/de OR cochrane:ab OR embase:ab OR psycinfo:ab OR cinahl:ab OR medline:ab OR ((systematic NEAR/1 (review OR overview)):ab,ti) OR ((meta NEAR/1 analy*):ab,ti) OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/de) NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	**497640**
#4	#3 AND (2010-2020)/py NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	**2714**
#3	#1 AND #2 **Nose tumor and endoscopic surgery**	**5189**
#2	'endoscopic surgery'/exp OR 'endoscopic sinus surgery'/exp OR endoscopic:ti,ab,kw OR endonasal:ti,ab,kw OR ess:ti,ab,kw OR fess:ti,ab,kw	**437611**
#1	'nose tumor'/exp OR 'nose cancer'/exp OR 'sinonasal cancer'/exp OR 'sinonasal malignancy'/exp OR 'sinonasal melanoma'/exp OR 'maxilla resection'/exp OR maxillectom*:ti,ab,kw OR (((sinonasal OR nose OR paranasal* OR nasal) NEAR/3 (cancer* OR neoplasm* OR tumor* OR tumour* OR malignan* OR carcinoma)):ti,ab,kw)	**30403**

Ovid/Medline 11 juni 2020

1	exp Nose Neoplasms/ or ((sinonasal or nose or paranasal* or nasal) adj3 (cancer* or neoplasm* or tumor* or tumour* or malignan* or carcinoma)).ti,ab,kf. (19689)
2	exp Endoscopy/ (350535)
3	1 and 2 (1392)
4	(exp Surgical procedures, operative/ not exp endoscopy/) or (open surgery or open resect*).ti,ab,kf. or (open and resect*).ti. or external surgery.ti,ab,kf. or medial maxillectom*.ti,ab,kf. or midfacial degloving.ti,ab,kf. or weber ferguson.ti,ab,kf. or open versus endoscopic.ti,ab,kf. or endoscopic versus open.ti,ab,kf. (2792219)
5	3 and 4 (129)
6	limit 5 to yr="2010 -Current" (69)
7	(meta-analysis/ or meta-analysis as topic/ or (meta adj analy$).tw. or ((systematic* or literature) adj2 review$1).tw. or (systematic adj overview$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (449896)
8	(exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (1991318)
9	Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or consecutive*.tw. or Cross sectional.tw. or Cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/ (Onder exp cohort studies vallen ook longitudinale, prospectieve en retrospectieve studies) (3451052)
10	6 and 7 (7) **SR**
11	6 and 8 (4)
12	6 and 9 (41)
13	11 not 10 (3) **RCT**
14	12 not 11 not 10 (38) **OBS**

Embase 11 juni 2020

No.	Query	Results
#19	#13 AND #18	**0**
#18	20502772	**1**
#17	#15 NOT #14 NOT #13 **Observationeel P en I en C**	**76**
#16	#14 NOT #13 **RCT P en I en C**	**14**
#15	#7 AND #12	**92**
#14	#6 AND #12	**19**
#13	**#5 AND #12 SR P en I en C**	**17**
#12	#4 AND #11	**217**
#11	'open surgery'/exp OR 'open surgery':ti,ab,kw OR 'open resect*':ti,ab,kw OR ('open':ti AND 'resect*':ti) OR 'external surgery':ti,ab,kw OR ((external NEAR/3 approach):ti,ab,kw) OR 'medial maxillectom*':ti,ab,kw OR 'midfacial degloving':ti,ab,kw OR 'weber ferguson':ti,ab,kw OR 'open versus endoscopic':ti,ab,kw OR 'endoscopic versus open':ti,ab,kw	**39034**

#10	#4 AND #7 **Observationeel P en I**	**1168**
#9	#4 AND #6 **RCT P en I**	**510**
#8	#4 AND #5 **SR P en I**	**113**
#7	'major clinical study'/de OR 'clinical study'/de OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR 'prospective study'/de OR 'comparative study'/de OR 'cohort analysis'/de OR ((cohort NEAR/1 (study OR studies)):ab,ti) OR (('case control' NEAR/1 (study OR studies)):ab,ti) OR (('follow up' NEAR/1 (study OR studies)):ab,ti) OR (observational NEAR/1 (study OR studies)) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti)	**5972509**
#6	('clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti) NOT 'conference abstract':it	**2400633**
#5	('meta analysis'/de OR cochrane:ab OR embase:ab OR psycinfo:ab OR cinahl:ab OR medline:ab OR ((systematic NEAR/1 (review OR overview)):ab,ti) OR ((meta NEAR/1 analy*):ab,ti) OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/de) NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	**497640**
#4	#3 AND (2010-2020)/py NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	**2700**
#3	#1 AND #2	**5189**
#2	'endoscopic surgery'/exp OR 'endoscopic sinus surgery'/exp OR endoscopic:ti,ab,kw OR endonasal:ti,ab,kw OR ess:ti,ab,kw OR fess:ti,ab,kw	**437611**
#1	'nose tumor'/exp OR 'nose cancer'/exp OR 'sinonasal cancer'/exp OR 'sinonasal malignancy'/exp OR 'sinonasal melanoma'/exp OR 'maxilla resection'/exp OR maxillectom*:ti,ab,kw OR (((sinonasal OR nose OR paranasal* OR nasal) NEAR/3 (cancer* OR neoplasm* OR tumor* OR tumour* OR malignan* OR carcinoma)):ti,ab,kw)	**30359**

Module 16.2 Behandeling neus- en neusbijholte carcinoom - toevoeging chemotherapie

Uitgangsvraag

Wat is de rol van chemotherapie toegevoegd aan radiotherapie als primaire behandeling bij patiënten met neus(bij)holtecarcinoom?

Inleiding

Het is niet duidelijk wat de beste manier is om chemotherapie in te zetten voor de behandeling van neusholte- en neusbijholtecarcinoom, van alle histologische subtypes. Chemotherapie kan op verschillende manieren worden toegepast: vóór de operatie, na de operatie of als primaire behandeling. Chemotherapie wordt vaak gebruikt in combinatie met radiotherapie.

Search and select

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

What are the effects of chemotherapy added to radiotherapy, compared to radiotherapy alone in patients with nasal cavity and paranasal sinus carcinomas?

P: patients with nasal cavity and paranasal sinus carcinoma;
I: chemotherapy added to radiotherapy;
C: radiotherapy;
O: overall survival, disease-free survival, distant metastasis-free survival, complications/adverse events, quality of life.

Relevant outcome measures

The guideline development group considered overall survival and disease-free survival as a crucial outcome measure for decision making; and distant metastasis-free survival, complications/adverse events and quality of life as important outcome measures for decision making.

The guideline development group defined the outcome measures as follows:

Overall survival	Time from randomisation to death from any cause, with a minimum follow-up of 5 years
Disease-free survival	Time during and after cancer treatment that the patient survives without any signs or symptoms of cancer recurrence, with a minimum follow-up of 5 years
Distant metastasis-free survival	Time to appearance of a distant metastasis, with a minimum follow-up of 5 years
Complications/adverse events	All negative effects related to the treatment (lethal, acute/serious, chronic)
Quality of life (QoL)	Overall QoL or regarding a specific domain, measured with a validated and reliable instrument, such as the SF-36 or EORTC QLQ-C30 or EORTC QLQ-HN35/43.

Clinically relevant difference

The guideline development group defined a minimal clinically relevant difference at a minimum of a median follow-up period of three years) *(in line with "NVMO-commissie ter Beoordeling van Oncologische Middelen (BOM)")* of:

- Overall survival: > 5% difference, or > 3% and HR <0.7.
- Relapse-free survival: HR< 0.7.

And, in case of absence of a clinically relevant difference in overall survival or relapse-free survival:

- Quality of life: A minimal clinically important 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.
- Complications/adverse events: Statistically significant less complications/adverse events.

Search and select (Methods)
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until Jun 17th, 2020. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 298 hits.

Studies were selected based on the following criteria: included patients with nasal cavity and paranasal sinus carcinoma, compared chemotherapy added to radiotherapy with radiotherapy alone, reported at least one of the outcomes of interest, the study design was a systematic review (SR) or randomized controlled trial (RCT), and were written in English language.

Nineteen studies were initially selected based on title and abstract screening. After reading the full text and thorough assessment of the studies, 19 studies were excluded (see the table with reasons for exclusion under the tab Methods) and no studies were included.

Data-synthesis
Results from RCTs and observational studies were described and synthesized (preferably by meta-analysis) separately. A priori, the guideline development group decided that observational studies should be of sufficient quality to allow a useful GRADE assessment and to allow conclusions that can guide the recommendations. The guideline development group used the following criteria for eligible observational studies of sufficient quality:

- Compared at least two interventions.
- Included at least 50 patients.
- Corrected for at least one plausible confounder, for example by matching cases and controls, stratification, or statistical correction by performing a multivariable analysis.

Results
No studies were included in the analysis of the literature.

Summary of literature
Description of studies
Not applicable.

Results
No studies were found that reported on the crucial and important outcome measures.

Certainty of the evidence
No studies were selected that reported on the crucial and important outcome measures, and therefore, GRADE could not be applied, and no conclusions could be drawn on the effect of chemotherapy added to radiotherapy, on overall survival.

Conclusions
Crucial outcome measures

Overall survival

- **GRADE**	No studies were found that could answer the question on the effects of chemotherapy added to radiotherapy on overall survival.

Disease-free survival

- **GRADE**	No studies were found that could answer the question on the effects of chemotherapy added to radiotherapy on disease-free survival.

Important outcome measures

Distant metastasis-free survival, complications/adverse events and quality of life

- **GRADE**	No studies were found that could answer the question on the effects of chemotherapy added to radiotherapy, on important outcome measures.

Overwegingen - van bewijs naar aanbeveling

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

Er zijn geen gerandomiseerde studies of kwalitatief goede vergelijkende observationele studies gevonden die de effecten van chemotherapie toegevoegd aan radiotherapie hebben onderzocht bij neus- en neusbijholtecarcinomen. Er kunnen daarom geen conclusies worden getrokken op basis van de wetenschappelijke literatuur ter onderbouwing van een aanbeveling.

Een narrative review van **Bossi (2015)** beschreef de rol van systemische therapie als onderdeel van een multidisciplinaire aanpak van (locally advanced) neus en neusbijholtecarcinomen. Zij rapporteerden dat, omdat het een zeldzame ziekte is, er alleen beperkte ervaringen zijn met kleine aantallen patiënten, en dat er tot nu toe geen prospectieve, gerandomiseerd trials zijn uitgevoerd (Bossi, 2015). Zij concludeerden dat, net zoals bij andere types hoofd-halstumoren, een multidisciplinaire aanpak voor diagnose en behandeling nodig is voor neus- en neusbijholtecarcinomen. Ondanks dat er geen gerandomiseerde trials zijn, suggereren data van meerdere observationele studies dat systemische therapie mogelijk een bijdrage kan leveren in het verbeteren van overleving, met een mogelijke rol in orgaan-/structuurbehoud. Echter er is meer onderzoek nodig om de exacte rol van chemotherapie en de optimale volgorde ten opzichte van lokale behandelingen vast te stellen.

Er bestaan echter wel kleine series die voor bijvoorbeeld esthesioneuroblastoom een mogelijk voordeel laten zien van de toevoeging van chemotherapie, bijvoorbeeld in geval van inductie bij irresectabele~~inoperabele~~ tumoren (Fiani, 2019). In overleg binnen het team en met de patiënt kan besloten worden tot chemotherapie.

Waarden en voorkeuren van patiënten (en eventueel hun verzorgers)

Een recidief na behandeling van neus- of neusbijholtecarcinoom na chirurgie, meestal gevolgd door radiotherapie, heeft een negatieve impact op de overleving en de kwaliteit van leven van de patiënt. De toevoeging van chemotherapie aan de behandeling zou van grote waarde kunnen zijn als dit de locoregionale controle zou verhogen. Gezien de mogelijke toxiciteit van de chemotherapie moet bij voorkeur de meerwaarde zijn aangetoond.

Er zijn echter geen gerandomiseerde studies of kwalitatief goede vergelijkende observationele studies gevonden die de effecten van chemotherapie toegevoegd aan radiotherapie hebben onderzocht bij neus- en neusbijholtecarcinomen. Er kunnen daarom geen conclusies worden getrokken op basis van de wetenschappelijke literatuur ten aanzien van de belangrijkste doelen van de interventie voor de patiënt en eventueel verzorger(s) en

er is niet bekend welke voor- en nadelen van de interventies de patiënt ziet en welke waarde de patiënt aan deze voor- en nadelen (prioritering van de uitkomstmaten) hecht. De eventuele belasting voor, en de belastbaarheid van de patiënt is onbekend. En er zijn dan ook geen subgroepen waarbij de waarden en voorkeuren van patiënten (en eventueel hun verzorgers) anders zijn.

Kosten (middelenbeslag)
Er zijn geen gerandomiseerde studies of kwalitatief goede vergelijkende observationele studies gevonden die de effecten van chemotherapie toegevoegd aan radiotherapie hebben onderzocht bij neus- en neusbijholtecarcinomen. Er kunnen daarom geen conclusies worden getrokken op basis van de wetenschappelijke literatuur ten aanzien van kosten (middelenbeslag), echter de ervaring bij andere hoofd-halscarcinomen is dat toevoeging van cisplatin geen grote impact heeft op de totale kosten van de behandeling.

Aanvaardbaarheid, haalbaarheid en implementatie
Er zijn geen gerandomiseerde studies of kwalitatief goede vergelijkende observationele studies gevonden die de effecten van chemotherapie toegevoegd aan radiotherapie hebben onderzocht bij neus- en neusbijholtecarcinomen. Er kunnen daarom geen conclusies worden getrokken op basis van de wetenschappelijke literatuur ten aanzien van de aanvaardbaarheid en haalbaarheid van de interventies (bijvoorbeeld procesevaluatie). Echter de ervaring bij andere hoofd-halscarcinomen leert dat chemoradiatie een toxische behandeling is en als zodanig door patiënten wordt ervaren. ~~Echter gezien~~Gezien het ontbreken van evidence is implementatie van chemotherapie als standaardbehandeling in de curatieve setting bij neus- en neusbijholtecarcinomen niet aan de orde.

Aanbeveling
Aanbeveling-1
Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies
~~In kleine studies lijkt er een mogelijk voordeel te zijn van inductiechemotherapie bij een inoperabel proces of voor functiebehoud, met name bij SNUC (ongedifferentieerd carcinoom) en esthesioneuroblastoma. Ondanks gebrek aan evidence kan dit na overleg in het team met patiënt als optie besproken worden.~~
Er zijn geen gerandomiseerde studies of kwalitatief goede vergelijkende observationele studies gevonden die de effecten van chemotherapie toegevoegd aan radiotherapie hebben onderzocht bij neus(bij)holtecarcinomen, daarom kan de werkgroep geen aanbeveling doen welke behandeling de voorkeur verdient.

De werkgroep kan geen aanbeveling geven over de rol van chemotherapie toegevoegd aan radiotherapie als primaire behandeling van neus(bij)holtecarcinoom, omdat onderzoek hiernaar ontbreekt.

Literatuur
Bossi, P., Saba, N. F., Vermorken, J. B., Strojan, P., Pala, L., De Bree, R., ... & Takes, R. P. (2015). The role of systemic therapy in the management of sinonasal cancer: a critical review. Cancer treatment reviews, 41(10), 836-843.
Fiani, B., Quadri, S. A., Cathel, A., Farooqui, M., Ramachandran, A., Siddiqi, I., ... & Siddiqi, J. (2019). Esthesioneuroblastoma: a comprehensive review of diagnosis, management, and current treatment options. World neurosurgery, 126, 194-211.

Bijlagen bij module 16.2

Implementatieplan

Aanbeveling	Tijdspad voor implementatie: < 1 jaar, 1 tot 3 jaar of > 3 jaar	Verwacht effect op kosten	Randvoorwaarden voor implementatie (binnen aangegeven tijdspad)	Mogelijke barrières voor implementatie[1]	Te ondernemen acties voor implementatie[2]	Verantwoordelijken voor acties[3]	Overige opmerkingen
Behandeling neus- en neusbijholtecarcinoom - toevoeging chemotherapie~~Niet van toepassing~~	-	-	-	-	-	-	Niet van toepassing. De werkgroep kon geen aanbeveling doen over de rol van chemotherapie toegevoegd aan radiotherapie als primaire behandeling, omdat onderzoek hiernaar ontbreekt.

[1] Barrières kunnen zich bevinden op het niveau van de professional, op het niveau van de organisatie (het ziekenhuis) of op het niveau van het systeem (buiten het ziekenhuis). Denk bijvoorbeeld aan onenigheid in het land met betrekking tot de aanbeveling, onvoldoende motivatie of kennis bij de specialist, onvoldoende faciliteiten of personeel, nodige concentratie van zorg, kosten, slechte samenwerking tussen disciplines, nodige taakherschikking, et cetera.
[2] Denk aan acties die noodzakelijk zijn voor implementatie, maar ook acties die mogelijk zijn om de implementatie te bevorderen. Denk bijvoorbeeld aan controleren aanbeveling tijdens kwaliteitsvisitatie, publicatie van de richtlijn, ontwikkelen van implementatietools, informeren van ziekenhuisbestuurders, regelen van goede vergoeding voor een bepaald type behandeling, maken van samenwerkingsafspraken.
[3] Wie de verantwoordelijkheden draagt voor implementatie van de aanbevelingen, zal tevens afhankelijk zijn van het niveau waarop zich barrières bevinden. Barrières op het niveau van de professional zullen vaak opgelost moeten worden door de beroepsvereniging. Barrières op het niveau van de organisatie zullen vaak onder verantwoordelijkheid van de ziekenhuisbestuurders vallen. Bij het oplossen van barrières op het niveau van het systeem zijn ook andere partijen, zoals de NZA en zorgverzekeraars, van belang.

Evidence tables

Not applicable.

Table of excluded studies

Author and year	Reason for exclusion
Mehta, 2020	Narrative review
Khoury, 2019	Does not match PICO (no comparison of intervention and control)
Wang, 2019	Does not match PICO (patients)
Fiani, 2019	Background article. Does not match PICO (not comparing intervention and control)
Alotaibi, 2019	Does not match PICO (no comparison of intervention and control)
Homma, 2019	Dose-finding trial. Does not match PICO (not comparing intervention and control)
Marinelli, 2018	Does not match PICO (wrong comparison)

Morand, 2017	Does not match PICO (wrong comparison)
van der Laan, 2016	Does not match PICO (wrong comparison)
Rivero, 2016	Does not match PICO (wrong comparison)
Hoeben, 2016	Narrative review
De Bonnecaze, 2016	Does not match PICO (not comparing intervention and control)
Bossi, 2015	Narrative review
Mourad, 2013	Does not match PICO (no comparison of intervention and control)
Xu, 2013	Does not match PICO (no comparison of intervention and control)
Kang, 2012	Does not match PICO (wrong comparison)
Reiersen, 2012	Does not match PICO (wrong comparison)
Zanation, 2010	Narrative review
Khademi, 2009	Does not match PICO (wrong comparison)

Literature search strategy

Algemene informatie

Richtlijn: Hoofd- Haltstumoren	
Uitgangsvraag: 16.2 Neus(bijholte)carcinoom chemotherapie radiotherapie	
Database(s): Ovid/Medline, Embase	Datum: 17-6-2020
Periode: 2005-2020	Talen: niet van toepassing
Literatuurspecialist: Ingeborg van Dusseldorp	

Zoekopbrengst

	EMBASE	OVID/MEDLINE	Som	Ontdubbeld
SRs	46	118	164	146
RCTs	80	91	171	152

Zoekverantwoording

Ovid/Medline

1	exp Nose Neoplasms/ or (maxilla resection or maxillectom*).ti,ab,kf. or ((sinonasal or nose or paranasal* or nasal) adj4 (cancer* or neoplasm* or malignan* or carcinoma or tumor* or tumour*)).ti,ab,kf. (21412)
2	exp Antineoplastic Agents/ or exp Chemotherapy, Adjuvant/ or exp Taxoids/ or exp Anthracyclines/ or exp Cyclophosphamide/ or exp Immunosuppressive Agents/ or (chemotherapeutics:ti,ab or chemotherapy or anti cancer drug or anti neoplastic agent or anticancer agent or anticancer drug or anticancerogen or anticarcinogen or anticarcinogenic agents or antineoplastics or antitumor agent or antitumor drug or antitumour agent or antitumour drug or cancer inhibitor or carcinostatic drug or tumor inhibitor or tumour inhibitor or taxo* or anthracyclin or cyclophosphamid*).ti,ab,kf. (1517777)
3	exp Radiotherapy/ or (bioradiant therapy or bucky ray or bucky therap* or radio therap* or radio treatment or radiohypophysectomy or radiotherap* or roentgen therap* or roentgen treatment or rontgen therap* or therapeutic radiology or x radiotherapy or x ray therap* or x ray treatment or x-ray therapy or irradiati* or radiati*).ti,ab,kf. (696044)
4	exp Chemoradiotherapy/ or exp Combined Modality Therapy/ or (systemic therap* or systemic treatment or chemoradiati* or chemoradiotherap* or radiochemotherap* or targeted therap* or combined modality therap* or multimodal cancer therap* or multimodality cancer therap* or multiple modality cancer therap* or multiple modality treatment*).ti,ab,kf. (337201)
5	(2 and 3) or 4 (418695)
6	1 and 5 (2412)
7	limit 6 to yr="2005 -Current" (1407)
8	(meta-analysis/ or meta-analysis as topic/ or (meta adj analy$).tw. or ((systematic* or literature) adj2 review$1).tw. or (systematic adj overview$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (451257)
9	(exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic*

	adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (1994323)
10	Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or consecutive*.tw. or Cross sectional.tw. or Cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/ (Onder exp cohort studies vallen ook longitudinale, prospectieve en retrospectieve studies) (3455953)
11	7 and 8 (118) **SR**
12	7 and 9 (99)
13	7 and 10 (621)
14	12 not 11 (91) **RCT**
15	13 not 12 not 11 (537) **OBS**

Embase

No.	Query	Results
#18	'meta analysis (topic)'/exp	42094
#17	#1 AND #15	0
#16	#9 AND #15	1
#15	role AND systemic AND therapy AND in AND the AND management AND of AND sinona sal AND cancer AND bossi AND 2015	1
#14	#12 NOT #11 NOT #10	512
#13	#11 NOT #10	80
#12	#3 AND #9	573
#11	#2 AND #9	88
#10	#1 AND #9	48
#9	#8 AND (2005-2020)/py NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	1482
#8	#4 AND #7	2549
#7	#5 OR #6	512337
#6	'systemic therapy'/exp OR 'systemic therapy':ti,ab,kw OR 'systemic treatment':ti,ab,kw OR 'chemoradiotherapy'/exp OR 'chemoradiati*':ti,ab,kw OR 'chemoradiotherap*':ti,ab,kw OR 'radiochemotherap*':ti,ab,kw OR 'targeted therapy'/exp OR 'targeted therap*':ti,ab,kw OR 'multimodality cancer therapy'/exp OR 'combined modality therap*':ti,ab,kw OR 'multimodal cancer therap*':ti,ab,kw OR 'multimodality cancer therap*':ti,ab,kw OR 'multiple modality cancer therap*':ti,ab,kw OR 'multiple modality treatment*':ti,ab,kw	260564
#5	('chemotherapy'/exp OR 'antineoplastic agent'/exp OR 'taxoid'/exp OR 'anthracycline'/exp OR 'cyclophosphamide'/exp OR 'immunosuppressive agent'/exp OR 'chemotherapeutics':ti,ab OR 'chemotherapy':ti,ab OR 'anti cancer drug':ti,ab,kw OR 'anti neoplastic agent':ti,ab,kw OR 'anticancer agent':ti,ab,kw OR 'anticancer drug':ti,ab,kw OR 'anticancerogen':ti,ab,kw OR 'anticarcinogen':ti,ab,kw OR 'anticarcinogenic agents':ti,ab,kw OR 'antineoplastics':ti,ab,kw OR 'antitumor	349062

	agent':ti,ab,kw OR 'antitumor drug':ti,ab,kw OR 'antitumour agent':ti,ab,kw OR 'antitumour drug':ti,ab,kw OR 'cancer inhibitor':ti,ab,kw OR 'carcinostatic drug':ti,ab,kw OR 'tumor inhibitor':ti,ab,kw OR 'tumour inhibitor':ti,ab,kw OR 'taxo*':ti,ab,kw OR 'anthracyclin':ti,ab,kw OR cyclophosphamid*:ti,ab,kw) AND ('radiotherapy'/exp OR 'bioradiant therapy':ti,ab,kw OR 'bucky ray':ti,ab,kw OR 'bucky therapy':ti,ab,kw OR 'radio therapy':ti,ab,kw OR 'radio treatment':ti,ab,kw OR 'radiohypophysectomy':ti,ab,kw OR 'radiotherapy':ti,ab,kw OR 'roentgen therapy':ti,ab,kw OR 'roentgen treatment':ti,ab,kw OR 'rontgen therapy':ti,ab,kw OR 'therapeutic radiology':ti,ab,kw OR 'x radiotherapy':ti,ab,kw OR 'x ray therapy':ti,ab,kw OR 'x ray treatment':ti,ab,kw OR 'x-ray therapy':ti,ab,kw OR irradiati*:ti,ab,kw OR radiati*:ti,ab,kw)	
#4	'nose cancer'/exp OR 'sinonasal cancer'/exp OR 'sinonasal malignancy'/exp OR 'sinonasal melanoma'/exp OR 'maxilla resection'/exp OR maxillectom*:ti,ab,kw OR (((sinonasal OR nose OR paranasal* OR nasal) NEAR/4 (cancer* OR neoplasm* OR malignan* OR carcinoma OR tumor* OR tumour*)):ti,ab,kw)	15836
#3	'major clinical study'/de OR 'clinical study'/de OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR 'prospective study'/de OR 'comparative study'/de OR 'cohort analysis'/de OR ((cohort NEAR/1 (study OR studies)):ab,ti) OR (('case control' NEAR/1 (study OR studies)):ab,ti) OR (('follow up' NEAR/1 (study OR studies)):ab,ti) OR (observational NEAR/1 (study OR studies)) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti)	5976979
#2	('clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti) NOT 'conference abstract':it	2400633
#1	('meta analysis'/de OR 'meta analysis (topic)'/exp OR cochrane:ab OR embase:ab OR psycinfo:ab OR cinahl:ab OR medline:ab OR ((systematic NEAR/1 (review OR overview)):ab,ti) OR ((meta NEAR/1 analy*):ab,ti) OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/de) NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	523227

Module 17.2 Behandeling nasofarynxcarcinoom - inductie chemotherapie

Uitgangsvraag
Wat is de plaats van inductie chemotherapie bij de behandeling van het nasofarynxcarcinoom?

Inleiding
De toevoeging van chemotherapie als inductie of adjuvant regime aan chemoradiatie therapie is in verschillende studies onderzocht, met wisselende resultaten. De toxiciteit van systemische therapie na chemoradiatie blijft een actueel onderwerp.

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

What are the effects of induction chemotherapy or induction chemotherapy + concurrent chemoradiation therapy compared with concurrent chemoradiation therapy alone in patients with T3/T4 nasopharynx carcinomas?

P: patients with nasopharynx carcinoma (T-stage 3-4);
I: induction chemotherapy or induction therapy + concurrent chemoradiotherapy;
C: concurrent chemoradiotherapy;
O: overall survival, disease-free survival, distant metastasis-free survival, complications/adverse events, quality of life.

Relevant outcome measures
The guideline development group considered overall survival, disease-free survival and toxicity as a critical outcome measure for decision making; and distant metastasis-free survival, complications/adverse events and quality of life as important outcome measures for decision making.

The guideline development group defined the outcome measures as follows:

Overall survival	Time from randomisation to death from any cause, with a minimum follow-up of 5 years
Disease-free survival	Time during and after cancer treatment that the patient survives without any signs or symptoms of cancer recurrence, with a minimum follow-up of 5 years
Distant metastasis-free survival	Time to appearance of a distant metastasis, with a minimum follow-up of 5 years
Complications/adverse events/toxicity	All negative effects related to the treatment (lethal, acute/serious, chronic)
Quality of life (QoL)	Overall QoL or regarding a specific domain, measured with a validated and reliable instrument, such as the SF-36 or EORTC QLQ-C30.

Clinically relevant difference
The guideline development group defined a minimal clinically relevant difference at a minimum of a median follow-up period of three years) *(in line with "NVMO-commissie ter Beoordeling van Oncologische Middelen (BOM)")* of:

- Overall survival: > 5% difference, or > 3% and HR< 0.7.
- Relapse-free/disease-free survival: HR <0.7.

And, in case of absence of a clinically relevant difference in overall survival or relapse-free survival:

- Quality of life: A minimal clinically important 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.
- Complications/adverse events: Statistically significant less complications/adverse events.

Data-analysis
A meta-analysis was performed to pool the results of the included studies. We used a random-effect model.

Search and select (Methods)
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until June 17th, 2020. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 189 hits. Studies were selected based on the following criteria:
- included patients with nasopharynx carcinoma;
- compared induction chemotherapy or induction therapy + concurrent chemoradiotherapy with concurrent chemoradiotherapy alone;
- reported at least one of the outcomes of interest;
- the study design is a systematic review (SR) (preferably of randomized controlled trials; RCTs), or RCT;
- written in English language.

Based on title and abstract screening, 44 studies were initially selected. After reading the full text and thorough assessment of the studies, 43 studies were excluded (see table with reasons for exclusion under the tab Methods), and one study was included.

Results
One SR was 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
We included the SR of **Wang (2020)** in the analyses. They searched the scientific literature up to September 2019. Inclusion criteria of this systematic review were: prospective studies in previously untreated patients with nasopharynx carcinoma (NPC); studies were registered clinical trials and registration numbers were provided; study design was randomized controlled clinical studies; the experimental group was treated with induction chemotherapy (IC) combined with concurrent chemoradiation therapy (CCRT), and the control group was treated with CCRT alone; and studies were published in English language. Neoadjuvant chemotherapy described in the articles was deemed as induction chemotherapy. Exclusion criteria were: IC or CCRT was combined with target therapy, or conference abstracts.

In total, nine papers, describing the results of seven RCTs were included, with 2311 patients, of whom 1160 patients were randomised to IC+CCRT and 1151 patients were randomised to CCRT alone. Type and dosage of IC, chemotherapy (CT) and radiotherapy (RT) are described in the evidence table.

Four studies reported results after three-year follow-up (Fountzilas, 2012; Frikha, 2018; Tan, 2015; Zhang, 2019), two studies reported results on both three- and five-years follow-up, in two separate articles (Cao, 2017 & Yang, 2019; Sun, 2016 & Li, 2019), and one study reported results after five-year follow-up (Hong, 2018). Three studies were done in China (Cao, 2017 & Yang, 2019; Sun, 2016 & Li, 2019; Zhang, 2019), and the rest in Taiwan (Hong, 2018), Singapore (Tan, 2015), France/Tunisia (Frikha, 2018), and Europe (country not specified) (Fountzilas, 2012). Study characteristics and distributions of important patient characteristics (WHO types and clinical stage) is reported per study in Table 17.1.

Wang (2020) performed a meta-analysis using a fixed-effect model. All enrolled trials were identified as high quality (a score of ≥3), using the Jadad scoring scale. This SR was considered to have high quality, according to the AMSTAR criteria.

Table 17.1 Overview of study characteristics included in the SR of Wang (2020)

Author (year)	Country	Patient population	Scheme	Pathology	WHO	Intervention	Control	Clinical stage	Intervention	Control
Fountzilas (2011)	Europe	Biopsy-proven, previously untreated WHO type I, II or III NPC; stage IIB–IVB (AJCC 2002)	Cis/VP16/Taxol		I	7 (10%)	5 (7%)	IIB	14 (19%)	15 (22%)
					II	15 (21%)	15 (22%)	III	27 (38%)	27 (39%)
					III	50 (69%)	49 (71%)	IVA	19 (26%)	10 (14%)
								IVB	12 (17%)	17 (25%)
Tan (2015)	Singapore	Newly diagnosed with World Health Organization type 2 or 3 NPC, Union for International Cancer Control (1997) stage T3-4NxM0 or TxN2-3M0	Taxane versus non-Taxane		II	6 (7%)	6 (7%)	III	50 (58%)	53 (62%)
					III	80 (93%)	80 (93%)	IVA	16 (19%)	11 (13%)
								IVB	20 (23%)	22 (26%)
Sun/Li (2016/ 2019)	China	Patients with previously untreated, non-distant metastatic, newly histologically confirmed non-keratinising stage III–IVB nasopharyngeal carcinoma (except T3–4N0; 7th UICC and AJCC)). Age <59 years.	TPF	non-keratinising	Not reported			III	129 (54%)	133 (56%)
								IVA	73 (30%)	80 (33%)
								IVB	39 (16%)	26 (11%)
Cao/Yang (2017/ 2019)	China	Previously untreated, biopsy-proven WHO types II-III NPC; Stage III-IVB disease, excluding T3N0-1 (UICC/AJCC 6th edition). Age <60 years	Cis/5-FU		Not reported			II	1 (<1%)	0 (0%)
								III	117 (49%)	133 (56%)
								IV	120 (50%)	105 (44%)
Frikha (2018)	France/ Tunisia	Histological WHO type 2 or 3, stage T2b, T3, T4 and/or N1-N3, M0	TPF	WHO II-III	II	4 (10%)	7 (17%)	Not reported		
					III	36 (90%)	34 (83%)			
Hong (2018)	Taiwan	Histologically proved stage IVA or IVB NPC (fifth edition of the AJCC/UICC staging system, 1997). Ages <70 years.	MEPFL		I	1 (<1%)	0 (0%)	IVA-T4N0–2	111 (46%)	113 (47%)
					IIa	65 (27%)	71 (30%)	IVB-N3a	57 (24%)	56 (23%)
					IIb	173 (72%)	169 (70%)	IVB-N3b	71 (30%	71 (30%)
Zhang (2019)	China	Histologic confirmation of nonkeratinizing nasopharyngeal carcinoma; no previous treatment for cancer; nondistant metastatic, newly diagnosed stage III to IVB (AJCC–UICC 7th edition). Age <65 years.	Cis/Gem	non-keratinising	Not reported			III	111 (46%)	120 (50%)
								IVA	104 (43%)	94 (40%)
								IVB	27 (11%)	24 (10%)

Results

Crucial outcome measures

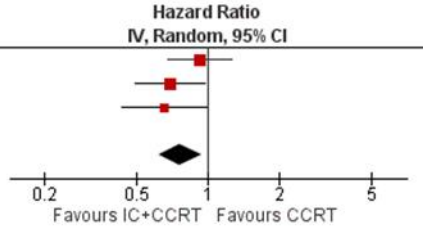
Overall survival

Three studies addressed this outcome at **five-year** follow-up (Hong, 2018; Li, 2019; Yang, 2019). In total, 1435 patients were analysed, with 718 patients in the IC+CCRT arm and 717 in the CCRT arm. In the IC+CCRT arm 588/718 (82%) patients were alive at 5 years follow-up, and in the CCRT arm 532/717 (74%). The hazard ratio was 0.76 (95% CI 0.61 to 0.95) in favour of IC+CCRT, using a random-effect model (Figure 17.2). The risk difference was 8% (95% CI: 4 to 12), which is clinically relevant.

Figure 17.2 Forest plot for 5-year overall survival of IC+CCRT versus CCRT alone

Study or Subgroup	log[Hazard Ratio]	SE	IC+CCRT Total	CCRT Total	Weight	Hazard Ratio IV, Random, 95% CI	Year
Hong 2018	-0.0801	0.1627	239	240	39.7%	0.92 [0.67, 1.27]	2018
Yang 2019	-0.3711	0.1746	238	238	35.2%	0.69 [0.49, 0.97]	2019
Li 2019	-0.4308	0.2108	241	239	25.2%	0.65 [0.43, 0.98]	2019
Total (95% CI)			**718**	**717**	**100.0%**	**0.76 [0.61, 0.95]**	

Heterogeneity: Tau² = 0.00; Chi² = 2.28, df = 2 (P = 0.32); I² = 12%
Test for overall effect: Z = 2.44 (P = 0.01)

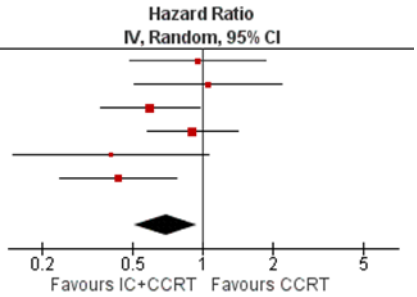


Six studies addressed this outcome at **three-year follow-up** (Cao, 2017; Fountzilas, 2012; Frikha, 2018; Sun, 2016; Tan, 2015; Zhang, 2019). In total, 1832 patients were analysed, with 921 patients in the IC+CCRT arm and 911 patients in the CCRT arm. The hazard ratio was 0.69 (95% CI 0.51 to 0.94) in favour of IC+CCRT (Figure 17.3).

Figure 17.3 Forest plot for 3-year overall survival of IC+CCRT versus CCRT alone

Study or Subgroup	log[Hazard Ratio]	SE	IC+CCRT Total	CCRT Total	Weight	Hazard Ratio IV, Random, 95% CI	Year
Fountzilas 2012	-0.0513	0.3483	72	69	14.5%	0.95 [0.48, 1.88]	2012
Tan 2015	0.0488	0.3751	86	86	13.0%	1.05 [0.50, 2.19]	2015
Sun 2016	-0.5276	0.2521	241	239	22.0%	0.59 [0.36, 0.97]	2016
Cao 2017	-0.1076	0.231	238	238	24.2%	0.90 [0.57, 1.41]	2017
Frikha 2018	-0.9163	0.5004	42	41	8.2%	0.40 [0.15, 1.07]	2018
Zhang 2019	-0.844	0.2975	242	238	18.0%	0.43 [0.24, 0.77]	2019
Total (95% CI)			**921**	**911**	**100.0%**	**0.69 [0.51, 0.94]**	

Heterogeneity: Tau² = 0.05; Chi² = 7.49, df = 5 (P = 0.19); I² = 33%
Test for overall effect: Z = 2.36 (P = 0.02)



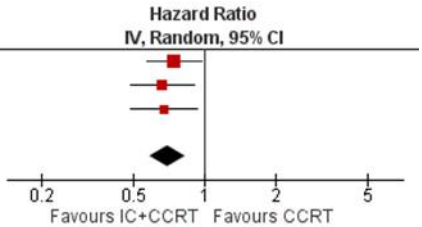
Disease-free survival

Three studies addressed this outcome at **five-year follow-up** (Hong, 2018; Li, 2019; Yang, 2019). In total, 1435 patients were analysed, with 718 patients in the IC+CCRT arm and 717 in the CCRT arm. In the IC+CCRT arm 507/718 (71%) patients were disease-free at 5 years follow-up, and in the CCRT arm 429/717 (60%). The hazard ratio was 0.70 (95% CI 0.51 to 0.94) (Figure 17.4). The risk difference was 11% (95% CI: 6 to 16), which is clinically relevant.

Figure 17.4 Forest plot for 5-year disease-free survival of IC+CCRT versusCCRT alone

Study or Subgroup	log[Hazard Ratio]	SE	IC+CCRT Total	CCRT Total	Weight	Hazard Ratio IV, Random, 95% CI	Year
Hong 2018	-0.3025	0.137	239	240	42.4%	0.74 [0.56, 0.97]	2018
Yang 2019	-0.4155	0.1625	238	238	30.1%	0.66 [0.48, 0.91]	2019
Li 2019	-0.4005	0.1702	241	239	27.5%	0.67 [0.48, 0.94]	2019
Total (95% CI)			**718**	**717**	**100.0%**	**0.70 [0.58, 0.83]**	

Heterogeneity: Tau² = 0.00; Chi² = 0.35, df = 2 (P = 0.84); I² = 0%
Test for overall effect: Z = 4.07 (P < 0.0001)

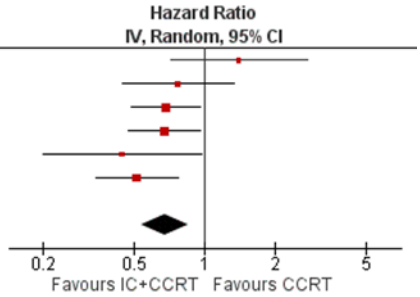


Six studies addressed this outcome at **three-year** follow-up (Cao, 2017; Fountzilas, 2012; Frikha, 2018; Sun, 2016; Tan, 2015; Zhang, 2019). In total, 1832 patients were analysed, with 921 patients in the IC+CCRT arm and 911 patients in the CCRT arm. The hazard ratio was 0.67 (95% CI 0.53 to 0.86) (Figure 17.5).

Figure 17.5 Forest plot for 3-year disease-free survival of IC+CCRT versus CCRT alone

Study or Subgroup	log[Hazard Ratio]	SE	IC+CCRT Total	CCRT Total	Weight	Hazard Ratio IV, Random, 95% CI	Year
Fountzilas 2012	0.3365	0.3464	72	69	10.0%	1.40 [0.71, 2.76]	2012
Tan 2015	-0.2614	0.2855	86	86	13.4%	0.77 [0.44, 1.35]	2015
Sun 2016	-0.3857	0.1777	241	239	24.4%	0.68 [0.48, 0.96]	2016
Cao 2017	-0.4005	0.1809	238	238	23.9%	0.67 [0.47, 0.96]	2017
Frikha 2018	-0.821	0.4023	42	41	7.8%	0.44 [0.20, 0.97]	2018
Zhang 2019	-0.6733	0.2069	242	238	20.6%	0.51 [0.34, 0.77]	2019
Total (95% CI)			**921**	**911**	**100.0%**	**0.67 [0.53, 0.86]**	

Heterogeneity: Tau² = 0.03; Chi² = 7.60, df = 5 (P = 0.18); I² = 34%
Test for overall effect: Z = 3.23 (P = 0.001)



<u>Important outcome measures</u>

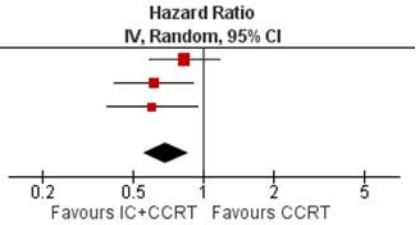
Distant metastasis-free survival

Three studies addressed this outcome at **five-year** follow-up (Hong, 2018; Li, 2019; Yang, 2019). In total, 1435 patients were analysed, with 718 patients in the IC+CCRT arm and 717 in the CCRT arm. The hazard ratio was 0.69 (95% CI 0.55 to 0.87) (Figure 17.6).

Figure 17.6 Forest plot for 5-year distant metastasis-free survival of IC+CCRT versus CCRT alone

Study or Subgroup	log[Hazard Ratio]	SE	IC+CCRT Total	CCRT Total	Weight	Hazard Ratio IV, Random, 95% CI	Year
Hong 2018	-0.1924	0.1798	239	240	42.0%	0.82 [0.58, 1.17]	2018
Yang 2019	-0.4943	0.2027	238	238	33.0%	0.61 [0.41, 0.91]	2019
Li 2019	-0.5108	0.233	241	239	25.0%	0.60 [0.38, 0.95]	2019
Total (95% CI)			**718**	**717**	**100.0%**	**0.69 [0.55, 0.87]**	

Heterogeneity: Tau² = 0.00; Chi² = 1.72, df = 2 (P = 0.42); I² = 0%
Test for overall effect: Z = 3.19 (P = 0.001)

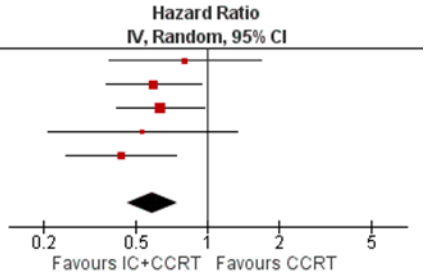


Five studies addressed this outcome at **three-year** follow-up (Cao, 2017; Frikha, 2018; Sun, 2016; Tan, 2015; Zhang, 2019). In total, 1691 patients were analysed, with 849 patients in the IC+CCRT arm and 842 patients in the CCRT arm. The hazard ratio was 0.58 (95% CI 0.45 to 0.74) (Figure 17.7).

Figure 17.7 Forest plot for 3-year distant metastasis-free survival of IC+CCRT versus CCRT alone

Study or Subgroup	log[Hazard Ratio]	SE	IC+CCRT Total	CCRT Total	Weight	Hazard Ratio IV, Random, 95% CI	Year
Tan 2015	-0.2231	0.3798	86	86	11.0%	0.80 [0.38, 1.68]	2015
Sun 2016	-0.5276	0.2381	241	239	28.0%	0.59 [0.37, 0.94]	2016
Cao 2017	-0.462	0.2191	238	238	33.1%	0.63 [0.41, 0.97]	2017
Frikha 2018	-0.6349	0.4723	42	41	7.1%	0.53 [0.21, 1.34]	2018
Zhang 2019	-0.844	0.2767	242	238	20.7%	0.43 [0.25, 0.74]	2019
Total (95% CI)			**849**	**842**	**100.0%**	**0.58 [0.45, 0.74]**	

Heterogeneity: Tau² = 0.00; Chi² = 2.07, df = 4 (P = 0.72); I² = 0%
Test for overall effect: Z = 4.33 (P < 0.0001)



Complications/adverse events

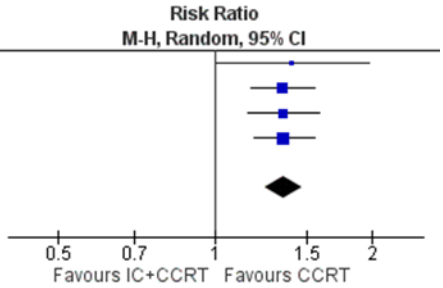
Four studies addressed this outcome (Cao, 2017; Syn, 2016; Tan, 2015; Zhang, 2019). In total, 1608 patients were analysed, with 807 patients in the IC+CCRT arm and 801 in the CCRT arm.

In the IC+CCRT arm 561/807 (70%) reported grade ≥ 3 adverse events, compared to 411/801 (51%) in the CCRT arm (risk ratio (RR): 1.35; 95% CI 1.25 to 1.47), in favour of CCRT (Figure 17.8).

Figure 17.8 Forest plot for grade ≥ 3 adverse events of IC+CCRT versus CCRT alone

Study or Subgroup	IC+CCRT Events	IC+CCRT Total	CCRT Events	CCRT Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Tan 2015	45	86	32	86	5.5%	1.41 [1.00, 1.98]	2015
Sun 2016	175	241	129	239	32.6%	1.35 [1.17, 1.55]	2016
Cao 2017	158	238	117	238	25.9%	1.35 [1.15, 1.58]	2017
Zhang 2019	183	242	133	238	36.0%	1.35 [1.18, 1.55]	2019
Total (95% CI)		**807**		**801**	**100.0%**	**1.35 [1.25, 1.47]**	
Total events	561		411				

Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 3 (P = 1.00); I² = 0%
Test for overall effect: Z = 7.39 (P < 0.00001)



During overall treatment: In hematological toxicities, there were no significant differences in leukopenia (risk ratio (RR): 1.77, 95% CI: 0.98 to 3.19, p = 0.06) and anemia (RR: 2.97, 95% CI: 0.20 to 44.40, p = 0.43) between IC + CCRT group and CCRT group. However, the IC + CCRT group showed significantly higher risks of neutropenia (RR: 3.93, 95% CI: 1.78 to 8.68, p = 0.0007) and thrombocytopenia (RR: 6.55, 95% CI: 2.58 to 16.63, p < 0.0001) than the CCRT group.

In non-hematological toxicities, patients treated with IC + CCRT showed significantly higher risks of nausea (RR: 1.43, 95% CI: 1.09 to 1.87, p = 0.01), vomiting (RR: 1.40, 95% CI: 1.08 to 1.82, p = 0.01) and hepatotoxicity (RR: 5.37, 95% CI: 1.40 to 20.58, p = 0.01) rather than mucositis (RR: 1.04, 95% CI: 0.87 to 1.24, p = 0.68) and dermatitis (RR: 0.73, 95% CI: 0.37 to 1.44, p = 0.37) in comparison with patients treated with CCRT.

Quality of life (QoL)
One study addressed this outcome (Tan, 2015), with 86 patients in the IC+CCRT arm and 86 in the CCRT arm. They reported that the mean global QOL scores of the EORTC QLQ-30 module were balanced between the 2 arms. The IC+CCRT arm had significantly poorer symptom scores for dyspnea (24.3 versus 15.3; P=0.014) and diarrhea (15.2 versus 9.3; P=0.018) during CCRT compared with the CCRT alone arm. However, these differences were no longer significant during follow-up. There were no statistically significant differences in any of the functional scales between the two arms. For the EORTC H&N35 module, the control arm had significantly poorer scores for pain, swallowing, and use of pain killers during CCRT, and for social contact at the third month of follow-up, compared with the GCP arm.

<u>Certainty of the evidence</u>
<u>*Crucial outcome measures*</u>
Overall survival (5 year)
The certainty of the evidence regarding overall survival started high, as the evidence originated from an RCT. The level of evidence was downgraded by one level for imprecision (the pooled estimate crossed the line of clinically relevant difference), and indirectness (study population may not be comparable to Dutch population of nasopharynx carcinoma patients). We did not downgrade for risk of bias (lack of blinding), because overall survival was considered as a 'hard' outcome measure. Level of evidence was graded as low.

Disease-free survival (5 year)
The certainty of the evidence regarding disease-free survival started high, as the evidence originated from an RCT. The level of evidence was downgraded by one level for imprecision (the pooled estimate crossed the line of clinically relevant difference), and indirectness (study population may not be comparable to Dutch population of nasopharynx carcinoma patients). We did not downgrade for risk of bias (lack of blinding), because disease-free survival was considered as a 'hard' outcome measure. Level of evidence was graded as low.

Important outcome measures
Distant metastasis-free survival (5 year)
The certainty of the evidence regarding distant metastasis-free survival started high, as the evidence originated from an RCT. The level of evidence was downgraded by one level for imprecision (the pooled estimate exceeded clinically relevant difference), and indirectness (study population may not be comparable to Dutch population of nasopharynx carcinoma patients). We did not downgrade for risk of bias (lack of blinding), because distant metastasis-free survival was considered as a 'hard' outcome measure. Level of evidence was graded as low.

Complications/adverse events
The certainty of the evidence regarding complications/adverse events started high, as the evidence originated from an RCT. The level of evidence was downgraded by one level for risk of bias (participants, care providers and outcome assessors were not blinded) and one level for imprecision (small number of included patients). Level of evidence was graded as low.

Quality of life
The certainty of the evidence regarding quality of life started high, as the evidence originated from an RCT, and was downgraded by three levels because of risk of bias (one level for study limitations: participants, care providers and outcome assessors were not blinded); very serious imprecision (two levels because data originated from only one study with a very small number of included patients); publication bias. Level of evidence was graded as very low.

Conclusions
Crucial outcome measures
Overall survival (5 year)

Low GRADE	Induction chemotherapy combined with concurrent chemoradiation therapy may result in a slight increase of overall survival in WHO subtype 2/3, stage III/ IV, excluding T3N0 nasopharyngeal cancer patients at 5-year follow-up, when compared to concurrent chemoradiation therapy alone. *Sources: (Hong, 2018; Li, 2019; Yang, 2019)*

Disease-free survival (5 year)

Low GRADE	Induction chemotherapy combined with concurrent chemoradiation therapy may result in an increase of disease-free survival in WHO subtype 2/3, stage III/ IV, excluding T3N0 nasopharyngeal cancer patients at 5-year follow-up, when compared to concurrent chemoradiation therapy alone. *Sources: (Hong, 2018; Li, 2019; Yang, 2019)*

Important outcome measures
Distant metastasis-free survival (5 year)

Low GRADE	Induction chemotherapy combined with concurrent chemoradiation therapy may result in an increase of distant metastasis-free survival in WHO subtype 2/3, stage III/ IV, excluding T3N0 nasopharyngeal cancer patients at 5-year follow-up, when compared to concurrent chemoradiation therapy alone. *Sources: (Hong, 2018; Li, 2019; Yang, 2019)*

Complications/adverse events

Low GRADE	Induction chemotherapy combined with concurrent chemoradiation therapy may increase grade ≥ 3 adverse events in advanced nasopharyngeal cancer patients when compared to concurrent chemoradiation therapy alone. *Sources: (Cao, 2017; Sun, 2016; Tan, 2015; Zhang, 2019)*

Quality of life

Very low GRADE	We are unsure about the effect of induction chemotherapy combined with concurrent chemoradiation therapy on quality of life in advanced nasopharyngeal cancer patients when compared to chemoradiation therapy alone. *Sources: (Tan, 2015)*

Overwegingen - van bewijs naar aanbeveling

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

De combinatie van inductie chemotherapie met concomitante chemoradiatie therapie lijkt de algehele overleving, ziektevrije overleving en afstandsmetastase vrije overleving van patiënten met stadium III/IV, nasofarynxcarcinoom te verbeteren ten opzichte van concomitante chemoradiatie therapie alleen, maar het leidt mogelijk ook tot meer complicaties en bijwerkingen. De overall bewijskracht van de cruciale uitkomstmaten is laag.

Echter we dienen te beseffen dat het overgrote aantal patiënten komt uit studies uitgevoerd in Aziatische landen waarbij nasofarynxcarcinoom ten dele een andere etiologie heeft en het doorgaans een ongedifferentieerd niet-verhoornend carcinoom betreft. Zo worden in het Westen meer tumoren gezien die niet ongedifferentieerd zijn; het betreft vaker een plaveiselcelcarcinomen (PCC), die waarschijnlijk een correlatie met roken hebben.

Bij analyse van de individuele studies blijkt dat bij alle positieve studies (Cao, 2017; Hong, 2018; Li, 2019; Sun, 2016; Yang, 2019) alleen WHO subtype 2/3 patiënten zijn geselecteerd. Er is dus geen evidence dat inductie chemotherapie bij WHO subtype 1 leidt tot betere overleving, het type dat in het Westen bij 1 op 3 patiënten wordt gezien. Voor de patiënten met een WHO subtype 2/3 werden niet alle stadium III/IV patiënten geselecteerd in de positieve studies. De studie van Hong (2018) betrof alleen stadium IV. Stadium T3N0-N1 werden uitgesloten in de studies van Sun (2016), Cao (2017) en Yang (2019); Stadium T3-T4 N0 in de studie van Li (2019). Op basis van deze analyse luidt de conclusie dat voor stadium IV WHO subtype 2/3 er evidence is dat inductie chemotherapie leidt tot betere algehele overleving, ziektevrije overleving en afstandsmetastase vrije overleving. Hiervoor is voor stadium III T3N0 geen evidence. Patiënten met stadium III T3N1 (Cao, 2017; Yang, 2019) en stadium IVa T4N0 (Li, 2019; Sun, 2016) werden in enkele studies uitgesloten. De conclusie voor deze stadia luidt dat inductie chemotherapie mogelijk tot een betere overleving leidt, en voor deze stadia kan worden overwogen om inductie chemotherapie toe te voegen aan concomitante chemoradiatie therapie.

De meta-analyse van Fang (2021) suggereert dat inductie chemotherapie en concomitante chemoradiatie voor een geselecteerde groep patiënten met een nasofarynxcarcinoom kan leiden tot een betere overleving.

Waarden en voorkeuren van patiënten (en eventueel hun verzorgers)

Het belangrijkste doel van de interventie voor de patiënt is betere overleving en deze lijkt, met inductie chemotherapie iets beter dan zonder. Dit moet wel worden afgewogen tegen de toegenomen toxiciteit. Derhalve is van belang om te zien welke patiëntencategorie het meeste voordeel heeft bij toevoeging van inductie chemotherapie. Op basis van de boven vermelde analyse betreft dit de groep patiënten met een ongedifferentieerde tumor, omdat deze patiëntengroep de grootste kans op afstand metastasen heeft. Tevens dienen patiënten, gezien de toxiciteit van de behandeling en de nog volgende chemoradiatie~~, in principe < 70 jaar te zijn en een~~ WHO 0-1 te hebben om in aanmerking te komen voor inductie chemotherapie. Het risico bestaat anders dat patiënten niet aan hun concomitante chemotherapie toekomen, welke waarschijnlijk belangrijker voor de overleving is dan inductie chemotherapie. Voor plaveiselcelcarcinoom van de nasofarynx is superioriteit van inductiechemotherapie niet aangetoond en heeft ook gezien de verhoogde toxiciteit concomitante chemoradiotherapie zonder inductiechemotherapie de voorkeur.

Kosten (middelenbeslag)
Inductie chemotherapie gevolgd door concomitante chemoradiotherapie leidt tot een aanzienlijke verlenging van de behandelduur voor de patiënt, en hogere kosten als gevolg van de toegevoegde inductiechemotherapie. Daarnaast kan verhoogde toxiciteit ook tot een toename in kosten leiden. Dit moet gewogen worden tegen een besparing door minder noodzaak tot eventuele salvage therapie (waarvan mogelijkheden voor de primaire tumor beperkt zijn) en een (beperkt) verlies in levensjaren. Voor de Nederlandse situatie zijn geen studies naar kosteneffectiviteit voor de behandeling van nasofarynxcarcinomen uitgevoerd.

Voor de subgroep met een goede algehele conditie ~~< 70 jaar~~ en een ongedifferentieerd stadium III (exclusief T3N0 en mogelijk T3N1) en met name stadium IV zijn de baten mogelijk hoger dan de kosten.

Aanvaardbaarheid, haalbaarheid en implementatie
Inductie chemotherapie gevolgd door concomitante chemoradiotherapie wordt vaker toegepast bij zeer uitgebreide hoofd-halstumoren en wordt in het algemeen redelijk verdragen, maar er is wel een risico dat (bij een klein percentage, te halen uit de gerandomiseerde studies) dat door de toxiciteit van het inductie deel het concomitante deel (samen met de radiotherapie) niet of niet volledig kan worden gegeven. Chemotherapie is een haalbare interventie, maar de patiënt moet wel ~~jonger dan 70 jaar zijn en in~~ een WHO conditie 0 tot 1, een goede nierfunctie en geen aanmerkelijk gehoorverlies hebben.

Als bezwaar geldt een toegenomen belasting voor de patiënt tegenover een relatief kleine winst. In Nederland heeft iedereen voldoende toegang tot een hoofd-halsoncologisch centrum zodat implementatie van IC goed haalbaar is. Deze zorg wordt alleen geleverd in een hoofd-halsoncologisch centrum, waarvan er 8 in Nederland zijn en 6 een preferred partner hebben. Daar is voldoende expertise aanwezig. Wanneer in plaats van fotonen, op basis van geschatte lagere kans op toxiciteit, protonen een deel van de behandeling vormen, dan kan de reisafstand een belemmering vormen, niet in financiële maar in praktische zin. Het kan betekenen dat de chemotherapie en radiotherapie in twee centra plaatsvinden of dat naast de radiotherapie ook de chemotherapie in het protonencentrum zal worden gegeven. Er is een goede afstemming nodig tussen het hoofd-halsoncologisch centrum en het protoneninstituut.

Aanbeveling
Aanbeveling-1
Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies

Op basis van een meta-analyse van gerandomiseerde studies uitgevoerd in voornamelijk Aziatische landen naar het voordeel van inductie chemotherapie gevolgd door concomitante chemoradiotherapie voor stadium IV en geselecteerde patiënten met stadium III nasofarynx carcinomen kan worden geconcludeerd dat hiermee de ziektevrije overleving wordt verbeterd, met name de afstand metastase vrije overleving en in mindere mate de algehele overleving, ten koste van een verhoogde acute toxiciteit. Dit geldt echter niet voor patiënten met stadium T3N0. Voor stadium T3N1 en stadium T4N0 geldt dat ze in diverse studies zijn uitgesloten. Voor patiënten met deze stadia kan inductie chemotherapie gevolgd door chemoradiatie worden overwogen.

In de Aziatische landen zijn de nasofarynxcarcinomen voornamelijk ongedifferentieerde tumoren. In Nederland is 1/3 van de tumoren een plaveiselcelcarcinoom met een associatie met roken, een hoger risico op locoregionaal recidief en minder kans op afstand metastasen.

Voor het plaveiselcelcarcinoom is er geen bewijs om in stadium III/IV inductie chemotherapie gevolgd door CCRT aan te bevelen. De beperkte winst moet afgewogen worden tegen de toegenomen toxiciteit en dit moet met de patiënt besproken worden.

Voor patiënten ~~< 70 jaar,~~ met een WHO conditie 0 tot 1 met een ongedifferentieerd nasofarynxcarcinoom voor stadium IV en een selectie stadium III wordt inductiechemotherapie gevolgd door concomitante chemoradiotherapie aanbevolen.

Voor stadium T3N0 wordt inductie chemotherapie niet aanbevolen. Voor T3N1 en T4N0 kan inductie chemotherapie worden overwogen.

Voor het plaveiselcelcarcinoom stadium III/IV wordt inductie chemotherapie gevolgd door chemoradiatie niet aanbevolen. Een winst van inductie chemotherapie is niet aangetoond en er is risico op toegenomen toxiciteit.

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Bijlagen bij module 17.2

Implementatieplan

Aanbeveling	Tijdspad voor implementatie: < 1 jaar, 1 tot 3 jaar of > 3 jaar	Verwacht effect op kosten	Randvoorwaarden voor implementatie (binnen aangegeven tijdspad)	Mogelijke barrières voor implementatie[1]	Te ondernemen acties voor implementatie[2]	Verantwoordelijken voor acties[3]	Overige opmerkingen
Behandeling nasofarynxcarcinoom - inductie chemotherapie~~1~~	< 1 jaar	Beperkte stijging van kosten	Reeds mogelijk in alle hoofd-halsoncologische centra	Geen	Geen	NVKNO	Reeds mogelijk in centra.

[1] Barrières kunnen zich bevinden op het niveau van de professional, op het niveau van de organisatie (het ziekenhuis) of op het niveau van het systeem (buiten het ziekenhuis). Denk bijvoorbeeld aan onenigheid in het land met betrekking tot de aanbeveling, onvoldoende motivatie of kennis bij de specialist, onvoldoende faciliteiten of personeel, nodige concentratie van zorg, kosten, slechte samenwerking tussen disciplines, nodige taakherschikking, et cetera.
[2] Denk aan acties die noodzakelijk zijn voor implementatie, maar ook acties die mogelijk zijn om de implementatie te bevorderen. Denk bijvoorbeeld aan controleren aanbeveling tijdens kwaliteitsvisitatie, publicatie van de richtlijn, ontwikkelen van implementatietools, informeren van ziekenhuisbestuurders, regelen van goede vergoeding voor een bepaald type behandeling, maken van samenwerkingsafspraken.
[3] Wie de verantwoordelijkheden draagt voor implementatie van de aanbevelingen, zal tevens afhankelijk zijn van het niveau waarop zich barrières bevinden. Barrières op het niveau van de professional zullen vaak opgelost moeten worden door de beroepsvereniging. Barrières op het niveau van de organisatie zullen vaak onder verantwoordelijkheid van de ziekenhuisbestuurders vallen. Bij het oplossen van barrières op het niveau van het systeem zijn ook andere partijen, zoals de NZA en zorgverzekeraars, van belang.

Evidence tables

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Wang, 2020	SR and meta-analysis of RCTs *Literature search up to 11/09/2019* **A**: Fountzilas, 2012 **B**: Tan, 2015 **C1**: Sun, 2016 **C2**: Li, 2019 **D1**: Cao, 2017 **D2**: Yang, 2019 **E**: Frikha, 2018 **F**: Hong, 2018 **G**: Zhang, 2019 Study design: **A**: phase II RCT **B**: phase II/III RCT **C**: phase III RCT **D**: phase III RCT **E**: phase III RCT **F**: phase III RCT **G**: phase III RCT Setting and country: **A:** Europe **B:** Singapore **C**: China **D**: China	**Inclusion criteria SR:** (1) prospective studies in previously untreated patients with NPC (2) studies were registered clinical trials, and registration numbers were provided (3) randomized controlled clinical studies (4) the experiment group was treated with IC combined with CCRT, and the control group was treated with CCRT alone (5) neoadjuvant chemotherapy described in the articles was deemed as induction chemotherapy	**IC + CCRT** *Induction chemotherapy:* **A**: Epi 75 mg/m^2, Pac 175 mg/m2 and DDP 75 mg/m^2 every 21 days for 3 cycles **B**: Gem 1000 mg/m^2, CBP area under the concentration-time-curve 2.5, and Pac 70 mg/m^2 (day 1 and 8) every 21 days for 3 cycles **C**: Doc 60mg/m^2, DDP 60 mg/m^2 and 5-FU 600 mg/m^2 every 21 days for 3 cycles **D**: DDP 80mg/m^2 and 5-FU 800 mg/m^2 (day 1–5) every 21 days for 2 cycles **E**: Doc 75mg/m2, DDP 75 mg/m^2 and 5-FU 750 mg/m^2/day day (1–5) every 21 days for 3 cycles **F**: Mit 8 mg/m^2, Epi 60 mg/m^2, and DDP 60 mg/m^2	**CCRT** *Radiotherapy:* **A**: 2D-CRT, 3DCRT **B**: 2D-CRT, IMRT **C**: IMRT **D**: 2D-CRT, IMRT **E**: IMRT, non-IMRT **F**: 3D-CRT, IMRT **G**: IMRT *Concurrent chemotherapy:* **A**: DDP 40 mg/m^2 every week **B**: DDP 40 mg/m^2 every week **C**: DDP 100 mg/m^2 every 21 days for 3 cycles **D**: DDP 80 mg/m^2 every 21 days for 3 cycles **E**: DDP 40 mg/m^2 every week **F**: DDP 30 mg/m^2 every week **G**: DDP 100 mg/m^2 every 21 days for 3 cycles 2D/2D-CRT: 2/3-dimensional conformal radiotherapy	End-point of follow-up: **A**: 3 years **B**: 3 years **C**: 3 years / 5 years **D**: 3 years / 5 years **E**: 3 years **F**: 5 years **G**: 3 years For how many participants were no complete outcome data available? Not reported.	5-year overall survival Effect measure: Hazard ratio (95% CI): **A**: *not reported* **B**: *not reported* **C2**: 0.65 (0.43 – 0.98) **D2**: 0.69 (0.49 – 0.97) **E**: *not reported* **F**: 0.92 (0.67 – 1.27) **G**: *not reported* **Pooled effect (random effects model): 0.76 (95% CI 0.61 to 0.95) favoring IC+CCRT** **Heterogeneity (I^2): 12%** 3-year overall survival Effect measure: Hazard ratio (95% CI): **A**: 0.95 (0.48 – 1.88) **B**: 1.05 (0.50 – 2.19) **C1**: 0.59 (0.36 – 0.97) **D1**: 0.90 (0.57 – 1.41) **E**: 0.40 (0.15 – 1.07) **F**: *not reported* **G**: 0.43 (0.24 – 0.77) **Pooled effect (random effects model): 0.69 (95% CI 0.51 to 0.94) favoring IC+CCRT**	Remarks - Authors of the SR presented pooled analysis with a fixed effect model, while we used a random effects model. - Authors used the Jadad scoring scale, and all enrolled trials were identified as high quality (a score of ≥3). - Individual study characteristics and results are extracted from the SR (unless stated otherwise) Author's conclusion - IC combined with CCRT significantly improved the survival in locoregional advanced NPC patients. Moreover, toxicities were well tolerated during IC and CCRT. Further clinical trials are warranted to confirm the optimal induction chemotherapeutic regimen in the future. Sensitivity analyses

	E: France/Tunisia **F**: Taiwan **G**: China <u>Inclusion period:</u> **A**: 2003–2008 **B**: 2004–2012 **C**: 2011–2013 **D**: 2008–2015 **E**: 2009–2012 **F**: 2003–2009 **G**: 2013–2016 <u>Source of funding and conflicts of interest:</u> Non-commercial funding was reported. Authors reported no conflicts of interest.	(6) studies published in English. **Exclusion criteria SR:** (1) IC or CCRT combined with target therapy was excluded (2) conference abstracts *9 articles reporting on 7 studies were included* **Important patient characteristics at baseline:** <u>N, total, intervention/control</u> **A**: 141, 72/69 **B**: 172, 86/86 **C**: 480, 241/239 **D**: 476, 238/238 **E**: 83, 42/41 **F**: 479, 239/240 **G**: 480, 242/238 *Mean age (range)* **A**: I: 49 (19–82)	on day 1, 5-FU 450 mg/m^2 and Leu 30 mg/m^2 on day 8 **G**: Gem 1 g/m^2 (day 1 and 8) and DDP 80 mg/m^2 every 21 days for 3 cycles Epi: epirubicin Pac: paclitaxel DDP: cisplatin Gem: gemcitabine CBP: carboplatin Doc: docetaxel: 5-FU: 5-fluorouracil Mit: mitomycin Leu: leucovorin	IMRT: intensity modulated radiotherapy DDP: cisplatin		**Heterogeneity (I^2): 33%** <u>5-year disease-free survival</u> *Failure-free survival (FFS): FFS was defined as the date of randomization to documented disease progression (the date of locoregional/distant failure or death from any cause, whichever occurred first)* Effect measure: Hazard ratio (95% CI): **A**: *not reported* **B**: *not reported* **C2**: 0.67 (0.48 – 0.94) **D2**: 0.66 (0.48 – 0.91) **E**: *not reported* **F**: 0.74 (0.56 – 0.97) **G**: *not reported* **Pooled effect (random effects model): 0.70 (95% CI 0.58 to 0.83) favoring IC+CCRT** **Heterogeneity (I^2): 0%** <u>5-year disease-free survival</u> Effect measure: Hazard ratio (95% CI): **A**: 1.40 (0.71 – 2.76) **B**: 0.77 (0.44 – 1.35) **C1**: 0.68 (0.48 – 0.96)	Not applicable <u>Heterogeneity</u> Not applicable

		C: 51 (15–79) **B**: I: 49 (42–55) C: 52 (457) **C**: I: 42 (36–49) C: 44 (39–50) **D**: I: 44 (19–65) C: 42 (21–66) **E**: I: 46 C: 48 **F**: I: 45 (15–69) C: 47 (19–70) **G**: I: 46 (18–64) C: 45 (20–64) *Sex, n/N (%)* **A:** I: 55/72 (76%) C: 48/69 (70%) **B**: I: 71/86 (83%) C: 63/86 (73%) **C**: I: 193/241 (80%) C:174/239 (73%) **D**: I: 173/238 (73%) C: 190/238 (80%) **E**: I: 28/42 (67%) C: 32/41 (78%) **F**: I: 176/239 (74%) C: 179/240 (75%)				**D1**: 0.67 (0.47 – 0.96) **E**: 0.44 (0.20 – 0.97) **F**: *not reported* **G**: 0.51 (0.34 – 0.77) **Pooled effect (random effects model): 0.67 (95% CI 0.53 to 0.86) favoring IC+CCRT** **Heterogeneity (I2): 34%** <u>5-year distant metastasis-free survival (DMFS)</u> Effect measure: Hazard ratio (95% CI): **A**: *not reported* **B**: *not reported* **C2**: 0.60 (0.38 – 0.95) **D2**: 0.61 (0.41 – 0.91) **E**: *not reported* **F**: 0.82 (0.58 – 1.17) **G**: *not reported* **Pooled effect (random effects model): 0.69 (95% CI 0.60 to 0.87) favoring IC+CCRT** **Heterogeneity (I^2): 0%** <u>3-year distant metastasis-free survival (DMFS)</u> Effect measure: Hazard ratio (95% CI): **A**: *not reported* **B**: 0.80 (0.38 – 1.68)	

		G: I: 182/242 (75%) C: 164/238 (69%) *Stage* **A**: IIb - IVb **B**: III - IVb **C**: III - IVb **D**: III - IVb **E**: T2b, T3, T4 and/or N1-N3, M0 **F**: IVa-IVb **G**: IVa-IVb ***WHO type (I, II, III)*** *n (%)* **A:** I: 7 (10%) / 15 (21%) / 50 (69%) C: 5 (7%) / 15 (22%) / 49 (71%) **B:** I: 0 (0%) / 6 (7%) / 90 (93%), C: 0 (0%) / 6 (7%) / 90 (93%) **C:** not reported **D**: not reported **E**: I: 0 (0%) / 4 (10%) / 36 (90%), C: 0 (0%), 7 (17%) / 34 (83%)				**C1**: 0.59 (0.37 – 0.94) **D1**: 0.63 (0.41 – 0.97) **E**: 0.53 (0.21 – 1.34) **F**: *not reported* **G**: 0.43 (0.25 – 0.74) **Pooled effect (random effects model): 0.58 (95% CI 0.45 to 0.74) favoring IC+CCRT** **Heterogeneity (I^2): 0%** <u>Adverse events</u> *Defined as grade ≥ 3 adverse event rate* Effect measure % I and %C, RR (95% CI) **A**: *not reported* **B**: I: 52%, C: 37%, p<0.05 RR: 1.41 (1.00 – 1.98) **C**: I: 73%, C: 54%, p>0.05 RR: 1.35 (0.17 – 1.55) **D**: I: 66%, C: 49%, p<0.05 RR: 1.35 (1.15 – 1.58) **E**: *not reported* **F**: *not reported* **G**: I: 76%, C: 56%, p>0.05 RR: 1.35 (1.18 – 1.55) **Pooled effect (random effects model): 1.35 (95% CI 1.25 to 1.47) favoring CCRT** **Heterogeneity (I2): 0%** <u>Quality of life</u>	

		F: I: I: 1 (<1%) / IIa: 65 (27%) / IIb: 173 (72%), C: I: 0 (0%) / IIa: 71 (30%) / IIb: 169 (70%), **G**: not reported ***History of smoking*** *Yes, n (%)* A: I: 28 (39%), C: 25 (36%) B: not reported C: not reported *Groups comparable at baseline?* Not reported in SR				**A**: *not reported* **B**: measured with EORTC QLQ-C30 and EORTC QLQ-H&N35: The mean global QOL scores of the QLQ-30 module were balanced between the 2 arms. The IC+CCRT arm had significantly poorer symptom scores for dyspnea (24.3 versus 15.3; P=0.014) and diarrhea (15.2 versus 9.3; P=0.018) during CCRT compared with the control arm. However, these differences were no longer significant during follow-up. There were no statistical differences in any of the functional scales between the two arms. For the H&N35 module, the control arm had significantly poorer scores for pain, swallowing, and use of pain killers during CCRT, and for social contact at the third month of follow-up, compared with the GCP arm. **C1**: *not reported* **C2**: *not reported*	

						D1: *not reported* **D2**: *not reported* **E**: *not reported* **F**: *not reported*	

Quality assessment

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

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

Study	Appropriate and clearly focused question?[1]	Comprehensive and systematic literature search?[2]	Description of included and excluded studies?[3]	Description of relevant characteristics of included studies?[4]	Appropriate adjustment for potential confounders in observational studies?[5]	Assessment of scientific quality of included studies?[6]	Enough similarities between studies to make combining them reasonable?[7]	Potential risk of publication bias taken into account?[8]	Potential conflicts of interest reported?[9]
Wang, 2020	Yes	Yes	Yes	Yes	Not applicable	Yes (Jadad score)	Yes	No	Yes

1. **Research question (PICO) and inclusion criteria should be appropriate and predefined.**
2. **Search period and strategy should be described; at least Medline searched; for pharmacological questions at least Medline + EMBASE searched.**
3. **Potentially relevant studies that are excluded at final selection (after reading the full text) should be referenced with reasons.**
4. **Characteristics of individual studies relevant to research question (PICO), including potential confounders, should be reported.**
5. **Results should be adequately controlled for potential confounders by multivariate analysis (not applicable for RCTs).**
6. **Quality of individual studies should be assessed using a quality scoring tool or checklist (Jadad score, Newcastle-Ottawa scale, risk of bias table et cetera).**
7. **Clinical and statistical heterogeneity should be assessed; clinical: enough similarities in patient characteristics, intervention and definition of outcome measure to allow pooling? For pooled data: assessment of statistical heterogeneity using appropriate statistical tests (for example Chi-square, I^2)?**
8. **An assessment of publication bias should include a combination of graphical aids (for example funnel plot, other available tests) and/or statistical tests (for example, Egger regression test, Hedges-Olken). Note: If no test values or funnel plot included, score "no". Score "yes" if mentions that publication bias could not be assessed because there were fewer than 10 included studies.**
9. **Sources of support (including commercial co-authorship) should be reported in both the systematic review and the included studies. Note: To get a "yes," source of funding or support must be indicated for the systematic review AND for each of the included studies.**

Table of excluded studies

Author and year	Reason for exclusion
Ahn, 2019	Narrative review
Al-Rajhi, 2020	Does not match PICO (wrong comparison): low-dose fractioned radiotherapy + IC versus IC alone
Blanchard, 2015	Does not add extra RCTs to Wang (2020)
Chen, 2018	Does not add extra RCTs to Wang (2020)
Chen, 2018	No full-text available
Chen, 2015	Does not add extra RCTs to Wang (2020)
Fountzilas, 2012	Included in Wang (2020) BMC Cancer
Frikha, 2018	Included in Wang (2020) BMC Cancer
He, 2019	Does not match PICO (wrong comparison)
Hong, 2018	Included in Wang (2020) BMC Cancer
Huang, 2015	Does not match PICO (wrong comparison)
Huang, 2012	Does not match PICO (wrong comparison)
Huang, 2012	Non-English publication
Jin, 2019	Does not match PICO (wrong comparison): TPF+CCRT versus PF+CCRT
Kong, 2017	Wrong study design (not randomised)
Lee, 2015	Does not match PICO (wrong comparison)
Li, 2019	Does not add extra RCTs to Wang (2020)
Li, 2019	Included in Wang (2020) BMC Cancer
Li, 2017	Non-English publication
Liang, 2013	Does not add extra RCTs to Wang (2020)
Liu, 2018	Does not add extra RCTs to Wang (2020)
OuYang, 2019	Does not add extra RCTs to Wang (2020)
Petit, 2019	Does not add extra RCTs to Wang (2020)
Ribassin-Majed, 2017	Does not add extra RCTs to Wang (2020)
Song, 2015	Does not add extra RCTs to Wang (2020)
Song, 2015	Duplicate met Song (2015) hierboven
Tan, 2018	Does not add extra RCTs to Wang (2020)
Tian, 2015	Does not match PICO (wrong comparison)
Wang (Peirong), 2020	Does not add extra RCTs to Bi-Chen Wang (2020)
Wang, 2019	Does not match PICO (wrong comparison): low HDL-C versus high HDL-C
Xu, 2019	Wrong study design (not randomised)
Yang, 2019	Included in Wang (2020) BMC Cancer
Yang, 2018	Does not match PICO (wrong comparison)
You, 2017	Does not add extra RCTs to Wang (2020)
Yu, 2016	Does not add extra RCTs to Wang (2020)
Zang, 2018	Wrong study design (not randomised)
Zeng, 2016	Wrong study design (not randomised)
Zhang, 2019	Does not match PICO (wrong comparison)
Zhang, 2019	Included in Wang (2020) BMC Cancer
Zhang, 2018	Does not match PICO (wrong outcomes, prediction model)
Zhang, 2012	Does not match PICO (wrong comparison)
Zhao, 2019	Wrong study design (not randomised)
Zhou, 2020	Does not add extra RCTs to Wang (2020)

Literature search strategy

Algemene informatie

Richtlijn:Hoofd- halstumoren	
Uitgangsvraag: UV17.2 inductie chemotherapie	
Database(s): OVID/Medline, Embase	Datum: 17-6-2020
Periode: 2010-2020, 2019-2020	Talen: niet van toepassing
Literatuurspecialist: Ingeborg van Dusseldorp	

Zoekopbrengst

	EMBASE	OVID/MEDLINE	Ontdubbeld
SRs	34	23	37
RCTs	135	88	152
Totaal			189

Zoekverantwoording

OVID/Medline

1	exp Nasopharyngeal Neoplasms/ or ((epipharyn* or nasopharyn* or nasofaryn* or rhinopharyn* or rhinofaryn*) adj4 (cancer* or neoplasm* or tumor* or tumour* or malignan* or carcinom*)).ti,ab,kf. (21563)
2	exp Induction Chemotherapy/ or induction chemotherap*.ti,ab,kf. (9689)
3	1 and 2 (398)
4	limit 3 to yr="2010 -Current" (297)
5	(meta-analysis/ or meta-analysis as topic/ or (meta adj analy$).tw. or (systematic*or literature adj2 review$1).tw. or (systematic adj overview$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (292565)
6	(exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (1994323)
7	4 and 5 (23) **SR**
8	4 and 6 (109)
9	8 not 7 (88) **RCT**

Embase

No.	Query	Results
#16	#10 NOT #9 NOT #8	**211**
#15	#9 NOT #8 **RCT**	**135**
#14	#7 AND #12 **Artikel Chen wel gevonden zonder studiedesign filters**	**1**
#13	#11 AND #12 **Artikel Chen niet gevonden met studiedesign filters**	**0**
#12	nasopharyngeal AND carcinoma AND chen AND 2019 AND lancet	**4**
#11	#8 OR #9 OR #10	**380**
#10	#3 AND #7	**325**
#9	#2 AND #7	**159**
#8	#1 AND #7 **SR**	**34**
#7	#6 AND (2010-2020)/py NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	**481**
#6	#4 AND #5	**828**
#5	'induction chemotherapy'/exp OR 'induction chemotherap*':ti,ab,kw	**19850**

#4	'nasopharynx carcinoma'/exp OR 'nasopharynx tumor'/exp OR (((epipharyn* OR nasopharyn* OR nasofaryn* OR rhinopharyn* OR rhinofaryn*) NEAR/4 (cancer* OR neoplasm* OR tumor* OR tumour* OR malignan* OR carcinom*)):ti,ab,kw)	**30696**
#3	'major clinical study'/de OR 'clinical study'/de OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR 'prospective study'/de OR 'comparative study'/de OR 'cohort analysis'/de OR ((cohort NEAR/1 (study OR studies)):ab,ti) OR (('case control' NEAR/1 (study OR studies)):ab,ti) OR (('follow up' NEAR/1 (study OR studies)):ab,ti) OR (observational NEAR/1 (study OR studies)) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti)	**5976979**
#2	('clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti) NOT 'conference abstract':it	**2400633**
#1	('meta analysis'/de OR 'meta analysis (topic)'/exp OR cochrane:ab OR embase:ab OR psycinfo:ab OR cinahl:ab OR medline:ab OR ((systematic NEAR/1 (review OR overview)):ab,ti) OR ((meta NEAR/1 analy*):ab,ti) OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/de) NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	**523227**

Bijlage 1 Kennislacunes

Inleiding
Tijdens de herziening van de richtlijn 'Hoofd-Halstumoren' is systematisch gezocht naar onderzoeksbevindingen die nuttig konden zijn voor het beantwoorden van de uitgangsvragen. Een deel (of een onderdeel) van de hiervoor opgestelde zoekvragen is met het resultaat van deze zoekacties te beantwoorden, een groot deel echter niet. Door gebruik te maken van de evidence-based methodiek (EBRO) is duidelijk geworden dat er nog kennislacunes bestaan. De werkgroep is van mening dat (vervolg)onderzoek wenselijk is om in de toekomst een duidelijker antwoord te kunnen geven op vragen uit de praktijk. Om deze reden heeft de werkgroep per module aangegeven op welke vlakken nader onderzoek gewenst is.

Moduletitel	Kennislacune
Diagnostiek afstandsmetastasen	Wat zijn de indicaties voor onderzoek naar afstandsmetastasen ten tijde van de initiële diagnostiek van patiënten met een hoofd-halstumor? Met welke diagnostische onderzoeken moet onderzoek naar afstandsmetastasen verricht worden?
Afkappunt invasiediepte cT1-2N0	What is the risk of lymph node metastases, sensitivity, and negative predictive value per millimeter tumor depth of invasion (or tumor thickness) in patients with cT1-2N0 oral cavity carcinomas when elective neck dissection, sentinel node biopsy and watch and wait strategy carcinomas are used as reference standard?
Type beleid negatieve hals cT1-2N0	What are the (un)beneficial effects of elective neck dissection on neck recurrence, survival, and mortality compared to an observation strategy in patients with cT1-2N0 oral cavity carcinomas?
Type interventie negatieve hals cT1-2N0	What are the (un)beneficial effects of a sentinel lymph node biopsy on recurrence, disease specific survival, quality of life, shoulder morbidity, hematomas, pain, and postoperative oedema compared to an elective neck dissection in patients with cT1-2N0 oral cavity carcinomas? (larger sample sizes are needed to increase precision of estimates, no data on the occurrence of hematomas and postoperative oedema)
Behandeling T1-T2N0 hypofarynxcarcinoom	Er zijn goede, vergelijkende studies nodig om de rol van radiotherapie en chirurgie vast te stellen zodat de volgende vraag kan worden beantwoord: "Wat is de optimale behandeling van de primaire tumor van kleine hypofarynxcarcinomen?"
Behandeling Tis/T1 glottisch larynxcarcinoom	What are the effects of radiotherapy compared to surgical treatment (open surgery/endolaryngeal surgery) in patients with Tis/T1 glottic laryngeal carcinomas? → RCT op survival en functie en goed omschreven welke procedures verricht worden Bij welke uitbreiding van T1 is laserchirurgie of radiotherapie de beste behandeling? → vergelijking radiotherapie en laserchirurgie per vereist ELS type.
Behandeling van Tis/T1 supraglottische larynxcarcinomen	Er zijn goede, vergelijkende studies nodig om de rol van horizontale supraglottische laryngectomie en endoscopische behandeling of radiotherapie vast te stellen zodat de volgende vraag kan worden beantwoord: "Op welke wijze dienen Tis/T1 supraglottische larynxcarcinomen behandeld te worden?"
Endoscopische chirurgie maligne neus(bij)holtetumoren	Wat is de beste chirurgische behandeling voor (subgroepen) maligne neus(bij)holtetumoren, een uitwendige open benadering of een endoscopische benadering?
Behandeling neus- en neus(bij)holte carcinoom – toevoeging chemotherapie	Er zijn goede, vergelijkende studies nodig om de rol van chemotherapie en de optimale volgorde t.o.v. lokale behandelingen vast te stellen zodat de volgende vraag kan worden beantwoord: "Wat zijn de effecten van chemotherapie toegevoegd aan radiotherapie, vergeleken met radiotherapie alleen bij patiënten met neus- en neusbijholtecarcinomen?"

Behandeling nasofarynxcarcinoom – inductie chemotherapie	De resultaten komen nu nagenoeg alleen uit Aziatische studies. De etiologie van de nasofarynxcarcinomen die gevonden worden in Aziatische en westerse landen als Nederland verschilt echter, met name in de verhouding EBV+ ongedifferentieerde nasofarynxcarcinomen en plaveiselcelcarcinomen. Ook is onduidelijk bij welk stadium tumoren (de meeste) winst te halen is.

Bijlage 2 Geldigheid en onderhoud

Moduletitel	**Eerstvolgende beoordeling actualiteit richtlijn**
Diagnostiek afstandsmetastasen	2027
Afkappunt invasiediepte cT1-2N0	2027
Type beleid negatieve hals cT1-2N0	2027
Type interventie negatieve hals cT1-2N0	2027, tenzij eerder relevant studies beschikbaar komen
Behandeling T1-T2N0 hypofarynxcarcinoom	2027, tenzij eerder relevant studies beschikbaar komen
Behandeling Tis/T1 glottisch larynxcarcinoom	2027
Behandeling van Tis/T1 supraglottische larynxcarcinomen	2027
Endoscopische chirurgie maligne neus(bij)holtetumoren	2027
Behandeling neus- en neus(bij)holte carcinoom – toevoeging chemotherapie	2027
Behandeling nasofarynxcarcinoom – inductie chemotherapie	2027