Bijlagen bij Conceptrichtlijnmodules Cluster Hoofd-halstumoren

1e cyclus modulair onderhoud

INITIATIEF
Cluster Hoofd-halstumoren

IN SAMENWERKING MET
Nederlandse Vereniging voor Keel-Neus-Oorheelkunde en Heelkunde van het Hoofd-Halsgebied (NVKNO)
Nederlandse Vereniging voor Radiotherapie en Oncologie (NVRO)
Nederlandse Internisten Vereniging (NIV)
Nederlandse Vereniging voor Mondziekten, Kaak- en Aangezichtschirurgie (NVMKA)
Vereniging Klinische Genetica Nederland (VKGN)
Patiëntenvereniging Hoofd-Hals (PVHHT)
Nederlandse Vereniging voor Patiënten met Paragangliomen (NVPG)
Koninklijk Nederlands Genootschap voor Fysiotherapie (KNGF)
Koninklijke Nederlandse Maatschappij tot bevordering der Tandheelkunde (KNMT)

MET ONDERSTEUNING VAN
Het Kennisinstituut van de Federatie Medisch Specialisten.

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

Colofon

Conceptrichtlijnmodules cluster [naam cluster]

© 20xx

Alle rechten voorbehouden.

De tekst uit deze publicatie mag worden verveelvoudigd, opgeslagen in een geautomatiseerd gegevensbestand, of openbaar gemaakt in enige vorm of op enige wijze, hetzij elektronisch, mechanisch door fotokopieën of enige andere manier, echter uitsluitend na voorafgaande toestemming van de uitgever. Toestemming voor gebruik van tekst(gedeelten) kunt u schriftelijk of per e-mail en uitsluitend bij de Richtlijnendatabase aanvragen.

Inhoudsopgave

Dit document bevat de achtergrondinformatie behorende bij de moduleteksten uit het cluster Hoofd-halstumoren. Het staat u vrij om commentaar op deze bijlagen te geven; dit is niet noodzakelijk.

Bijlage 1 Verantwoording 1 4
Bijlage 2 Literatuursamenvatting module 1 inclusief alle bijlagen 9
Bijlage 3 Verantwoording 2 57
Bijlage 4 Literatuursamenvatting module 2 inclusief alle bijlagen 63
Bijlage 5 Verantwoording 3 94
Bijlage 6 Literatuursamenvatting module 3 inclusief alle bijlagen 99
Bijlage 7 Verantwoording 4 108
Bijlage 8 Literatuursamenvatting module 4 inclusief alle bijlagen 113
Bijlage 9 Verantwoording 5 152
Bijlage 10 Literatuursamenvatting module 5 inclusief alle bijlagen 157

Bijlage 1 Verantwoording 1

Voor meer details over de gebruikte richtlijnmethodologie verwijzen wij u naar de Werkwijze. Relevante informatie voor de ontwikkeling/herziening van deze richtlijnmodule is hieronder weergegeven.

Initiatief
Initiatief: Cluster Hoofd-halstumoren

Samenstelling van de werkgroep
Voor het ontwikkelen van de richtlijnmodule is eind 2024 een multidisciplinair cluster ingesteld. Het cluster Hoofd-halstumoren bestaat uit meerdere richtlijnen (zie hier de actuele clusterindeling). De stuurgroep bewaakt het proces van modulair onderhoud binnen het cluster. De expertisegroepsleden brengen hun expertise in, indien nodig. De volgende personen uit het cluster zijn betrokken geweest bij de herziening van deze module:

Clusterstuurgroepleden

- Prof. dr. R. (Remco) de Bree, voorzitter (NVKNO)
- Dr. M. (Mischa) de Ridder (NVRO)
- Dr. L.A. (Lot) Devriese (NIV)
- Prof. dr. M.J.H. (Max) Witjes (NVMKA)
- Dr. H.P.M. (Dirk) Kunst (NVKNO)
- R.A. (Rob) Burdorf (PVHH)

Betrokken clusterexpertisegroepleden

- Dr. M. (Marije) Slingerland (NIV)
- Dr. C.M.L. (Chantal) Driessen (NIV)
- P. (Pieter) Stoffels (PVHH)

Met ondersteuning van

- Dr. A. (Anja) van der Hout (Kennisinstituut van de Federatie Medisch Specialisten)
- Dr. E. (Eline) Pruijn-de Heus (Kennisinstituut van de Federatie Medisch Specialisten)
- Dr. J. (Jing) de Haan-Du (Kennisinstituut van de Federatie Medisch Specialisten)
- Drs. J. (Joline) Rohof (Kennisinstituut van de Federatie Medisch Specialisten)
- Dr. M.S. (Michiel) Oerbekke (Kennisinstituut van de Federatie Medisch Specialisten)
- Alies Oost (Kennisinstituut van de Federatie Medisch Specialisten)

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

Clusterstuurgroepleden

Tabel 1 Gemelde (neven)functies en belangen stuurgroep

Naam	Hoofdfunctie	Nevenwerkzaamheden	Persoonlijke financiële belangen	Persoonlijke relaties	Extern gefinancierd onderzoek	Intellectuele belangen en reputatie	Overige belangen	Datum	Restrictie
Prof. dr. R. (Remco) de Bree	KNO-arts / hoofd-halschirurg	Onbetaald: Board member	Geen	Geen	KWF. Ultrasound and microbubbles to improve tumor perfusion of head	Geen	Geen	12-12-2024	Restricties ten aanzien

(voorzitter)	Hoogleraar / afdelingshoofd UMC Utrecht	Dutch Head and Neck Society (NWHHT) Chair Research Steering Committee Dutch Head and Neck Society (NWHHT) Member Clinical Audit Board Dutch Head and Neck Audit (DHNA) Chair committtee Revision Dutch Head and Neck Tumor Guidelines Board member Patient advocacy group Patiëntenvereniging Hoofd-Hals (PVHH) Chair advisory committee research data Dutch registries (PRISMA) Chair Dutch section Collegium Oto-Rhino-Laryngologicum Amicitiae Sacrum (CORLAS) Council Member International Academy of Oral Oncology (IAOO)			and neck cancers. co-applicant ZonMw. Metastatic-directed stereotactic body radiation therapy of oligometastases in head and neck squamous cell carcinoma patients. Projectleider KWF. Personalized follow-up in HPV-related oropharyngeal cancer patients using liquid biopsies. Projectleider Maurits en Anna de Kock Stichting en Vaillantfonds. Fluorescentie geassisteerde reconstructieve chirurgie: beoordeling van vitaliteit van weefsels. Projectleider 1. KWF- FDG-PET/CT to reduce the need for sentinel lymph node biopsy in early stage oral cancer (Projectleider JA) 2. KWF - Ex vivo 7T MRI of resection specimen of oral cancer to improve margin control (Projectleider NEE) 3. KWF - Sentinel lymph node detection in early oral cancer using [68Ga]Ga-tilmanocept PET/CT lymphoscintigra (Projectleider JA) 4. Nutricia - Perioperative nutritional intervention with Fortifit Energy® in combination with excersice verstus standard of care (Projectleider JA) 5. Hanarth Fonds - Triage of Patients with High-risk Oral Squamous cell Carcinoma using Artificial Intelligence (TOSCA) (Projectleider NEE)				van besluitvorming betreffende perioperatieve voedingsinterventies. Indien relevant: Vice-voorzitter aan te stellen voor wanneer perioperatieve voedingsinterventies worden besproken.
Dhr. Dr. M. (Mischa) de Ridder	Radiotherapeut-oncoloog UMC Utrecht	Secretaris LPRHHT van de NVRO. Lid METC NED-MED	Geen	Geen	Elekta: To evaluate evidence for eventual transition from PDR treatments to HDR treatments in case of possib (Projectleider JA). Hanarth fonds: Improved response assessment after (chemo)-	Geen	Geen	3-1-2025	Geen restricties.

					radiotherapy for locally advanced head and neck squamous (Projectleider NEE).				
Mevr. Dr. L.A. (Lot) Devriese	Internist UMC Utrecht	Dit project en eerder bij FMS kwaliteits agenda. Werkgroep binnen NVMO, CieOOM, off-label oncologische medicatie (vacatiegelden naar UMC Utrecht). Bestuurslid NWHHT	Geen	Geen	Ja, als lokale PI van studies gesponsord door Farma. Met uitbetaling aan de werkgever, niet aan mij persoonlijk. 1. ISAPharm - Fase 3 onderzoek ISA101b (Projectleider NEE) 2. MERUS - Fase 3 onderzoek petosemtamab (Projectleider NEE) 3. CISLOW studie - Fase 2 IIS gesponsord door ZOnMw (Projectleider NEE)	Geen	Geen	14-11-2024	Geen restricties.
Prof. dr. M.J.H. (Max) Witjes	MKA chirurg-HH oncoloog Universitair Medisch Centrum Groningen	Geen	Geen	Geen	• Fluoguide FG001sponsor initiated trial (2024): Determination of Optimal Dose for Visualization of Inadequate Margins in Oral Squamous Cell Carcinoma Using FG001. Protocol: 2024-514508-14-00. Witjes MJH Voskuil FJ, Fluoguide team. (budget € 378.293) (Projectleider JA) • NIH grant (National Institute of Dental and Craniofacial Research 2023) : Ex vivo intraoperative surgical basal margin analysis in head and neck cancer resection: clinical validation (1R01DE033449-01). Tichauer K, J Broncovic & Witjes MJH, Voskuil FJ.(budget USD 2.5Milj) (Projectleider JA) • SNN Grant (2023) : JTF application for IMPACT-Implants . (Budget € 3.6 Milj) Kraeima J, Witjes MJH, Veldsink JW & Center for Business Development UMCG. (Projectleider NEE) • KWF Kankerbestrijding: RUG 13215 (2021) Witjes MJH, GB Halmos, WM Nagengast. Real-time targeted fluorescence endoscopy in patients for detection of unknown primary cancers of the head and neck area (REFLECT study) (Budget €476.000) (Projectleider JA) • WJ Thijn stichting (2021) : Witjes MJH lichtgevende stoffen helpen de chirurg	Geen	Geen	16-1-2025	Restricties ten aanzien van besluitvorming betreffende de bepaling van de optimale dosis voor visualisatie van onvoldoende snijmarges bij oraal plaveiselcelcarcinoom.

					de tumor beter te verwijderen. (Budget €250.000). (Projectleider JA)				
Dhr. H.P.M. (Dirk) Kunst	KNO-arts; Radboudumc-MUMC+	Voorzitter van het "Radboudumc-MUMC+ Expertisecentrum Schedelbasispathologie" Voorzitter "Academische Alliantie Schedelbasispathologie Radboudumc-MUMC+" Voorzitter "Landelijk Overleg Expertisecentra Schedelbasispathologie" (LOES) President van de "European Skull Base Society" (ESBS) Betrokkenheid patientenverenigingen: Neurofibromatose type 2 patientenvereniging Paragangliomen patientenvereniging	Geen	Geen	Euregio: Hoofd-hals paragangliomen; verschillen management Nederland Duitsland (projectleider JA). TU Eindhoven/Tilburg (aflopende ZonMw studie), over voorspellen van groei obv MRI scans bij brughoektumoren (projectleider NEE).	Geen	Geen	14-2-2025	Geen restricties.
Dhr. R.A. (Rob) Burdorf	Neem niet meer deel aan het arbeidsproces (met pensioen)	Lid wetenschappelijke advies commissie van de PVHH	Geen	Geen	Geen	Geen	Geen	12-11-2024	12-11-2024

Betrokken clusterexpertisegroepleden

Tabel 2 Gemelde (neven)functies en belangen expertisegroep

Naam	Hoofdfunctie	Nevenwerkzaam-heden	Persoonlijke financiële belangen	Persoonlijke Relaties	Extern gefinancierd onderzoek	Intellectuele belangen en reputatie	Overige belangen	Datum	Actie

Marije Slingerland (NIV)	Internist-oncoloog (LUMC)	Interview/podcast voor BMS (éénmalig, betaald, onderwerp: informatievoorziening op maat bij oesofagus- en maagkanker in de palliatieve zorg)	Geen	Geen	Geen	Geen	Geen	06-07-2026	Geen restricties.
Chantal Driessen (NIV)	Internist-oncoloog (Radboudumc)	Medical Information Officer	Geen	Geen	Geen	Geen	Geen	22-06-2026	Geen restricties.
Pieter Stoffels (PVHH)	Geen	Geen	Geen	Geen	Geen	Geen	Geen	22-06-2026	Geen restricties.

Kwalitatieve raming van mogelijke financiële gevolgen in het kader van de Wkkgz

Bij de richtlijnmodule voerden de clusterleden conform de Wet kwaliteit, klachten en geschillen zorg (Wkkgz) een kwalitatieve raming uit om te beoordelen of de aanbevelingen mogelijk leiden tot substantiële financiële gevolgen. Bij het uitvoeren van deze beoordeling is de richtlijnmodule op verschillende domeinen getoetst (zie het stroomschema bij Werkwijze).

Module	Uitkomst raming	Toelichting
Module [naam]	[geen/ mogelijk] financiële gevolgen	[plaatsen desbetreffende uitkomst 1, 2, 3, 4 of 5]

Bijlage 2 Literatuursamenvatting module 1 inclusief alle bijlagen

Introduction

The palliative care of patients with head and neck cancers has changed in recent years with the introduction of immunotherapies such as pembrolizumab and nivolumab. The use of these therapies is often based on the combined positive score (CPS), but there is practice variation in its determination and application. There is a need for clear guidance for the optimal use of systemic therapy in the palliative care of patients with head and neck cancer.

Search and select

A systematic review of the literature was performed to answer the following question(s): What is the effect of systemic therapy compared to other systemic therapies or best supportive care in patients with incurable or distant metastatic head and neck cancer on overall survival, progression-free survival, quality of life, and toxicity?

Table 1. PICO

Patients	Patients with incurable or metastatic head- and neck squamous cell carcinoma
Intervention	Systemic therapy
Control	Other systemic therapy or best supportive care
Outcomes	Overall survival, progression-free survival, quality of life, toxicity
Other selection criteria	Study design: systematic reviews, RCTs, age > 18 years, systemic agents that appeared in an advisory report of the CieBOM (NVMO) for recurrent / metastatic head and neck squamous cell carcinoma (R/M HNSCC)

Relevant outcome measures

The guideline panel considered overall survival, progression-free survival, quality of life, and toxicity as a **critical** outcome measure for decision making.

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

The guideline panel defined the following thresholds as a minimal clinically (patient) important differences based on the 2023 PASKWIL-criteria for palliative treatment:

- Overall survival (OS):
    - When the median OS in the control group is ≤ 12 months:
        - mOS >12 weeks and HR <0.70, or
        - an increase of ≥10% patients on the ≥2-year OS at the last moment >20% of the patients in the intervention group are alive at ≥2 years
    - When the median OS in the control group is > 12 months:
        - mOS >16 weeks and HR <0.70, or
        - an increase of ≥10% patients on the ≥3-year OS at the last moment >20% of the patients in the intervention group are alive at ≥3 years
- Progression-free survival (PFS):
    - When the median OS in the control group is >12 months:
        - PFS >16 weeks and HR <0.70
- 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.
- Toxicity

- Adverse events:
  - Lethal: 5% difference (between intervention and control)
  - Acute/severe: 25% difference (between intervention and control)

Search and select (Methods)

A systematic literature search was performed by a medical information specialist using the following bibliographic databases: Embase.com and Ovid/Medline all. Both databases were searched from 2015 to October 31, 2025 for systematic reviews. Systematic searches were completed using a combination of controlled vocabulary and natural language keywords. The overall search strategy was derived from the following primary search concepts: (1) head- and neck cancer; (2) incurable or metastatic; (3) systemic therapy. Duplicates were removed using EndNote software. After deduplication a total of 1160 records were imported for title/abstract screening.

A guideline methodologist created a preselection by excluding obvious non-relevant hits. For example, studies solely concerning types of tumors not in the head and neck region (e.g. renal, gastric, hepatic). Thereafter, 212 potentially relevant studies remained. Two members of the guideline panel further screened the studies, in a double-blind fashion. Initially, they selected 37 studies based on their title and abstract screening. After reading the full text, the body of evidence of 26 potentially relevant (systematic) reviews were mapped in an overview. Systematic reviews were selected when they searched multiple databases, assessed the risk of bias in individual studies, included studies examining systemic agents in patients having recurrent or metastatic head and neck squamous cell carcinoma, and were complementary and together covered a large body of evidence. Overall, 34 studies were excluded (see the exclusion table under the tab 'Evidence tabellen'), and 3 systematic reviews were selected (Li, 2025; Lau 2020; Zhan, 2021).

From these systematic reviews, individual randomized controlled trials were selected when they matched our PICO and the investigated systemic agents appeared in an advisory report of the CieBOM of the NVMO for recurrent and/or metastatic head and neck squamous cell carcinoma. From seven relevant advisory reports available in February 2026, we identified pembrolizumab (whether or not with chemotherapy), nivolumab, and combinations of cetuximab, a platinum containing chemotherapy, and/or 5-fluorouracil. Eight publications were selected for the synthesis of head-to-head comparisons (Bourhis, 2006; Burtness, 2005; Burtness, 2019; Cohen, 2019; Ferris, 2016; Ferris, 2018; Harrington, 2023; Vermorken, 2008). Conference abstracts, posters, or presentations were excluded.

As we progressed our synthesis, we became aware of separate publications describing quality of life outcomes which were not selected in the systematic reviews we had used to identify RCTs. An additional systematic literature search was therefore performed by a medical information specialist using the following bibliographic databases: Embase.com and Ovid/Medline all. Databases were searched from 2005 to March 19th 2026 for systematic reviews and RCTs. Searches were completed using a combination of controlled vocabulary and natural language keywords. The search strategy was derived from the following primary search concepts: (1) head and neck squamous cell carcinoma; (2) Pembrolizumab/ Nivolumab/ Cetuximab; (3) quality of life. Duplicates were removed using EndNote software. After deduplication a total of 274 records were presented for title/abstract screening. Fifteen publications were initially selected based on their title and abstract for full text screening. Cohort studies, conference abstracts, posters, or presentations were excluded. Finally, four additional articles providing information about patients' quality of life from an RCT investigating pembrolizumab (whether or not with chemotherapy), nivolumab, or

combinations of cetuximab, a platinum containing chemotherapy, and/or 5-fluorouracil were included.

Summary of literature

Description of studies

A total of three systematic reviews were included in the analysis of the literature (Li, 2025; Zhan, 2021; Lau, 2020).

Li (2025) conducted a systematic review and network meta-analysis on the efficacy of immune checkpoint inhibitors for the treatment of head and neck cancers. The search included articles up to April 2024. Inclusion criteria for inclusion of research were: (1) adult patients (≥18 years old) with pathologically confirmed head and neck cancers (HNC); (2) patients were treated with immune checkpoint inhibitors (ICIs) of any kind; (3) study design was an RCT, blinding was not mandatory for inclusion; (4) outcomes reported were overall survival (OS) and/or progression-free survival (PFS). A total of ten studies were included in the systematic review.

Zhan (2021) performed a Bayesian network meta-analysis on optimal second-line systemic treatment for R/M HNSCC. They focused on addressing the efficacy and toxicity of the available systemic treatments. For the systematic review, a search was performed up to June 2021. To be included, the articles had to be RCTs and patients had to have confirmed R/M HNSCC. Chemotherapy, targeted therapy, and immunotherapy or a combination of the therapies were eligible for inclusion.

Lau (2020) wrote a systematic review focusing on OS and PFS in regard to systemic therapy in R/M HNSCC patients. They searched from 1990 up to May 2018. Research was included if: the participants were adults (≥18 years old) diagnosed with HNC, the interventions ware ICIs of any kind, the study was an RCT (blinding was not mandatory for inclusion), and the outcome contains OS and/or PFS.

Important study characteristics of the individual RCTs selected from these systematic reviews are summarized in table 2 (Bourhis, 2006; Burtness, 2005; Burtness, 2019; Cohen, 2019; Ferris, 2016; Ferris, 2018; Harrington, 2023; Vermorken, 2008). The assessment of the risk of bias is summarized in the risk of bias tables (under the tab ‘Evidence tabellen’).

Table 2. Characteristics and methodological quality assessment of included studies

Study	Comparison	Author	Participants	Follow-up	Outcome measures	Comments	Risk of bias (per outcome measure)*
EXTREME R/M HNSCC Inclusion criteria: ≥18 years old, histologically or cytologically confirmed recurrent or metastatic HNSCC, ineligibility for local therapy, at least one lesion measurable with CT or MRI bidimensionally, Karnofsky score ≥70, adequate hematologic / renal / hepatic function, available tumor tissue for EGFR expression evaluation. Exclusion criteria: Surgery or irradiation within previous four weeks, previous systemic chemotherapy (unles part of multimodal	I: Cetuximab + cisplatin or carboplatin + 5-fluorouracil C: cisplatin or carboplatin + 5-fluorouracil	Vermorken (2008) Messía (2010)	N at baseline: I: 222 C: 220 Age, years (median): I: 56 C: 57 Median duration of disease, months: I: 15.5 (IQR: 10.3-27.0) C: 15.8 (IQR: 9.5) Previous treatment: I: Radiotherapy (85%), chemotherapy (41%) C: Radiotherapy (86%), chemotherapy (36%)	Median duration of treatment was 18 weeks (IQR: 8-29). OS survival data was reported up to 24 months (according to the presented survival analysis) PFS was reported up to 15 months (according to the presented survival analysis)	Overall survival (OS), Progression-free survival (PFS), Adverse events (AE), quality of life (QoL)		Analyses were performed by the trial sponsor. Unclear blinding

treatment for locally advanced disiease completed ≥ 6 months before study entry), nasopharyngeal carcinoma, other concomitant anti-cancer therapy. **First-line treatment**							
KEYNOTE-048 R/M HNSCC Inclusion criteria: Histologically- or cytologically-confirmed recurrent or metastatic head and neck squamous cell carcinoma considered incurable by local therapies, no prior systemic therapy administered in the recurrent/ metastatic setting **First-line treatment**	I1: Pembrolizumab I2: Pembrolizumab + chemotherapy (a platinum and 5-fluorouracil) C: cetuximab with chemotherapy (a platinum and 5-fluorouracil)	Harrington (2023), Burtness (2019), Rischin (2022)	N at baseline I1: 301 I2: 281 C: 300 Age, years (median, range) I1: 62.0 (56.0-68.0) I2: 61.0 (55.0-68.0) C: 61.0 (54.5 – 68.0) Sex (n male, %) I1: 250 (83) I2: 224 (80) C: 261 (87) Current or former smoker (n, %): I1: 239 (79) I2: 224 (80) C: 234 (78)	Harrington: The median study follow-up was 45.0 months (IQR, 41.0-49.2) Burtness: final analysis, median follow-up was 11.5 months (IQR 5.1−25.7) in the pembrolizumab alone group, 13.0 months (6.4−26.6) in the pembrolizumab with chemotherapy group, and 10.7 months (6.6−19.7) in the	Overall survival (OS), progression-free survival (PFS), safety, quality of life (QoL)	N/A	The funder participated in the study design, data collection, data analysis, data interpretation, and writing of the report. No blinding.

				cetuximab with chemotherapy group			
KEYNOTE-040 R/M HNSCC Inclusion criteria: Histologically- or cytologically-confirmed recurrent or metastatic head and neck squamous cell carcinoma considered incurable by local therapies, failure of prior platinum therapy **Second-line treatment**	I: Pembrolizumab C: Standard of care chemotherapy (investigator's choice of standard doses of methotrexate, docetaxel, or cetuximab intravenously)	Cohen (2019) Harrington (2021)	N at baseline I: 247 C: 248 Age, years (median, range) I: 60.0 (55-66) C: 60.0 (54-66) Sex (n male, %) I: 207 (84) C: 205 (83) Current or former smoker (n, %): I: 179 (72) C: 182 (73)	The median follow-up from randomization to data cutoff or death, whichever came first, was 7·5 months. For the pembrolizumab group 8·4 months [3·3–14·5] and 7·1 months [3·7–12·4] for the standard-of-care group	Overall survival (OS), progression-free survival (PFS), quality of life (QoL)	N/A	The funder participated in the study design, data collection, data analysis, data interpretation, and writing of the report. No blinding.
CheckMate-141 R/M HNSCC Inclusion criteria: Histologically confirmed recurrent or metastatic SCCHN (oral cavity, pharynx, larynx), stage III/IV and not amenable to local therapy with curative intent (surgery or radiation therapy with or without	I: Nivolumab C: Chemotherapy (weekly intravenous administration of methotrexate at a dose of 40 to 60 mg per square meter of body-surface area, docetaxel at a dose of 30 to 40 mg per square meter, or cetuximab at a dose of 250 mg per square meter after a loading dose of 400 mg per square meter)	Ferris (2016) Ferris (2018) Harrington (2017)	N at baseline I: 240 C: 121 Age, years (median, range) I: 59 (29-83) C: 61 (28-78) Sex (n male, %) I: 197 (82.1) C: 103 (85.1) Current or former smoker (n, %): I: 191 (79.6)	Ferris (2016): The median duration of follow-up for overall survival was 5.1 months (0-16.8) Ferris (2018): Minimum follow-up of 24.2 months	Overall survival (OS), progression-free survival (PFS), adverse events (AEs), quality of life (QoL)	N/A	The trial was designed in collaboration with the sponsor. No blinding.

chemotherapy), tumor progression or recurrence within 6 months of last dose of platinum therapy **Second-line treatment**			C: 85 (70.2)				
Bourhis, 2006 R/M HNSCC Inclusion criteria: recurrent or metastatic SCCHN not suitable for local therapy, disease measurable by computed tomography or magnetic resonance imaging, and recovery from relevant toxicities of previous treatment Exclusion criteria: prior systemic chemotherapy, except if as part of multimodality treatment for locally advanced disease; previous treatment with	I: cetuximab + cisplatin + 5FU C: cetuximab + carboplatin + 5FU	Bourhis (2006)	N at baseline I: 27 C: 26 Age, years (median, range) I: 55 (33-77) C: 56 (34-68) Sex (n male) I: 24 C: 24	N/A	Safety/tolerability, time to progression, overall survival (OS)	N/A	

cumulative cisplatin dose more than 300 mg/m2 **First-line treatment**							
Burtness, 2005 R/M HNSCC **First/second-line treatment not specified**	I: cisplatin + cetuximab C: cisplatin + placebo	Burtness (2005)	N at baseline I: 57 C: 60 Age, years (median, range) I: 60.6 (39.8-85.7) C: 58.3 (32.2-83.5) Sex (n male, %) I: 41 (71.9) C: 50 (83.3)	Median follow-up time among the seven patients censored for OS was 31 months, with a minimum of 16 and a maximum follow-up time for survivors of 47 months	Progression-free survival (PFS), overall survival (OS), safety	30% of patients in the cisplatin and cetuximab arm and 15% of those in the cisplatin and placebo arm had received prior systemic therapy.	

*For further details, see risk of bias table in the appendix. We have used the assessments of Li (2025) and Lau (2020).

Results

First line treatments

1. **Overall survival (OS)**

a) Pembrolizumab

The researchers of the KEYNOTE-048 trial (Harrington, 2023; Burtness, 2019) investigated pembrolizumab alone or pembrolizumab + platinum + 5-fluorouracil (pembrolizumab + chemotherapy) with cetuximab + platinum + 5-fluorouracil (cetuximab + chemotherapy). Burtness (2019) reported results after a median follow-up of 11.5 months. Comparing pembrolizumab alone to cetuximab + chemotherapy gave an HR of 0.85 (95%CI 0.71-1.03). For pembrolizumab + chemotherapy compared to cetuximab + chemotherapy, the HR was 0.77 (95%CI, 0.63-0.93).

Harrington (2023) described the results at a median follow-up of 45 months. In the overall sample, comparing pembrolizumab alone (median survival 11.5 months) to cetuximab + chemotherapy (median survival of 10.7 months) gave an HR of 0.80 (95%CI, 0.68 – 0.96) as reported by Harrington (2203). The overall survival rate at 48 months was 15.4% in the pembrolizumab alone group, compared to 6.6% in the cetuximab + chemotherapy group. In the sample with PD-L1 CPS ≥20, the HR of pembrolizumab + chemotherapy (n=133, median survival 14.9 months) compared to cetuximab + chemotherapy (n=122, median survival 10.8 months) was 0.61 (95%CI: 0.46-0.81). Here, the OS rate at 48 months was 21.6% in the PD-L1 CPS ≥20 pembrolizumab alone group, compared to 8% in the PD-L1 CPS ≥20 cetuximab + chemotherapy group. In the PD-L1 CPS ≥1 population comparing pembrolizumab + chemotherapy (n=257, median survival 12.3 months) to cetuximab + chemotherapy (n=255, median survival 10.4 months), the HR was 0.74 (95%CI: 0.61-0.89). At 48 months, the OS rate in the PD-L1 CPS ≥20 pembrolizumab alone group was 16.7%, while this was 5.9% in the PD-L1 CPS ≥20 cetuximab + chemotherapy group.

The OS of pembrolizumab + chemotherapy (median survival 13.0 months) versus cetuximab + chemotherapy (median survival 10.7 months) comparison gave an HR of 0.70 (95%CI, 0.59-0.84). The overall survival rate at 48 months was 19.4% in the pembrolizumab + chemotherapy group, compared to 4.5% in the cetuximab + chemotherapy group. In the PD-L1 CSP ≥20 pembrolizumab + chemotherapy sample (n=126, median survival 14.7 months) versus PD-L1 CSP ≥20 cetuximab + chemotherapy sample (n=110, median survival 11.1 months), the HR was 0.62 (95%CI: 0.46-0.84). The OS rate at 48 months was 28.6% in the PD-L1 CSP ≥20 pembrolizumab + chemotherapy group and 6.6% in the PD-L1 CSP ≥20 cetuximab + chemotherapy group. For the sample with PD-L1 CPS ≥1, the HR was 0.64 (95%CI: 0.53-0.78) when comparing pembrolizumab + chemotherapy (n=242, median survival 13.6 months) to cetuximab + chemotherapy (n=235, median survival 10.6 months). The OS rate at 48 months was 21.8% in the PD-L1 CSP ≥1 pembrolizumab + chemotherapy group and 4.1% in the PD-L1 CSP ≥1 cetuximab + chemotherapy group.

b) Nivolumab

None of the included studies reported results on this outcome for use as a first-line treatment.

c) Combinations of cetuximab, a platinum, and/or 5-fluorouracil

Burtness (2005) performed a trial comparing cisplatin + placebo with cisplatin + cetuximab. The median OS for the control group was 7.9 months and 9.2 months for the experimental group (p=0.21, one-sided log rank). The 1-year survival rates for the control group were 31.7% (95%CI, 19.9-43.4) and for the cetuximab group the survival rates were 38.6% (95%CI, 26.0-51.2%). The 2-year survival rates were 15.8% (95%CI, 6.3-25.3%) for the cetuximab group and 9.4% (95%CI, 1.8-16.9%) for the control group.

Bourhis (2006) reported a median overall survival of 324 days (95%CI: 229-418) for the cisplatin + cetuximab + 5-fluorouracil group, while reporting a median survival of 260 days (95%CI: 238 – not estimable) in the carboplatin + cetuximab + FU group.

Vermorken (2008) compared cetuximab + chemotherapy (cisplatin/carboplatin + 5-fluorouracil) with chemotherapy only. A HR of 0.80 (95%CI: 0.64-0.99, p=0.04) over 24 months was reported, favoring the addition of cetuximab. An HR of 0.69 (95%CI: 0.53-0.91) was reported when comparing cetuximab + cisplatin and 5-fluorouracil to platinum with 5-fluorouracil (n=284). The HR was 0.98 (95%CI: 0.69-1.41) when comparing cetuximab + carboplatin and 5-fluorouracil to platinum with 5-fluorouracil (n=149).

2. Progression-free survival (PFS)

a) Pembrolizumab

In the KEYNOTE-048 trial, Burtness (2019) reported no significant between-group differences in progression-free survival (HR = 0.92, 95%CI: 0.77-1.10, p=0.170).
Harrington (2023) reported a HR of 1.29 (95%CI: 1.09-1.53, Cox regression: treatment as covariate and stratified by ECOG PS, HPV status, PD-L1 status) when comparing pembrolizumab alone to cetuximab + chemotherapy. The PSF rate at 48 months was 5.4% in the pembrolizumab alone group, compared to 1.7% in the cetuximab + chemotherapy group. In the sample with PD-L1 CPS ≥20, the HR of pembrolizumab alone (n=133, median PFS 3.4 months) compared to cetuximab + chemotherapy (n=122, median PFS 5.3 months) was 0.96 (95%CI: 0.74-1.26). At 48 months, the PFS rate was 8.8% in the PD-L1 CPS ≥20 pembrolizumab alone group, compared to 0% in the PD-L1 CPS ≥20 cetuximab + chemotherapy group. In the PD-L1 CPS ≥1 population comparing pembrolizumab alone (n=257, median PFS 3.2 months) to cetuximab + chemotherapy (n=255, median PFS 5.0 months), the HR was 1.14 (95%CI: 0.95-1.37). At 48 months, the PFS rate in the PD-L1 CPS ≥1 pembrolizumab alone group was 6.3%, while this was 1.2% in the PD-L1 CPS ≥1 cetuximab + chemotherapy group.
For pembrolizumab + chemotherapy compared to cetuximab + chemotherapy, Harrington 2023 reported an HR of 0.94 (95%CI: 0.70-1.12, Cox regression: treatment as covariate and stratified by ECOG PS, HPV status, PD-L1 status). The PFS rate at 48 months was 6.7% in the pembrolizumab + chemotherapy group, compared to 0% in the cetuximab + chemotherapy group. In the PD-L1 CSP ≥20 pembrolizumab + chemotherapy sample (n=126, median PFS 5.8 months) versus PD-L1 CSP ≥20 cetuximab + chemotherapy sample (n=110, median PFS 5.3 months), the HR was 0.76 (95%CI: 0.57-1.02). At 48 months, the PFS rate was 11.5% in the PD-L1 CSP ≥20 pembrolizumab + chemotherapy group and 0% in the PD-L1 CSP ≥20 cetuximab + chemotherapy group. For the sample with PD-L1 CPS ≥1, the HR was 0.86 (95%CI: 0.71-1.04) when comparing pembrolizumab + chemotherapy (n=242, median PFS 5.1 months) to cetuximab + chemotherapy (n=235, median PFS 5.0 months). The PFS rate at 48 months was 7.6% in the PD-L1 CSP ≥1 pembrolizumab + chemotherapy group and 0% in the PD-L1 CSP ≥1 cetuximab + chemotherapy group.

b) Nivolumab

None of the included studies reported results on this outcome for use as a first-line treatment.

c) Combinations of cetuximab, a platinum, and/or 5-fluorouracil

Burtness (2005) reported that the median PFS for cisplatin + placebo group was 2.7 months (95%CI, 1.9-3.8 months) and 4.2 months (95%CI, 3.71-5.55 months) for the cisplatin + cetuximab group (p=0.09, one-sided log-rank).

Bourhis (2006) investigated the time to progression. The median time to progression was 183 days (95%CI: 86 - 189) in the cisplatin + cetuximab + FU group, while reporting a median of 151 days (95%CI: 127 - 189) in the carboplatin + cetuximab + FU group.

Vermorken (2008) compared cetuximab + chemotherapy (cisplatin/carboplatin + 5-fluorouracil) with chemotherapy only. A HR of 0.54 (95%CI: 0.43-0.67, p<0.001) over 15 months was reported, favoring the addition of cetuximab. An HR of 0.54 (95%CI: 0.40-0.72) was reported when comparing cetuximab + cisplatin and 5-fluorouracil to platinum with 5-fluorouracil (n=284). The HR was 0.50 (95%CI: 0.35-0.72) when comparing cetuximab + carboplatin and 5-fluorouracil to platinum with 5-fluorouracil (n=149).

3. Quality of life

a) Pembrolizumab

Rischin (2022) reported the quality of life in the KEYNOTE-048 trial using the EQ-5D-3L, the EORTC QLQ-C30, and the EORTC H&N35 instruments. The sample consisted of patients receiving at least 1 dose of the study treatment and who completed at least 1 quality of life assessment. The pembrolizumab group (n=294 to n=191 at week 15) had a mean EORTC QLQ-C30 global health status of 64.66 (SD: 20.55) at week 15, while this was 63.27 (SD: 18.73) for the chemotherapy group (n=280 to n=182 at week 15). The between-group difference of the least square mean from baseline to week 15 was 0.24 (95%CI: -3.34 to 3.82). For the patients with PD-L1 CPS ≥1 in the pembrolizumab group (n=243 to n=166 at week 15) and chemotherapy group (n=225 to n=155 at week 15), the between-group difference of the least square mean from baseline to week 15 was -1.21 (95%CI: -5.07 to 2.65). For the patients with PD-L1 CPS ≥20 in the pembrolizumab group (n=122 to n=93 at week 15) and chemotherapy group (n=225 to n=155 at week 15), the between-group difference of the least square mean from baseline to week 15 was -1.00 (95%CI: -4.25 to 6.26). The pembrolizumab + chemotherapy group (n=270 to n=173 at week 15) had a mean EORTC QLQ-C30 global health status of 64.60 (SD: 21.10) at week 15, while this was 62.59 (SD: 18.80) for the chemotherapy group (n=260 to n=167 at week 15). The between-group difference of the least square mean from baseline to week 15 was 0.40 (95%CI: -3.36 to 4.26). For the patients with PD-L1 CPS ≥1 in the pembrolizumab + chemotherapy group (n=219 to n=149 at week 15) and chemotherapy group (n=209 to n=142 at week 15), the between-group difference of the least square mean from baseline to week 15 was -1.20 (95%CI: -5.38 to 2.98). For the patients with PD-L1 CPS ≥20 in the pembrolizumab + chemotherapy group (n=115 to n=82 at week 15) and chemotherapy group (n=98 to n=155 at week 67), the between-group difference of the least square mean from baseline to week 15 was 0.05 (95%CI: -5.64 to 5.74).

b) Nivolumab

None of the included studies reported results on this outcome for use as a first-line treatment.

c) Combinations of cetuximab, a platinum, and/or 5-fluorouracil

Messía (2010) reported the quality of life in the EXTREME trial. The QLQ-C30 and QLQ-H&N35 instruments were used. No QoL assessments were performed in some of the

participating trial countries. About 80% of the ITT population completed at least one questionnaire, resulting in n=291 participants for the QLQ-C30. Only 44% had an evaluable baseline and post-baseline assessment of the quality of life. The authors concluded that cetuximab can be added without adversely affecting the quality of life.

4. Toxicity

a) Pembrolizumab

Burtness (2019) and Harrington (2023) reported the adverse events in all groups. From the reported data we calculated the relative risk for 'any grade' of adverse events. See Table 3.

Table 3 – Relative risk of adverse events (any grade) calculated from data reported by Burtness (2019) and Harrington (2023).

	Pembrolizumab alone vs. cetuximab + chemotherapy	Pembrolizumab + chemotherapy vs. cetuximab + chemotherapy
Burtness (2019)		
Blood and lymphatic system disorders	0.39 (95%CI: 0.32-0.49)	1.13 (95%CI: 1.02-1.26)
Endocrine disorders	2.83 (95%CI: 1.79-4.46)	2.41 (95%CI: 1.50-3.86
Gastrointestinal disorders	0.68 (95%CI: 0.61-0.76)	0.99 (95%CI: 0.92-1.07)
General disorders and administration site conditions	0.74 (95%CI: 0.65-0.84)	1.03 (95%CI: 0.94-1.14)
Investigations	0.40 (95%CI: 0.34-0.46)	0.62 (95%CI: 0.55-0.69)
Metabolism and nutrition disorders	0.62 (95%CI: 0.53-0.73)	0.92 [0.81-1.05]
Respiratory, thoracic and mediastinal disorders	1.06 (95%CI: 0.88-1.26)	1.07 (95%CI: 0.90-1.29)
Skin and subcutaneous tissue disorders	0.39 (95%CI: 0.33-0.46)	0.43 (95%CI: 0.37-0.51)
Harrington (2023)		
Any treatment-related adverse event	0.60 (95%CI: 0.55-0.66)	1.45 (95%CI: 1.33-1.58)
CI: confidence interval		

b) Nivolumab

None of the included studies reported results on this outcome for use as a first-line treatment.

c) Combinations of cetuximab, a platinum, and/or 5-fluorouracil

Bourhis (2006) compared cetuximab in combination with cisplatin or carboplatin and 5-fluorouracil. The authors reported the most common adverse events (AEs). In the cisplatin group, the most common AEs were nausea (78%), asthenia (74%) and vomiting (74%), leucopenia (63%), acne-like rash (56%), fever (41%) and diarrhea (41%). For the carboplatin group, the most common AEs were asthenia (72%), acne-like rash (56%) nausea (52%), stomatitis (52%), thrombocytopenia (48%), mucositis (44%), rash (40%), leucopenia (32%) and constipation (32%). Common AEs were defined as presented in ≥30% of patients. There was a higher incidence of serious AEs in the cisplatin group compared to the carboplatin group, 67% and 32% respectively.

Bourhis (2006) also reported dose-limiting toxicities (DLTs). For each intervention, they had three groups with different doses of FU: low, middle and high. The low dose showed DLTs in 2 of 6 patients (33%) of the cisplatin patients and in 0 patients of the carboplatin group. At the middle dose, there was 1 patient (17%) with a DLT in the cisplatin group and 0 in the carboplatin group. At the highest dose level of FU, 4 of 12 patients (33%) in the cisplatin group and 2 of 12 (17%) in the carboplatin group experienced a DLT. Both were considered to be within acceptable tolerability limits.

Vermorken (2008) stated that there were no significant difference between-groups in grade 3-4 adverse events (p=0.19). There were cases of sepsis (cetuximab addition: n=9, chemotherapy: n=1, p=0.02), hypomagnesemia (cetuximab addition: n=11, chemotherapy: n=3, p=0.05), skin reactions (cetuximab addition: n=20, chemotherapy: n=1, p<0.001), anorexia (p=0.05, more cases in the cetuximab group). There were no statistically significant differences on the other monitored adverse events.

<u>Second line treatments</u>

1. Overall survival (OS)

a) Pembrolizumab

In the KEYNOTE-040 trial (Cohen, 2019), pembrolizumab was compared with standard of care (investigator's choice: methotrexate, docetaxel, cetuximab) as second-line treatment. In the overall sample OS was HR 0.80 (95%CI 0.65-0.98). In the sample with a PD-L1 CPS ≥1 (n=387), the HR was 0.74 (95%CI:0.58-0.93) favoring pembrolizumab, when compared to standard of care. The tumor proportion score was also used. In the sample with a tumor proportion score ≥ 50%, the group receiving pembrolizumab (n=64) was compared to the group receiving the investigators' choice (n=65. This resulted in an HR of 0.53 (95%CI: 0.35-0.81), favoring pembrolizumab.

b) Nivolumab

The CheckMate 141 trial compared nivolumab with investigator's choice of treatment as second-line treatment. The treatment effect on OS was reported by Ferris (2016). The unstratified HR of nivolumab versus standard therapy was 0.69 (95%CI, 0.53-0.91). In the 2-year update, Ferris (2018) reports an OS with an HR of 0.68 (95%CI, 0.54-0.86) with a minimum follow-up of 24.2 months. At 24 months the survival rate was 19.6% in the nivolumab group, and 6.0% in the investigators' choice group. Median survival was 7.7 months in the nivolumab group and 5.1 months in the investigators' choice group. In PD-L1 expressors (>1%), the HR was 0.55 (95%CI: 0.39-0.78) favoring nivolumab (n=96) when compared to the investigators' choice (n=63). Here, the median survival was 8.2 months in the pembrolizumab group, compared to 4.7 months in the investigators' choice.

c) Combinations of cetuximab, a platinum, and/or 5-fluorouracil

None of the included studies reported results on this outcome for use as a second-line treatment.

2. Progression-free survival (PFS)

a) Pembrolizumab

The KEYNOTE-040 trial (Cohen, 2019) shows a PFS with an HR of 0.96 (95%CI, 0.79-1.16) in the total intention-to-treat population. In the sample with a PD-L1 CPS ≥1 (n=387), the HR was 1.01 (95%CI: 0.81-1.26) when compared to standard of care. Here, the median PFS was 3.6 months in the pembrolizumab group, and 4.8 months in the investigators' choice group.

b) Nivolumab

The CheckMate 141 trial shows a treatment effect on PFS with a HR of 0.89 (95%CI, 0.70-1.13) as reported by Ferris (2016). With longer follow-up, the reported HR was 0.87 (95%FI, 0.68-1.11) (Ferris, 2018). In PD-L1 expressors (≥1%), the patients in the nivolumab group (n=96) had a median PFS of 2.1 months, where the median PFS was 2.0 months in the investigators' choice group (n=63). The HR was 0.59 (95%CI: 0.41-0.84).

c) *Combinations of cetuximab, a platinum, and/or 5-fluorouracil*

None of the included studies reported results on this outcome for use as a second-line treatment.

3. Quality of life

a) Pembrolizumab

Harrington (2021) reported the quality of life in the KEYNOTE-040 trial using the EQ-5D, EORTC QLQ-C30, and the EORTC H&N35 instruments. The number of participants declined over time (baseline: n=469, week 15: n=201). Time to deterioration on QLQ-C30 was a median of 4.8 months in the pembrolizumab group and 2.8 months in the investigators' choice group. Here, a HR of 0.79 (95%CI: 0.59-1.05) was reported, favoring pembrolizumab. The authors stated that patients receiving pembrolizumab had a stable functioning and symptoms with no notable differences from the investigators' choice group at week 15. According to the authors, there was no evidence of a differential quality of life benefit according to the PD-L1 status (i.e. both CPS and TPS).

b) Nivolumab

Ferris (2016) reported patient-reported quality of life assessed by the QLQ-C30, QLQ-H&N35, and EQ-5D-3L in the CheckMate 141 trial. The authors state that patients in the nivolumab group reported stable measures or slight improvements of QoL compared to the standard therapy group which reported worsening of physical, role, and social functioning as well as pain, sensory problems and social-contact problems. However, interpretation might be difficult because the number of patients on the study declined over the weeks (e.g. 54.6% and 47.1% were on the study at week 9 in the intervention and control group, respectively), there was a variable completion-rate of the questionnaires at the time-points, and within-group changes from baseline were reported. Between-group differences from baseline to week 9 and 15 were statistically tested on six subscales across instruments. At week 15, patients on nivolumab had no clinically relevant improvement or decline from baseline on the physical functioning, role functioning, social functioning, pain, sensory problems, and social-contact problems subscales. Here, patients receiving the standard therapy had a clinically relevant decline from baseline on all of these subscales but on pain, where there was a non-clinically relevant decline from baseline. All changes from baseline on these six subscales were statistically significant different between the groups at week 15 (p-values ranged from $p<0.001$ to $p=0.02$).

Harrington (2017) described the health-related quality of life in the Checkmate 141 trial. The QLQ-C30, QLQ-H&N35, and EQ-5D-3L instruments were used. Completion rates declined over time. From n=361 patients, only n=129 completed any of the instruments on baseline and at least one other moment. The authors state that nivolumab stabilized symptoms and functioning from baseline to weeks 9 (n≈83-86 [nivolumab group], n≈29-30 [investigators' choice group]), and 15 (n≈43-44 [nivolumab group], n≈13-14 [investigators' choice group]).

Furthermore, the authors state that patients benefitted from nivolumab regardless of the PD-L1 status.

c) *Combinations of cetuximab, a platinum, and/or 5-fluorouracil*

None of the included studies reported results on this outcome for use as a second-line treatment.

4. Toxicity

a) Pembrolizumab

Cohen (2019) reported treatment-related adverse events in the as-treated population. From the reported data we calculated relative risks and risk differences. See Table 4.

Table 4 – Relative risks and risk differences for treatment-related adverse events (any grade) from the as-treated data reported by Cohen (2019).

	Pembrolizumab group vs. standard care group	
	Relative risk	Risk difference
Any event	0.75 (95%CI: 0.67-0.84)	-0.21 (95%CI: -0.28 to -0.13)
Event leading to discontinuation of treatment	1.19 (95%CI: 0.57-2.49)	0.01 (95%CI: -0.03 to 0.05)
Event leading to death	1.90 (95%CI: 0.35-10.29)	0.01 (95%CI: -0.01 to 0.03)

b) Nivolumab

Ferris (2016) reported treatment-related adverse events. From the reported data, the following relative risk was calculated for 'any event' (nivolumab [n=236] vs. standard therapy [n=111]): 0.76 (95%CI: 0.66-0.88). At follow-up (Ferris, 2018), the relative risk was 0.78 (95%CI: 0.68-0.90) as calculated from the reported data from all treated patients (not intention to treat). This corresponded to a RD of -0.17 (95%CI: -0.27 to -0.08).

c) *Combinations of cetuximab, a platinum, and/or 5-fluorouracil*

None of the included studies reported results on this outcome for use as a second-line treatment.

Summary of Findings

First line treatments

Outcome	**Study results and measurements**	**Absolute effect estimates**	**Certainty of the Evidence** (Quality of evidence)	**Conclusions**
Pembrolizumab alone (overall)				
Overall survival	HR 0.80 (95%CI: 0.68-0.96) at a median follow-up of 45 months At 48 months, the survival rate in the pembrolizumab alone group was	-	**Low GRADE** Due to risk of bias[1]; due to imprecision[2,a,b]	Pembrolizumab alone may not have a clinically relevant effect on the overall survival compared to cetuximab combined with chemotherapy (platinum + 5-fluorouracil) in an overall R/M HNSCC population. It was also observed that <20% of patients in the intervention

	15.4%, while this rate was 6.6% in the cetuximab + chemotherapy group From 1 study (n=601)			group were alive at 48 months. *(Harrington, 2023)*
Progression-free survival	HR 1.29 (95%CI: 1.09-1.53) at a median follow-up of 45 months At 48 months, the PFS rate in the pembrolizumab alone group was 5.4%, while this rate was 1.7% in the cetuximab + chemotherapy group From 1 study (n=601)	-	**Low GRADE** Due to risk of bias[1]; due to imprecision[2,a,b]	Pembrolizumab alone may not have a clinically relevant effect on the progression-free survival compared to cetuximab combined with chemotherapy (platinum + 5-fluorouracil) in an overall R/M HNSCC population. *(Harrington, 2023)*
Quality of life	The between-group difference of the least square mean from baseline to week 15 was 0.24 (95%CI: -3.34 to 3.82). From 1 study (n=462 [week 15])	-	**Low GRADE** Due to risk of bias[1,3,a,b]	Pembrolizumab alone may not result in clinically relevant difference in quality of life compared to cetuximab combined with chemotherapy (platinum + 5-fluorouracil) in an overall R/M HNSCC population *(Rischin, 2022)*
Toxicity	RR 0.60 (95%CI: 0.55-0.66) for any treatment-related adverse event of any grade From 1 study (n= 601)	**371 fewer per 1000** (from 417 fewer to 315 fewer)	**Very low GRADE** Due to risk of bias[1,3,a,b]	Pembrolizumab alone may result in clinically relevant less treatment-related adverse events compared to cetuximab combined with chemotherapy (platinum + 5-fluorouracil) in an overall R/M HNSCC population. *(Harrington, 2023)*
Pembrolizumab alone (PD-L1 CPS ≥20)*				
Overall survival	HR 0.61 (95%CI: 0.46-0.81) At 48 months, the survival rate in the pembrolizumab alone group was 21.6%, while this rate was 8% in the cetuximab + chemotherapy group From 1 study (n=255)	-	**Low GRADE** Due to risk of bias[1]; due to imprecision[4,a,b]	Pembrolizumab alone may increase the overall survival compared to cetuximab combined with chemotherapy (platinum + 5-fluorouracil) in an PD-L1 CPS ≥20 R/M HNSCC population. In the intervention group, it was also observed that >20% of the patients were alive after 48 months and >10% difference over the control group. *(Harrington, 2023)*

Progression-free survival	HR 0.96 (95%CI: 0.74-1.26) At 48 months, the PFS rate in the pembrolizumab alone group was 8.8%, while this rate was 0% in the cetuximab + chemotherapy group From 1 study (n=255)	-	**Low GRADE** Due to risk of bias[1]; due to imprecision[4,a,b]	Pembrolizumab alone result in no clinically relevant effect on progression-free survival compared to cetuximab combined with chemotherapy (platinum + 5-fluorouracil) in an PD-L1 CPS ≥20 R/M HNSCC population. *(Harrington, 2023)*
Quality of life	The between-group difference of the least square mean from baseline to week 15 was -1.00 (95%CI: -4.25 to 6.26). From 1 study (n=248 [week 15])	-	**Very low GRADE** Due to risk of bias[1,3]; due to imprecision[4,a,b]	The evidence is uncertain about the effect of pembrolizumab alone on quality of life compared to cetuximab combined with chemotherapy (platinum + 5-fluorouracil) in an PD-L1 CPS ≥20 R/M HNSCC population *(Rischin, 2022)*
Toxicity	-	-	**No GRADE** (none of the included studies described results of toxicity of this first-line agent in patients with PD-L1 CPS ≥20 RM/HNSCC in a randomized fashion)	-
Pembrolizumab alone (PD-L1 CPS ≥1)*				
Overall survival	HR 0.61 (95%CI: 0.46-0.81) At 48 months, the survival rate in the pembrolizumab alone group was 16.7%, while this rate was 5.9% in the cetuximab + chemotherapy group From 1 study (n=512)	-	**Low GRADE** Due to risk of bias[1]; due to imprecision[4,a,b]	Pembrolizumab alone may increase the overall survival compared to cetuximab combined with chemotherapy (platinum + 5-fluorouracil) in an PD-L1 CPS ≥1 R/M HNSCC population. Although the HR point estimate indicates a relevant difference, it was also observed that <20% of patients in the intervention group were alive at 48 months, although a >10% difference over the control group. *(Harrington, 2023)*
Progression-free survival	HR 0.96 (95%CI: 0.74-1.26) At 48 months, the PFS rate in the pembrolizumab alone group was 8.8%, while this rate was 0% in the cetuximab + chemotherapy group	-	**Low GRADE** Due to risk of bias[1]; due to imprecision[4,a,b]	Pembrolizumab alone may not result in a clinically relevant effect on progression-free survival compared to cetuximab combined with chemotherapy (platinum + 5-fluorouracil) in an PD-L1 CPS ≥1 R/M HNSCC population. *(Harrington, 2023)*

	From 1 study (n=512)			
Quality of life	The between-group difference of the least square mean from baseline to week 15 was -1.21 (95%CI: -5.07 to 2.65). From 1 study (n=321 [week 15])	-	**Very low GRADE** Due to risk of bias[1,3]; due to imprecision[4,a,b]	The evidence is uncertain about the effect of pembrolizumab alone on quality of life compared to cetuximab combined with chemotherapy (platinum + 5-fluorouracil) in an PD-L1 CPS ≥1 R/M HNSCC population *(Rischin, 2022)*
Toxicity	-	-	**No GRADE** (none of the included studies described results of toxicity of this first-line combination treatment in patients with PD-L1 CPS ≥1 RM/HNSCC in a randomized fashion)	-
Pembrolizumab + platinum + 5-fluorouracil (overall)				
Overall survival	HR 0.70 (95%CI: 0.59-0.84) at a median follow-up of 45 months At 48 months, the survival rate in the pembrolizumab + chemotherapy group was 19.4%, while this rate was 4.5% in the cetuximab + chemotherapy group From 1 study (n=559)	-	**Low GRADE** Due to risk of bias[1]; due to imprecision[2,a,b]	Pembrolizumab with chemotherapy may not have a clinically relevant effect on the overall survival compared to cetuximab combined with chemotherapy (platinum + 5-fluorouracil) in an overall R/M HNSCC population. It was also observed that <20% of patients in the intervention group were alive at 48 months, although >10% difference over the control group. *(Harrington, 2023)*
Progression-free survival	HR 0.94 (95%CI: 0.70-1.12) at a median follow-up of 45 months At 48 months, the PFS rate in the pembrolizumab + chemotherapy group was 6.7%, while this rate was 0% in the cetuximab + chemotherapy group From 1 study (n=559)	-	**Low GRADE** Due to risk of bias[1]; due to imprecision[2,a,b]	Pembrolizumab with chemotherapy may not have a clinically relevant effect on the progression-free survival compared to cetuximab combined with chemotherapy (platinum + 5-fluorouracil) in an overall R/M HNSCC population. *(Harrington, 2023)*
Quality of life	The between-group difference of the least square mean from baseline to week 15 was 0.40	-	**Very low GRADE** Due to risk of bias[1,3]; due to imprecision[4,a,b]	The evidence is uncertain about the effect of pembrolizumab with chemotherapy on quality of life compared to cetuximab

	(95%CI: -3.36 to 4.26). From 1 study (n=340 [week 15])			combined with chemotherapy (platinum + 5-fluorouracil) in an overall R/M HNSCC population *(Rischin, 2022)*
Toxicity	RR 0.99 (95%CI: 0.69-1.02) for any treatment-related adverse event of any grade From 1 study (n= 559)	**10 fewer per 100** (from 39 fewer to 19 more)	**Very low GRADE** Due to risk of bias[1,3]; due to imprecision[2,a,b]	The evidence is uncertain about the effect of pembrolizumab with chemotherapy on toxicity compared to cetuximab combined with chemotherapy (platinum + 5-fluorouracil) in an overall R/M HNSCC population *(Harrington, 2023)*
Pembrolizumab + platinum + 5-fluorouracil (PD-L1 CPS ≥20)*				
Overall survival	HR 0.62 (95%CI: 0.46-0.84) At 48 months, the survival rate in the pembrolizumab + chemotherapy group was 28.6%, while this rate was 6.6% in the cetuximab + chemotherapy group From 1 study (n=236)	-	**Low GRADE** Due to risk of bias[1]; due to imprecision[4,a,b]	Pembrolizumab with chemotherapy may increase the overall survival compared to cetuximab combined with chemotherapy (platinum + 5-fluorouracil) in an PD-L1 CPS ≥20 R/M HNSCC population. In the intervention group, it was also observed that >20% of the patients were alive after 48 months and >10% difference over the control group. *(Harrington, 2023)*
Progression-free survival	HR 0.76 (95%CI: 0.57-1.02) at a median follow-up of 45 months At 48 months, the PFS rate in the pembrolizumab + chemotherapy group was 11.5%, while this rate was 0% in the cetuximab + chemotherapy group From 1 study (n=236)	-	**Low GRADE** Due to risk of bias[1]; due to imprecision[4,a,b]	Pembrolizumab with chemotherapy may not have a clinically relevant effect on the progression-free survival compared to cetuximab combined with chemotherapy (platinum + 5-fluorouracil) in an PD-L1 CPS ≥20 R/M HNSCC population. *(Harrington, 2023)*
Quality of life	The between-group difference of the least square mean from baseline to week 15 was 0.05 (95%CI: -5.64 to 5.74). From 1 study (n=149 [week 15])	-	**Very low GRADE** Due to risk of bias[1,3]; due to imprecision[4,a,b]	The evidence is uncertain about the effect of pembrolizumab with chemotherapy on quality of life compared to cetuximab combined with chemotherapy (platinum + 5-fluorouracil) in an PD-L1 CPS ≥20 R/M HNSCC population *(Rischin, 2022)*

Toxicity	-	-	**No GRADE** (none of the included studies described results of toxicity of this first-line combination treatment in patients with PD-L1 CPS ≥20 RM/HNSCC in a randomized fashion)	-
Pembrolizumab + platinum + 5-fluorouracil (PD-L1 CPS ≥1)*				
Overall survival	HR 0.64 (95%CI: 0.46-0.84) At 48 months, the survival rate in the pembrolizumab + chemotherapy group was 21.8%, while this rate was 4.1% in the cetuximab + chemotherapy group From 1 study (n=477)	-	**Low GRADE** Due to risk of bias[1]; due to imprecision[2,a,b]	Pembrolizumab with chemotherapy may increase the overall survival compared to cetuximab combined with chemotherapy (platinum + 5-fluorouracil) in an PD-L1 CPS ≥1 R/M HNSCC population. In the intervention group, it was also observed that >20% of the patients were alive after 48 months and >10% difference over the control group. *(Harrington, 2023)*
Progression-free survival	HR 0.86 (95%CI: 0.71-1.04) at a median follow-up of 45 months At 48 months, the PFS rate in the pembrolizumab + chemotherapy group was 7.6%, while this rate was 0% in the cetuximab + chemotherapy group From 1 study (n=477)	-	**Low GRADE** Due to risk of bias[1]; due to imprecision[2,a,b]	Pembrolizumab with chemotherapy may not have a clinically relevant effect on the progression-free survival compared to cetuximab combined with chemotherapy (platinum + 5-fluorouracil) in an PD-L1 CPS ≥1 R/M HNSCC population. *(Harrington, 2023)*
Quality of life	The between-group difference of the least square mean from baseline to week 15 was -1.20 (95%CI: -5.38 to 2.98). From 1 study (n=291 [week 15])	-	**Very low GRADE** Due to risk of bias[1,3]; due to imprecision[4,a,b]	The evidence is uncertain about the effect of pembrolizumab with chemotherapy on quality of life compared to cetuximab combined with chemotherapy (platinum + 5-fluorouracil) in an PD-L1 CPS ≥1 R/M HNSCC population *(Rischin, 2022)*
Toxicity	-	-	**No GRADE** (none of the included studies described results of toxicity of this first-line combination treatment in patients with PD-L1 CPS ≥1 RM/HNSCC in a randomized fashion)	-
Nivolumab				
Overall survival	-	-	**No GRADE**	-

			(none of the included studies described results of nivolumab as a first-line agent in patients with RM/HNSCC in a randomized fashion)	
Progression-free survival	-	-	**No GRADE** (none of the included studies described results of nivolumab as a first-line agent in patients with RM/HNSCC in a randomized fashion)	-
Quality of life	-	-	**No GRADE** (none of the included studies described results of nivolumab as a first-line agent in patients with RM/HNSCC in a randomized fashion)	-
Toxicity	-	-	**No GRADE** (none of the included studies described results of nivolumab as a first-line agent in patients with RM/HNSCC in a randomized fashion)	-
Cetuximab with cisplatin				
Overall survival	The 2-year survival rate for the cetuximab + cisplatin group was 15.8% (95%CI: 6.3-25.3), while this was 9.4% (95%CI: 1.8-16.9) for the cisplatin +placebo group. The median survival was 9.2 months for the cetuximab + cisplatin only group, compared to 7.9 months in the cisplatin + placebo group (p=0.21). From 1 study (n=117)	-	**Low GRADE** Due to very serious imprecision[5,a,b]	Cetuximab with cisplatin may have no clinically relevant effect on overall survival compared to cisplatin with a placebo in the R/M HNSCC population. *(Burtness, 2005)*
Progression-free survival	The median PFS for the cetuximab + cisplatin group was 4.2 (95%CI: 3.7-5.6) months, compared to 2.7 (95%CI: 1.9-3.8) months in the cisplatin + placebo group (p=0.08) From 1 study (n=117)	-	**Low GRADE** Due to very serious imprecision[5,a,b]	Cetuximab with cisplatin may have no clinically relevant effect on overall survival compared to cisplatin with a placebo in the R/M HNSCC population. *(Burtness, 2005)*
Quality of life	-	-	**No GRADE** (none of the included studies described results of quality of life of this first-line combination treatment in patients with RM/HNSCC in a randomized fashion)	-

Toxicity	-	-	**No GRADE** (none of the included studies described results of toxicity of this first-line combination treatment in patients with RM/HNSCC in a randomized fashion)	-
Cetuximab with a platinum and 5-fluorouracil				
Overall survival	HR 0.80 (95%CI: 0.64-0.99), comparing cetuximab + **platinum** with 5-fluorouracil to platinum with 5-fluorouracil. From 1 study (n=442)	-	**Low GRADE** Due to risk of bias[7], due to imprecision[2,a,b]	Cetuximab with platinum and 5-fluorouracil may not have a clinically relevant effect on the overall survival compared to a platinum (cisplatin or carboplatin) with 5-fluorouracil in an overall R/M HNSCC population. *(Vermorken, 2008)*
	HR 0.69 (95%CI: 0.53-0.91) for comparing cetuximab + **cisplatin** and 5-fluorouracil to platinum with 5-fluorouracil From 1 study (n=284)	-	**Low GRADE** Due to risk of bias[7], due to imprecision[4,a,b]	Cetuximab with cisplatin and 5-fluorouracil may have a clinically relevant effect on overall survival compared to platinum (cisplatin or carboplatin) and 5-fluorouracil in the R/M HNSCC population. *(Vermorken, 2008)*
	HR 0.98 (95%CI: 0.69-1.41) for comparing cetuximab + **carboplatin** and 5-fluorouracil to platinum with 5-fluorouracil From 1 study (n=149)	-	**Very low GRADE** Due to risk of bias[7], due to imprecision[5,a,b]	The evidence is very uncertain about the effects of cetuximab with carboplatin and 5-fluorouracil on the overall survival overall survival compared to platinum (cisplatin or carboplatin) and 5-fluorouracil in the R/M HNSCC population. *(Vermorken, 2008)*
	The median survival was 324 days (95%CI: 229-418) in the cetuximab + **cisplatin** and 5-fluorouracil group, while the survival was 260 days (95%CI: 238 – NA) in the cetuximab + **carboplatin** and 5-fluorouracil group From 1 study (n=37)	-	**Very low GRADE** Due to indirectness[6]; due to very serious imprecision[5,a,b]	The evidence is very uncertain about the effects of cisplatin compared to carboplatin, both in combination with cetuximab and 5-fluorouracil on the overall survival in the R/M HNSCC population. *(Bouhris, 2006)*
Progression-free survival	HR 0.54 (95%CI: 0.43-0.67 over 15 months), comparing cetuximab + **platinum** with 5-fluorouracil to platinum with 5-fluorouracil.	-	**Low GRADE** Due to risk of bias[7], due to imprecision[2,a,b]	Cetuximab with platinum and 5-fluorouracil may have a clinically relevant effect on the progression-free survival compared to a platinum (cisplatin or carboplatin) with 5-fluorouracil in an overall R/M HNSCC population.

	From 1 study (n=442)			*(Vermorken, 2008)*
	The median time to progression was 183 days (95%CI: 86-189) in the cetuximab + **cisplatin** and 5-fluorouracil group, while the progression-free survival was 151 days (95%CI: 127-189) in the cetuximab + **carboplatin** and 5-fluorouracil group From 1 study (n=37)	-	**Very low GRADE** Due to indirectness[6]; due to very serious imprecision[5,a,b]	The evidence is very uncertain about the effects of Cetuximab with platinum and 5-fluorouracil, both in combination with cetuximab and 5-fluorouracil on the progression-free survival in the R/M HNSCC population. *(Bouhris, 2006)*
Quality of life	The authors concluded that cetuximab could be added without adversely affecting the quality of life From 1 study (n=291)		**Very low GRADE** Due to risk of bias[7,8], due to imprecision[4,a,b]	The evidence is very uncertain about the effects of cetuximab with platinum and 5-fluorouracil on the quality of life compared to platinum (cisplatin or carboplatin) and 5-fluorouracil in the R/M HNSCC population. *(Messía, 2010)*
Toxicity	RR 1.07 (95%CI 0.96-1.18) for grade 3-4 adverse events. However, there were statistically significant more cases of grade 3-4 sepsis (9 vs. 1, p=0.02), hypomagnesemia (11 vs 3, p=0.05), skin reactions (20 vs 1, p<0.001), anorexia (11 vs. 3, p=0.05) in the cetuximab + **platinum** with 5-fluorouracil group, compared to the platinum with 5-fluorouracil group. From 1 study (n=434)	**53 more per 1000** (from 32 fewer to 137 more)	**Low GRADE** Due to very serious risk of bias[7,8]	Cetuximab with platinum and 5-fluorouracil may not result in a clinically relevant difference in overall grade 3-4 adverse events when compared to a platinum (cisplatin or carboplatin) with 5-fluorouracil in an overall R/M HNSCC population. *(Vermorken, 2008)*
	A higher rate of serious adverse events were reported for the cetuximab + **cisplatin** and 5-fluorouracil group (67%) than for the cetuximab +	-	**Very low GRADE** Due to indirectness[6]; due to very serious imprecision[5,a,b]	The evidence is very uncertain about the effects of cisplatin compared to carboplatin, both in combination with cetuximab and 5-fluorouracil on the toxicity in the R/M HNSCC population. *(Bouhris, 2006)*

	carboplatin and 5-fluorouracil group (32%). From1 study (n=53)			

1: Risk of bias: In the KEYNOTE-048 trial, the funder participated in the study design, data collection, data analysis, data interpretation, and writing of the report. Depending on the publication: Authors report one or multiple ties with the funder (honoraria, consulting or advisory roles, leadership, research funding, travel/accomodations, expenses, speaker's bureau, stock and other ownership). Some authors are employees of the study sponsor.
2: Imprecision: the 95%CI crosses one of the predefined borders of clinically relevant differences for decision-making.
3: Risk of bias: lack of blinding
4: Imprecision: the 95%CI crosses one of the predefined borders of clinically relevant differences for decision-making and/or there is a low number of participants in each group.
5: Imprecision: very low number of participants in each trial arm
6: Indirectness: Patients were selected during the study. The study consisted of two phases: only those patients having benefit from the treatment (regression or stable) remained in the study for part two, where they received the combination therapy of interest.
7: Risk of bias: The EXTREME trial was sponsored by a pharmaceutical company, which also performed the statistical analyses (Vermorken, 2008). Depending on the publication: Most authors report serving on paid advisory boards, receiving grant support from the study sponsor (unclear whether this concerned restricted or unrestricted grants) and/or receiving lecture fees from the study sponsor. Some authors were (ex)employees of the study sponsor.
8: Risk of bias: unclear whether there was (adequate) blinding
a: Heterogeneity could not be assessed
b: Publication bias could not be assessed
*: In this study, the CPS was defined as the number of PD-L1–positive cells (tumor cells, lymphocytes, and macrophages) divided by the total number of tumor cells multiplied by 100.

Second line treatments

Outcome	Study results and measurements	Absolute effect estimates	Certainty of the Evidence (Quality of evidence)	Conclusions
Pembrolizumab				
Overall survival	HR 0.80 (95%CI: 0.65-0.98), comparing pembrolizumab to investigator's choice (methotrexate, docetaxel, or cetuximab) From 1 study (n=495)	-	**Low GRADE** Due to risk of bias[1]; due to imprecision[2,a,b]	Pembrolizumab alone may not have a clinically relevant effect on the overall survival compared to the investigator's choice of therapy (methotrexate, docetaxel, or cetuximab) in an overall R/M HNSCC population. *(Cohen, 2019)*
Progression-free survival	HR 0.96 (95%CI: 0.79-1.16), comparing pembrolizumab to investigator's choice (methotrexate, docetaxel, or cetuximab) From 1 study (n=495)	-	**Low GRADE** Due to risk of bias[1]; due to imprecision[2,a,b]	Pembrolizumab alone may not have a clinically relevant effect on the pregression-free survival compared to the investigator's choice of therapy (methotrexate, docetaxel, or cetuximab) in an overall R/M HNSCC population. *(Cohen, 2019)*
Quality of life	HR 0.79 (95%CI: 0.59-1.05) for time to deterioration, comparing pembrolizumab to investigator's	-	**Very low GRADE** Due to risk of bias[1,3]; due to imprecision[2,a,b]	The evidence is very uncertain about the effects of pembrolizumab compared to the investigators' choice of therapy (methotrexate, docetaxel, or cetuximab) on

	choice (methotrexate, docetaxel, or cetuximab). The authors stated that patients receiving pembrolizumab had a stable functioning and symptoms with no notable differences from the investigators' choice group at week 15. From 1 study (n=201 [week 15])			the quality of life in the R/M HNSCC population. *(Harrington 2021)*
Toxicity	RR 0.75 (95%CI: 0.67-0.84) / RD -0.21 (95%CI: -0.28 to -0.13) for any treatment elated adverse event when comparing pembrolizumab to investigator's choice (methotrexate, docetaxel, or cetuximab) RD 0.01 (95%CI: -0.03 to 0.05) for event leading to discontinuation of treatment. RD 0.01 (95%CI: -0.01 to 0.03) for event leading to death. From 1 study (n=480)	**209 fewer per 1000** (from 276 fewer to 134 fewer)	**Very low GRADE** Due to risk of bias[1,3,4]; due to imprecision[2,a,b]	The evidence is very uncertain about the effects of pembrolizumab compared to the investigators' choice of therapy (methotrexate, docetaxel, or cetuximab) on the toxicity in the R/M HNSCC population. *(Cohen, 2019)*
Pembrolizumab (PD-L1 CPS ≥1)*				
Overall survival	HR 0.74 (95%CI: 0.58-0.93) comparing pembrolizumab to investigator's choice (methotrexate, docetaxel, or cetuximab) From 1 study (n=387)	-	**Low GRADE** Due to risk of bias[1]; due to imprecision[2,a,b]	Pembrolizumab alone may not have a clinically relevant effect on the overall survival compared to the investigator's choice of therapy (methotrexate, docetaxel, or cetuximab) in an PD-L1 CPS ≥1 R/M HNSCC population. *(Cohen, 2019)*
Progression-free survival	HR 1.01 (95%CI: 0.81-1.26), comparing pembrolizumab to investigator's choice (methotrexate,		**Low GRADE** Due to risk of bias[1]; due to imprecision[2,a,b]	Pembrolizumab alone may not have a clinically relevant effect on the progression-free survival compared to the investigator's choice of therapy (methotrexate, docetaxel, or cetuximab) in an

	docetaxel, or cetuximab). The median PFS was 3.6 months in the pembrolizumab group, and 4.8 months in the investigators' choice group From 1 study (n=387)			PD-L1 CPS ≥1 R/M HNSCC population. *(Cohen, 2019)*
Quality of life	The authors stated there was no evidence of a differential quality of life benefit according to the PD-L1 status (CPS ≥1) From 1 study (n=164 [week 15])		**Very low GRADE** Due to risk of bias[1,3]; due to imprecision[5,a,b]	The evidence is very uncertain about the effects of pembrolizumab compared to the investigators' choice of therapy (methotrexate, docetaxel, or cetuximab) on the quality of life in an PD-L1 CPS ≥1 R/M HNSCC population. *(Harrington 2021)*
Toxicity	-	-	**No GRADE** (none of the included studies described results of toxicity of this second-line agent in patients with PD-L1 CPS ≥1 RM/HNSCC in a randomized fashion)	-
Pembrolizumab (PD-L1 TPS ≥50%)*				
Overall survival	HR 0.53 (95%CI: 0.35-0.81) comparing pembrolizumab to investigator's choice (methotrexate, docetaxel, or cetuximab) From 1 study (n=129)	-	**Very low GRADE** Due to risk of bias[1]; due to imprecision[5,a,b]	The evidence is very uncertain about the effects of pembrolizumab compared to the investigators' choice of therapy (methotrexate, docetaxel, or cetuximab) on the toxicity in the R/M HNSCC population with PD-L1 TPS ≥50%. *(Cohen, 2019)*
Progression-free survival	-	-	**No GRADE** (none of the included studies described results of progression-free survival of this second-line agent in patients with PD-L1 TPS ≥50 RM/HNSCC in a randomized fashion)	-
Quality of life	The authors stated there was no evidence of a differential quality of life benefit according to the PD-L1 status (TPS ≥50%) From 1 study (n=54 [week 15])	-	**Very low GRADE** Due to risk of bias[1,3]; due to imprecision[5,a,b]	The evidence is very uncertain about the effects of pembrolizumab compared to the investigators' choice of therapy (methotrexate, docetaxel, or cetuximab) on the quality of life in an PD-L1 TPS ≥50% R/M HNSCC population. *(Harrington 2021)*
Toxicity	-	-	**No GRADE** (none of the included studies described results of toxicity of this second-line agent in patients	-

			with PD-L1 TPS ≥50 RM/HNSCC in a randomized fashion)	
Nivolumab				
Overall survival	HR 0.68 (95%CI: 0.54-0.86), comparing nivolumab to investigator's choice (methotrexate, docetaxel, or cetuximab. At 24 months the survival rate in the nivolumab group was 19.6%, and 6% in the investigators' choice group. From 1 study (n=361)	-	**Low GRADE** Due to risk of bias[6]; due to imprecision[2,a,b]	Nivolumab alone may have a clinically relevant effect on the overall survival compared to the investigators' choice of therapy (methotrexate, docetaxel, or cetuximab) in the R/M HNSCC population. *(Ferris, 2018)*
Progression-free survival	HR 0.87 (95%CI: 0.68-1.11), comparing nivolumab to investigator's choice (methotrexate, docetaxel, or cetuximab) From 1 study (n=361)	-	**Low GRADE** Due to risk of bias[6]; due to imprecision[2,a,b]	Nivolumab alone may not have a clinically relevant effect on the progression-free survival compared to the investigators' choice of therapy (methotrexate, docetaxel, or cetuximab) in the R/M HNSCC population. *(Ferris, 2018)*
Quality of life	The authors state that nivolumab stabilized symptoms and functioning from baseline to week 15. From 1 study (2 publications, n=58 [week 15])	-	**Very low GRADE** Due to risk of bias[3,6]; due to imprecision[5,a,b]	The evidence is very uncertain about the effects of Nivolumab compared to the investigators' choice of therapy (methotrexate, docetaxel, or cetuximab) on the quality of life in the HNSCC population. *(Ferris, 2016; Harrington 2017)*
Toxicity	RR 0.78 (95%CI: 0.68-0.90) for any adverse event when comparing nivolumab to investigator's choice (methotrexate, docetaxel, or cetuximab) From 1 study (n=347)	**174 fewer per 1000** (from 254 fewer to 79 fewer)	**Very low GRADE** Due to risk of bias[3,6,7]; due to imprecision[2,a,b]	The evidence is very uncertain about the effects of nivolumab alone compared to the investigators' choice of therapy (methotrexate, docetaxel, or cetuximab) on the toxicity in the R/M HNSCC population. *(Ferris, 2018)*
Nivolumab (PD-L1 membrane expression ≥1)***				
Overall survival	HR 0.55 (95%CI: 0.39-0.78) when comparing nivolumab to	-	**Very low GRADE** Due to risk of bias[6]; due to imprecision[5,a,b]	The evidence is very uncertain about the effects of nivolumab alone compared to the investigators' choice of

	investigator's choice (methotrexate, docetaxel, or cetuximab) From 1 study (n=159)			therapy (methotrexate, docetaxel, or cetuximab) on the overall survival in an PD-L1 CPS ≥1 R/M HNSCC population. *(Ferris, 2018)*
Progression-free survival	HR 0.59 when comparing nivolumab to investigator's choice (methotrexate, docetaxel, or cetuximab) From 1 study (n=159)		**Very low GRADE** Due to risk of bias[6]; due to imprecision[5,a,b]	The evidence is very uncertain about the effects of nivolumab alone compared to the investigators' choice of therapy (methotrexate, docetaxel, or cetuximab) on the progression-free survival in an PD-L1 CPS ≥1 R/M HNSCC population. *(Ferris, 2018)*
Quality of life	The authors state that nivolumab stabilized symptoms and functioning from baseline to week 15, regardless of PD-L1 status. From 1 study (2 publications, n=53 [baseline])	-	**Very low GRADE** Due to risk of bias[1,3]; due to imprecision[5,a,b]	The evidence is very uncertain about the effects of Nivolumab compared to the investigators' choice of therapy (methotrexate, docetaxel, or cetuximab) on the quality of life in an PD-L1 CPS ≥1 R/M HNSCC population. *(Ferris, 2016; Harrington 2017)*
Toxicity	-	-	**No GRADE** (none of the included studies described results of toxicity of this second-line agent in patients with PD-L1 CPS ≥1 RM/HNSCC in a randomized fashion)	-
Combinations of cetuximab, a platinum, and/or 5-fluorouracil				
Overall survival	-	-	**No GRADE** (none of the included studies described results of the combination of cetuximab, platinum, and/or 5-fluorouracil as a second-line agent in patients with RM/HNSCC in a randomized fashion)	-
Progression-free survival	-	-	**No GRADE** (none of the included studies described results of the combination of cetuximab, platinum, and/or 5-fluorouracil as a second-line agent in patients with RM/HNSCC in a randomized fashion)	-
Quality of life	-	-	**No GRADE** (none of the included studies described results of the combination of cetuximab, platinum, and/or 5-fluorouracil as a second-line agent in patients with RM/HNSCC in a randomized fashion)	-
Toxicity	-	-	**No GRADE** (none of the included studies described results of the combination of cetuximab, platinum, and/or 5-fluorouracil as a second-line agent in	-

			patients with RM/HNSCC in a randomized fashion)	

1: Risk of bias: The funder of the KEYNOTE-048 trial participated in the study design, data collection, data analysis, data interpretation, and writing of the report. Also note that in the intervention group n=1 (0.4%) discontinued by physician decision, while n=11 (4.4%) discontinued by physician decision. Depending on the publication: Most authors report one or multiple ties with the funder (grant support to the institution for clinical research related to the submitted work, personal fees for consultation or advice or lecturing, travel support for medical meetings, stock options). Some authors are employees of the study sponsor.
2: Imprecision: the 95%CI crosses one of the predefined borders of clinically relevant differences for decision-making.
3: Risk of bias: Lack of blinding.
4: Risk of bias: Analyses from as-treated population, not from the intention to treat population. Overall, n=15 were randomized but did not receive treatment and were excluded from this analysis (n=1 pembrolizumab group, n=14 standard care group). Here, n=10 of the n=14 in the standard care group (about 4%, 10/248) withdrew consent after randomization, but before receiving the assigned treatment. It was unclear whether the groups remained comparable. It does not seem there were prerandomization and/or postrandomization corrections.
5: Imprecision: very low number of participants in each trial arm
6: Risk of bias: The CHECKMATE-141 trial was designed in collaboration with the sponsor.Depending on the publication: Most authors report one or multiple ties with the sponsor (consultancy role, receiving grants [unclear whether restricted or unrestricted], personal fees, honoraria, advisory board fees). Some authors were employees of the sponsor.
7: Risk of bias: Analyses from as-treated population, not from the intention to treat population. Overall, n=14 were randomized but did not receive treatment and were excluded from this analysis (n=4 pembrolizumab group [1.7%], n=10 standard care group [8.3%]). Here, n=6 of the n=10 in the standard care group (about 5%, 6/121) withdrew consent after randomization, but before receiving the assigned treatment. It was unclear whether the groups remained comparable. It does not seem there were prerandomization and/or postrandomization corrections.
a: Heterogeneity could not be assessed
b: Publication bias could not be assessed
*: In this study, the CPS was defined as the number of PD-L1–positive cells (tumor cells, lymphocytes, and macrophages) divided by the total number of tumor cells multiplied by 100.
**: In this study, the tumor proportion score was defined as the percentage of tumor cells with membranous PD-L1 staining.
***: In this study, PD-L1 membrane expression was evaluated using rabbit antihuman PD-L1 antibody.

Kennisvragen

Tijdens de ontwikkeling van deze module is gebleken dat er binnen deze module passend bewijs is voor de onderbouwing van de aanbeveling en dus geen kennisvragen bestaan.

Verkeerslichtanalyse en Implementeren- en Agenderen-tabel

Verkeerslichtanalyse (ten behoeve van commentaar- en autorisatiefase)

Kruis aan		
	ROOD	Sterke aanbeveling tegen, geldend voor de gehele populatie, en waar passend bewijs voor is [1]
X	**ORANJE**	Aanbeveling waar geen passend bewijs is voor gehele populatie • Sterke aanbeveling tegen (geen passend bewijs voor gehele populatie en subpopulaties/ condities) • Conditionele aanbeveling (geen passend bewijs voor gehele populatie, maar wel passend bewijs voor een subgroep/-conditie (overweging))
	GROEN	Sterke aanbeveling voor, geldend voor de gehele populatie, en waar passend bewijs voor is [1,2]

[1] Er kan ook sprake zijn van passend bewijs bij een low of very low GRADE; bijvoorbeeld omdat er overwegingen zijn die zwaarwegend zijn in het aanbevolen beleid.

[2] Deze categorie geldt ook indien er passend bewijs is waaruit blijkt dat er geen voorkeur is voor één van de onderzochte interventies/diagnostiekmethoden/verwijspaden, voorbeeld: twee chirurgische technieken zijn even effectief, hebben vergelijkbare complicatierisico's, keuze is afhankelijk van het besluit dat de chirurg samen met de patiënt maakt.

Implementeren-tabel

De implementatietabel brengt in kaart welke factoren de uitvoering van een aanbeveling bevorderen of belemmeren, en welke aanvullende acties nodig zijn voor succesvolle invoering. De adviseur en (cluster)werkgroep vullen de tabel in op basis van gerichte vragen over het onderliggende probleem, relevante randvoorwaarden en mogelijke knelpunten. Op basis hiervan wordt geconcludeerd of een extra implementatie-impuls wenselijk is.

Implementatietabel

Vraag	***Antwoord:*** *Kruis aan en licht toe/ beschrijf*		***Toelichting keuze:***
I1. Wat was het onderliggende probleem om deze uitgangsvraag uit te werken?		**Ongewenste praktijkvariatie**	
		Nieuwe evidentie	
	x	**Anders**	**Update richtlijn (belangrijk onderwerp binnen de richtlijn)**
I2. Maak een inschatting over hoeveel patiënten het ongeveer gaat waar de aanbeveling betrekking op heeft?	**x**	**< 1000**	
		< 5000	
		5000-40.000	
		> 40.000	
I3. Is de aanbeveling onderdeel van een bredere set interventies of verwant aan andere richtlijnen of modules? Zo ja, hoe verhoudt zij zich daartoe en moet hiermee rekening worden gehouden bij de implementatie, of kan de aanbeveling als losstaand worden beschouwd?		**Ja**	**Richtlijn HH tumoren**
	X	**Nee**	
I4. Belemmeringen en kansen op verschillende niveaus voor landelijke toepassing van de aanbeveling:		**Belemmerende factoren**	**Bevorderende factoren/ kansen**
Richtlijn/ klinisch traject (innovatie)		**nvt**	**nvt**
Zorgverleners (artsen en verpleegkundigen)		**nvt**	**nvt**
Patiënt/ cliënt (naasten)		**nvt**	**nvt**
Sociale context		**nvt**	**nvt**

Organisatorische context		**nvt**	**nvt**
Financiële en juridische context			
I5. A) Welke personen/partijen zijn van belang bij het toepassen van de aanbeveling in de praktijk? (kruis aan) **B) Wat is er nodig van deze personen/partijen om de aanbeveling in de praktijk te kunnen brengen?** *Denk aan aanpassingen in gedrag, werkwijzen, beleid, samenwerking of andere randvoorwaarden.*		**A**	**B**
	x	Patiënt/ cliënt (naaste)	
	x	Professional	
	x	Beroepsvereniging, nl NVMO	
	x	Ziekenhuis (raad van bestuur/UMCNL (voorheen NFU)/NVZ)	
	x	Zorgverzekeraars/ NZa	
	x	Zorginstituut [duiding nodig]	
		Anders	
I6. Binnen welk tijdsbestek moet de aanbeveling zijn geïmplementeerd?	**x**	< 1 jaar	
		binnen 2-3 jaar	
I7. Conclusie: is er extra actie en/of ondersteuning nodig voor implementatie van de aanbeveling? *De reguliere implementatieroutes (publicatie en disseminatie via officiele kanalen, opname in professionele standaarden, scholing en nascholing, gebruik van bestaande ICT systemen, audits en visitaties) van de richtlijnmodule alleen is onvoldoende.*		Ja	
	x	Nee	
I8. Plaatsing op de Landelijke Implementatieagenda Medisch Specialistische zorg is gewenst. *Het gaat om zorg die (grotendeels) wordt uitgevoerd binnen de ziekenhuismuren. Succesvolle implementatie vraagt om actieve betrokkenheid en samenwerking van meerdere relevante partijen binnen de zorgpraktijk.*	**x**	Ja *	
		Nee	

**Deze aanbeveling komt mogelijk in aanmerking voor plaatsing op de Landelijke Implementatieagenda van het programma Zorg Evaluatie & Gepast Gebruik (ZE&GG), waarin alle betrokken partijen in de medisch-specialistische zorg samenwerken aan de implementatie van bewezen beste zorg. De Federatie levert namens het veld goed onderbouwde aanbevelingen aan, die zijn getoetst op de behoefte aan een implementatie-impuls. De onderwerpen op de Implementatieagenda zijn onderdeel van landelijke zorginkoopafspraken tussen zorgverzekeraars en*

zorgaanbieders. Voor de beoordeling van aanbevelingen uit richtlijnen wordt gebruikgemaakt van de implementatietabel. Op basis hiervan kunnen we de andere partijen goed informeren en gezamenlijk besluiten of plaatsing op de Implementatieagenda passend is.

Agenderen-tabel

Kennisvragen zijn vragen over bestaande zorg, die nog onvoldoende zijn onderbouwd met wetenschappelijke literatuur. Het richtlijncluster heeft een belangrijke rol bij het identificeren van kennisvragen bij het ontwikkelen van een richtlijnmodule. De input uit deze Agenderen-tabel wordt gebruikt bij het opstellen van een kennisagenda. Alle geïnventariseerde kennisvragen (vanuit achterban, patiënten en richtlijnen) op het gebied van zorgevaluatie worden beoordeeld door de kennisagenda werkgroep en daarna geprioriteerd door alle relevante partijen tijdens een prioriteringsbijeenkomst. Het is belangrijk om de kennisvraag scherp te formuleren, zodat resultaten van een zorgevaluatie onderzoek daadwerkelijk opgenomen kunnen worden in een richtlijnmodule.

Vraag	***Antwoord*** *Kruis aan*	*Vul in*
A1. Is onderzoek wenselijk om de <u>uitgangsvraag of zoekvraag</u> (met meer/voldoende zekerheid) te kunnen beantwoorden?		Nee. *Tijdens de ontwikkeling van deze module is gebleken dat er volgens het cluster sprake is van passend bewijs voor de uitgangsvraag en zoekvraag.* [Geef toelichting indien gewenst] *Ga verder bij vraag A5.*
		Ja
A2. Wat is de kennisvraag?	Kennis-vraag	[tekst] [a)]
	P	[tekst]
	I	[tekst]
	C	[tekst]
	O	[tekst]
A3. Waarom is dit een belangrijke kennisvraag?	Toelichting	[tekst] [b)]
A4. Welk onderzoeksdesign is passend om deze kennisvraag te beantwoorden?	x	RCT
		Observationeel onderzoek
		Kwaliteitsregistratie
		Anders, namelijk
	Toelichting	[tekst]
A5. Zijn er een andere kennisvragen naar voren gekomen die passen bij het <u>onderwerp van de module</u>, maar niet hetzelfde zijn als de uitgangs- of zoekvraag en waar *geen* passend bewijs voor is? *Bijvoorbeeld:* het onderwerp van de module is 'Behandeling van aandoening X', waarin behandeling A en behandeling B	x	Nee
		Ja

met elkaar worden vergeleken. De voor- en nadelen van behandeling C ten opzichte van A en/of B is dan nog een openstaande kennisvraag als hier geen passend bewijs voor is. Het past wel bij het onderwerp van deze module en de resultaten van zorgevaluatie onderzoek zouden wel in deze module geduid kunnen worden.		
A6. Wat is de kennisvraag?	Kennis-vraag	[tekst] [a)]
	P	[tekst]
	I	[tekst]
	C	[tekst]
	O	[tekst]
A7. Waarom is dit een belangrijke kennisvraag?	Toelichting	[tekst] [b)]
A8. Welk onderzoeksdesign is passend om deze kennisvraag te beantwoorden?		RCT
		Observationeel onderzoek
		Kwaliteitsregistratie
		Anders, namelijk:
	Toelichting	[tekst]

[a)] Formuleer hier de kennisvraag als een onderzoekvraag. Dit kan de zoekvraag zijn, maar kan ook afwijken. Om het juiste onderzoek te doen is het van groot belang dat de kennisvragen scherp geformuleerd worden, in de vorm van een PICO. Uitgangspunt is dat een kennisvraag met één zorgevaluatie onderzoek opgelost kan worden.

[b)] Beschrijf in 2 à 3 zinnen waarom dit een relevante kennisvraag is.

Literatuur

Bourhis J, Rivera F, Mesia R, Awada A, Geoffrois L, Borel C, Humblet Y, Lopez-Pousa A, Hitt R, Vega Villegas ME, Duck L, Rosine D, Amellal N, Schueler A, Harstrick A. Phase I/II study of cetuximab in combination with cisplatin or carboplatin and fluorouracil in patients with recurrent or metastatic squamous cell carcinoma of the head and neck. J Clin Oncol. 2006 Jun 20;24(18):2866-72. doi: 10.1200/JCO.2005.04.3547. Epub 2006 May 22. PMID: 16717293.

Burtness B, Goldwasser MA, Flood W, Mattar B, Forastiere AA; Eastern Cooperative Oncology Group. Phase III randomized trial of cisplatin plus placebo compared with cisplatin plus cetuximab in metastatic/recurrent head and neck cancer: an Eastern Cooperative Oncology Group study. J Clin Oncol. 2005 Dec 1;23(34):8646-54. doi: 10.1200/JCO.2005.02.4646. Erratum in: J Clin Oncol. 2006 Feb 1;24(4):724. PMID: 16314626.

Burtness B, Harrington KJ, Greil R, Soulières D, Tahara M, de Castro G Jr, Psyrri A, Basté N, Neupane P, Bratland Å, Fuereder T, Hughes BGM, Mesía R, Ngamphaiboon N, Rordorf T, Wan Ishak WZ, Hong RL, González Mendoza R, Roy A, Zhang Y, Gumuscu B, Cheng JD, Jin F, Rischin D; KEYNOTE-048 Investigators. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study. Lancet. 2019 Nov 23;394(10212):1915-1928. doi: 10.1016/S0140-6736(19)32591-7. Epub 2019 Nov 1. Erratum in: Lancet. 2020 Jan 25;395(10220):272. doi: 10.1016/S0140-6736(20)30116-1. Erratum in: Lancet. 2020 Feb 22;395(10224):564. doi: 10.1016/S0140-6736(20)30254-3. Erratum in: Lancet. 2021 Jun 12;397(10291):2252. doi: 10.1016/S0140-6736(21)01119-3. PMID: 31679945.

Cohen EEW, Soulières D, Le Tourneau C, Dinis J, Licitra L, Ahn MJ, Soria A, Machiels JP, Mach N, Mehra R, Burtness B, Zhang P, Cheng J, Swaby RF, Harrington KJ; KEYNOTE-040 investigators. Pembrolizumab versus methotrexate, docetaxel, or cetuximab for recurrent or metastatic head-and-neck squamous cell carcinoma (KEYNOTE-040): a randomised, open-label, phase 3 study. Lancet. 2019 Jan 12;393(10167):156-167. doi: 10.1016/S0140-6736(18)31999-8. Epub 2018 Nov 30. Erratum in: Lancet. 2019 Jan 12;393(10167):132. doi: 10.1016/S0140-6736(18)33261-6. PMID: 30509740.

Ferris RL, Blumenschein G Jr, Fayette J, Guigay J, Colevas AD, Licitra L, Harrington K, Kasper S, Vokes EE, Even C, Worden F, Saba NF, Iglesias Docampo LC, Haddad R, Rordorf T, Kiyota N, Tahara M, Monga M, Lynch M, Geese WJ, Kopit J, Shaw JW, Gillison ML. Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck. N Engl J Med. 2016 Nov 10;375(19):1856-1867. doi: 10.1056/NEJMoa1602252. Epub 2016 Oct 8. PMID: 27718784; PMCID: PMC5564292.

Ferris RL, Blumenschein G Jr, Fayette J, Guigay J, Colevas AD, Licitra L, Harrington KJ, Kasper S, Vokes EE, Even C, Worden F, Saba NF, Docampo LCI, Haddad R, Rordorf T, Kiyota N, Tahara M, Lynch M, Jayaprakash V, Li L, Gillison ML. Nivolumab vs investigator's choice in recurrent or metastatic squamous cell carcinoma of the head and neck: 2-year long-term survival update of CheckMate 141 with analyses by tumor PD-L1 expression. Oral Oncol. 2018 Jun;81:45-51. doi: 10.1016/j.oraloncology.2018.04.008. Epub 2018 Apr 17. PMID: 29884413; PMCID: PMC6563923.

Harrington KJ, Burtness B, Greil R, Soulières D, Tahara M, de Castro G Jr, Psyrri A, Brana I, Basté N, Neupane P, Bratland Å, Fuereder T, Hughes BGM, Mesia R, Ngamphaiboon N, Rordorf T, Wan Ishak WZ, Lin J, Gumuscu B, Swaby RF, Rischin D. Pembrolizumab With or Without Chemotherapy in Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma: Updated Results of the Phase III KEYNOTE-048 Study. J Clin Oncol. 2023 Feb 1;41(4):790-802. doi: 10.1200/JCO.21.02508. Epub 2022 Oct 11. PMID: 36219809; PMCID: PMC9902012.

Harrington KJ, Ferris RL, Blumenschein G Jr, Colevas AD, Fayette J, Licitra L, Kasper S, Even C, Vokes EE, Worden F, Saba NF, Kiyota N, Haddad R, Tahara M, Grünwald V, Shaw JW, Monga M, Lynch M, Taylor F, DeRosa M, Morrissey L, Cocks K, Gillison ML, Guigay J. Nivolumab versus standard, single-agent therapy of investigator's choice in recurrent or metastatic squamous cell carcinoma of the head and neck (CheckMate 141): health-related quality-of-life results from a randomised, phase 3 trial. Lancet Oncol. 2017 Aug;18(8):1104-1115. doi: 10.1016/S1470-2045(17)30421-7. Epub 2017 Jun 23. PMID: 28651929; PMCID: PMC6461049.

Harrington KJ, Soulières D, Le Tourneau C, Dinis J, Licitra LF, Ahn MJ, Soria A, Machiels JH, Mach N, Mehra R, Burtness B, Ellison MC, Cheng JD, Chirovsky DR, Swaby RF, Cohen EEW. Quality of Life With Pembrolizumab for Recurrent and/or Metastatic Head and Neck Squamous Cell Carcinoma: KEYNOTE-040. J Natl Cancer Inst. 2021 Feb 1;113(2):171-181. doi: 10.1093/jnci/djaa063. PMID: 32407532; PMCID: PMC7850527.

Lau A, Yang WF, Li KY, Su YX. Systemic Therapy in Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma- A Systematic Review and Meta-Analysis. Crit Rev Oncol Hematol. 2020 Sep;153:102984. doi: 10.1016/j.critrevonc.2020.102984. Epub 2020 May 30. PMID: 32569853.

Li J, Rahman NA, Mohamad S, Yang G, Zhao C. Efficacy of Immune Checkpoint Inhibitors in the Treatment for Head and Neck Cancer Patients: A Systematic Review and Network Meta-Analysis. Oncol Res. 2025 Aug 28;33(9):2263-2278. doi: 10.32604/or.2025.065911. PMID: 40918459; PMCID: PMC12408847.

Mesía R, Rivera F, Kawecki A, Rottey S, Hitt R, Kienzer H, Cupissol D, De Raucourt D, Benasso M, Koralewski P, Delord JP, Bokemeyer C, Curran D, Gross A, Vermorken JB. Quality of life of patients receiving platinum-based chemotherapy plus cetuximab first line for recurrent and/or metastatic squamous cell carcinoma of the head and neck. Ann Oncol. 2010 Oct;21(10):1967-1973. doi: 10.1093/annonc/mdq077. Epub 2010 Mar 24. PMID: 20335368; PMCID: PMC2946862.

Rischin D, Harrington KJ, Greil R, Soulières D, Tahara M, de Castro G Jr, Psyrri A, Braña I, Neupane P, Bratland Å, Fuereder T, Hughes BGM, Mesía R, Ngamphaiboon N, Rordorf T, Ishak WZW, Hong RL, Mendoza RG, Jia L, Chirovsky D, Norquist J, Jin F, Burtness B. Pembrolizumab alone or with chemotherapy for recurrent or metastatic head and neck squamous cell carcinoma: Health-related quality-of-life results from KEYNOTE-048. Oral Oncol. 2022 May;128:105815. doi: 10.1016/j.oraloncology.2022.105815. Epub 2022 Apr 2. PMID: 35381576.

Vermorken JB, Mesia R, Rivera F, Remenar E, Kawecki A, Rottey S, Erfan J, Zabolotnyy D, Kienzer HR, Cupissol D, Peyrade F, Benasso M, Vynnychenko I, De Raucourt D, Bokemeyer C, Schueler A, Amellal N, Hitt R. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med. 2008 Sep 11;359(11):1116-27. doi: 10.1056/NEJMoa0802656. PMID: 18784101.

Zhan ZJ, Yao WY, Zhang F, Qiu WZ, Liao K, Feng JH, Tan JY, Liu H, Yuan TZ, Zheng RH, Yuan YW. The Optimal Second-Line Systemic Treatment Model for Recurrent and/or Metastatic Head and Neck Squamous Cell Carcinoma: A Bayesian Network Meta-Analysis. Front Immunol. 2021 Aug 2;12:719650. doi: 10.3389/fimmu.2021.719650. PMID: 34413862; PMCID: PMC8367750.

Bijlagen bij module Palliatieve systeemtherapie incl. CPS

Risk of Bias tables

Li (2025) used the "Review Manager (RevMan) Version 5.4 The Cochrane Collaboration, 2020, for assessing the risk of bias in randomized trials". All studies were evaluated separately by two investigators. Lau (2020) performed a risk of bias assessment using the Cochrane Collaboration's Tool (Cochrane Handbook version 5.1.0).

Trial	Author	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
As assessed by Li (2025)								
KEYNOTE-048	Harrington (2023)	?	?	?	?	+	+	+
KEYNOTE-040	Cohen (2019)	+	+	?	+	+	+	?
CheckMate-141	Ferris (2018)	?	?	?	?	+	+	+
As assessed by Lau (2020)								
	Bourhis (2006)	?	?	NA	NA	+	+	+
	Burtness (2005)	+	?	NA	NA	+	+	+
KEYNOTE-040	Burtness (2019)	?	?	NA	NA	+	+	+
CheckMate-141	Ferris (2016)	+	?	NA	NA	+	+	?
	Ferris (2018)	+	+	NA	NA	+	+	?
EXTREME	Vermorken (2008)	+	+	NA	NA	+	+	?
NA: Not available +: low risk of bias ?: unclear risk of bias -: high risk of bias								

Table of excluded studies

Systematic review search

Reference	Reason for exclusion
Botticelli A, Cirillo A, Strigari L, Valentini F, Cerbelli B, Scagnoli S, Cerbelli E, Zizzari IG, Rocca CD, D'Amati G, Polimeni A, Nuti M, Merlano MC, Mezi S, Marchetti P. Anti-PD-1 and Anti-PD-L1 in Head and Neck Cancer: A Network Meta-Analysis. Front Immunol. 2021 Aug 9;12:705096. doi: 10.3389/fimmu.2021.705096. PMID: 34434192; PMCID: PMC8380817.	Does not seem to add significant new and/or relevant data compared to Li 2025, Zhan 2021, and Lau 2020 combined
Chen L, He JN, Zhao SJ, Peng LP, Mo DC, Yin SH. Efficacy and safety of PD-1/PD-L1 inhibitors combined with standard of care for locally advanced head and neck squamous cell carcinoma: A meta-analysis of randomized controlled trials. Crit Rev Oncol Hematol. 2025 May;209:104668. doi: 10.1016/j.critrevonc.2025.104668. Epub 2025 Feb 18. PMID: 39978426.	Does not seem to add significant new and/or relevant data compared to Li 2025, Zhan 2021, and Lau 2020 combined
Chen L, Mo DC, Hu M, He W, Yang QW, Tang J. Combination therapy with immune checkpoint inhibitors in recurrent or metastatic squamous cell carcinoma of the head and neck: A meta-analysis. Int Immunopharmacol. 2023 Jun;119:110270. doi: 10.1016/j.intimp.2023.110270. Epub 2023 May 5. PMID: 37150013.	Does not seem to add significant new and/or relevant data compared to Li 2025, Zhan 2021, and Lau 2020 combined
Chen L, Li YC, Hu M, Zhao SJ, Yang QW. Efficacy and safety of weekly versus triweekly cisplatin concurrent with radiotherapy in nasopharyngeal carcinoma: A meta-analysis. Medicine (Baltimore). 2022 Dec 30;101(52):e31842. doi: 10.1097/MD.0000000000031842. PMID: 36596073; PMCID: PMC9803506.	Does not seem to add significant new and/or relevant data compared to Li 2025, Zhan 2021, and Lau 2020 combined
Clarke E, Eriksen JG, Barrett S. The effects of PD-1/PD-L1 checkpoint inhibitors on recurrent/metastatic head and neck squamous cell carcinoma: a critical review of the literature and meta-analysis. Acta Oncol. 2021 Nov;60(11):1534-1542. doi: 10.1080/0284186X.2021.1964699. Epub 2021 Aug 19. PMID: 34410881.	Does not seem to add significant new and/or relevant data compared to Li 2025, Zhan 2021, and Lau 2020 combined
Dang S, Zhang S, Zhao J, Li X, Li W. Efficacy and safety of immune checkpoint inhibitors in recurrent or metastatic head and neck squamous cell carcinoma: A systematic review and meta-analysis of randomized clinical trials. Cancer Med. 2023 Oct;12(20):20277-20286. doi: 10.1002/cam4.6564. Epub 2023 Oct 10. PMID: 37814950; PMCID: PMC10652313.	Does not seem to add significant new and/or relevant data compared to Li 2025, Zhan 2021, and Lau 2020 combined
Han J, Zeng N, Tian K, Liu Z, She L, Wang Z, He J, Chen N. First-line immunotherapy combinations for recurrent or metastatic nasopharyngeal carcinoma: An updated network meta-analysis and cost-effectiveness analysis. Head Neck. 2023	Does not seem to add significant new and/or relevant data compared to Li 2025, Zhan 2021, and Lau 2020 combined

Sep;45(9):2246-2258. doi: 10.1002/hed.27452. Epub 2023 Jul 12. PMID: 37435624.	
Huang Y, Zhou H, Zhao G, Wang M, Luo J, Liu J. Immune Checkpoint Inhibitors Serve as the First-Line Treatment for Advanced Head and Neck Cancer. Laryngoscope. 2024 Feb;134(2):749-761. doi: 10.1002/lary.30971. Epub 2023 Aug 23. PMID: 37610169.	Does not seem to add significant new and/or relevant data compared to Li 2025, Zhan 2021, and Lau 2020 combined
Huang Z, Zheng S, Ding S, Wei Y, Chen C, Liu X, Li H, Xia Y. Prognostic role of programmed cell death ligand-1 expression in head and neck cancer treated with programmed cell death protein-1/programmed cell death ligand-1 inhibitors: A meta-analysis based on clinical trials. J Cancer Res Ther. 2021 Jul;17(3):676-687. doi: 10.4103/jcrt.JCRT_1606_20. PMID: 34269299.	Does not seem to add significant new and/or relevant data compared to Li 2025, Zhan 2021, and Lau 2020 combined
Jiang C, Wang S, Zhu L. Efficacy and safety of immunotherapy for head and neck squamous cell carcinoma: a meta-analysis of randomized clinical trials. Front Oncol. 2025 Jan 9;14:1489451. doi: 10.3389/fonc.2024.1489451. PMID: 39850817; PMCID: PMC11755100.	Does not seem to add significant new and/or relevant data compared to Li 2025, Zhan 2021, and Lau 2020 combined
Jiang M, Li J, Wei J, Yang X, Wang W. Advances in neoantigen-based immunotherapy for head and neck squamous cell carcinoma: a comprehensive review. Front Oncol. 2025 May 15;15:1593048. doi: 10.3389/fonc.2025.1593048. PMID: 40444094; PMCID: PMC12119297.	Wrong study design (narrative review)
Landre T, Des Guetz G, Chouahnia K, Fossey-Diaz V, Culine S. Immune Checkpoint Inhibitors for Patients Aged ≥ 75 Years with Advanced Cancer in First- and Second-Line Settings: A Meta-Analysis. Drugs Aging. 2020 Oct;37(10):747-754. doi: 10.1007/s40266-020-00788-5. PMID: 32681403.	Wrong populations
Meenu M, Dhiman P, Kumar M, Pradhan P, Pandey S. Real-World Evidence on the Effectiveness of Pembrolizumab in Patients With Recurrent/Metastatic/Unresectable Head and Neck Squamous Cell Cancer: A Systematic Review and Meta-Analysis. Cureus. 2025 Jan 1;17(1):e76709. doi: 10.7759/cureus.76709. PMID: 39748883; PMCID: PMC11694497.	Wrong study design (NRTs)
Petrelli F, Ghidini A, Sarno I, Iaculli A, Irene A, Moleri G, Rossitto M, Dottorini L. Adding immune checkpoint inhibitors to chemotherapy in elderly cancer patients: Beneficial for many but not all? Tumori. 2025 Aug;111(4):284-292. doi: 10.1177/03008916251328539. Epub 2025 Jun 6. PMID: 40476645.	Wrong populations
Poulose JV, Kainickal CT. Immune checkpoint inhibitors in head and neck squamous cell carcinoma:	No added value to the selected 3 studies

A systematic review of phase-3 clinical trials. World J Clin Oncol. 2022 May 24;13(5):388-411. doi: 10.5306/wjco.v13.i5.388. PMID: 35662989; PMCID: PMC9153072.	
Puttagunta P, Pamulapati SV, Bates JE, Gross JH, Stokes WA, Schmitt NC, Steuer C, Teng Y, Saba NF. Critical review of the current and future prospects of VEGF-TKIs in the management of squamous cell carcinoma of head and neck. Front Oncol. 2023 Dec 13;13:1310106. doi: 10.3389/fonc.2023.1310106. PMID: 38192624; PMCID: PMC10773827.	Wrong study design (narrarive review)
Wang H, Zhao Q, Zhang Y, Wei J, Wang B, Zheng Z, Liu S, Liu Z, Meng L, Xin Y, Jiang X. Efficacy and safety of systemic treatments for patients with recurrent/metastatic head and neck squamous cell carcinoma: A systematic review and network meta-analysis. Pharmacol Res. 2021 Nov;173:105866. doi: 10.1016/j.phrs.2021.105866. Epub 2021 Aug 30. PMID: 34474103.	Wrong populations
Xu Q, Huang S, Yang K. Combination immunochemotherapy for recurrent or metastatic head and neck squamous cell carcinoma: a systematic review and meta-analysis. BMJ Open. 2023 Jun 13;13(6):e069047. doi: 10.1136/bmjopen-2022-069047. PMID: 37311638; PMCID: PMC10277053.	Does not seem to add significant new and/or relevant data compared to Li 2025, Zhan 2021, and Lau 2020 combined
Yin G, Guo W, Duan H, Huang Z. Role of PD-1/PD-L1 inhibitors in the treatment of recurrent/metastatic head and neck squamous cell carcinoma: A systematic review and meta-analysis. Clin Otolaryngol. 2021 Sep;46(5):1013-1020. doi: 10.1111/coa.13772. Epub 2021 Apr 21. PMID: 33765363.	Does not seem to add significant new and/or relevant data compared to Li 2025, Zhan 2021, and Lau 2020 combined
Zhang J, Mao Y, Zhang Y, Wang X, Yin W, Ding L. Efficacy and safety of PD-1/PD-L1 inhibitors for relapsed/metastatic nasopharyngeal carcinoma: a systematic review and meta-analysis. Lett Drug Des Discov. 2025;22(8):100128. doi:10.1016/j.lddd.2025.100128.	No added value to the selected 3 studies
Zhu Y, Liu K, Ding D, Wang K, Liu X, Tan X. Chemo-Immunotherapy Regimes for Recurrent or Metastatic Nasopharyngeal Carcinoma: A Network Meta-Analysis and Cost-Effectiveness Analysis. Front Pharmacol. 2022 May 20;13:858207. doi: 10.3389/fphar.2022.858207. PMID: 35668931; PMCID: PMC9163401.	No added value to the selected 3 studies
Cao Y, Bai CM. Advances in immunotherapy for head and neck squamous cell carcinoma. Acta Academiae Medicinae Sinicae. 2025;47(5):850–862. doi:10.3881/j.issn.1000-503X.16477.	Article only available in Chinese
Clatot F, Even C, Daste A, Borel C, Fayette J, Chebbah M, Le Clanche S, Saada E. Defining a need for rapid response and practical guidance for recurrent and	Wrong design (Delphi consensus)

metastatic squamous cell carcinoma of the head and neck (R/M SCCHN) management in France: A Delphi consensus. PLoS One. 2025 Sep 19;20(9):e0332413. doi: 10.1371/journal.pone.0332413. Erratum in: PLoS One. 2025 Dec 22;20(12):e0339448. doi: 10.1371/journal.pone.0339448. PMID: 40971372; PMCID: PMC12448362.	
Daloiso A, Franz L, Mondello T, Tisato M, Negrisolo M, Zanatta P, de Filippis C, Astolfi L, Marioni G. Head and Neck Squamous Cell Carcinoma with Distant Metastasis: A Systematic Review and Meta-Analysis. Cancers (Basel). 2024 Nov 20;16(22):3887. doi: 10.3390/cancers16223887. PMID: 39594842; PMCID: PMC11592668.	Wrong PICO (concerns occurrence and patterns of distant metastases in HNSCC)

Quality of life search

Reference	Reason for exclusion
Aggarwal H, Punekar RS, Li L, Carter GC, Walker MS. Quality of life analysis of patients treated with cetuximab or cisplatin for locoregionally advanced squamous cell carcinoma of head and neck in the United States. Health Qual Life Outcomes. 2020 Jun 22;18(1):195. doi: 10.1186/s12955-020-01424-x. PMID: 32571349; PMCID: PMC7310203.	locoregional advanced HNSCC, whether or not with radiotherapy
Eden D, Ghose A, Moschetta M, Pérez-Fidalgo JA, Rassy E, Boussios S. Immunotherapy Combined With Standard Therapies in Head and Neck Squamous Cell Carcinoma - A Meta-analysis. Anticancer Res. 2024 Mar;44(3):861-878. doi: 10.21873/anticanres.16880. PMID: 38423658.	Wrong population, not specific for R/M HNSCC
Ferris RL, Blumenschein G Jr, Fayette J, Guigay J, Colevas AD, Licitra L, Harrington K, Kasper S, Vokes EE, Even C, Worden F, Saba NF, Iglesias Docampo LC, Haddad R, Rordorf T, Kiyota N, Tahara M, Monga M, Lynch M, Geese WJ, Kopit J, Shaw JW, Gillison ML. Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck. N Engl J Med. 2016 Nov 10;375(19):1856-1867. doi: 10.1056/NEJMoa1602252. Epub 2016 Oct 8. PMID: 27718784; PMCID: PMC5564292.	already included
Goerling U, Gauler T, Dietz A, Grünwald V, Knipping S, Guntinas-Lichius O, Frickhofen N, Lindeman HW, Fietkau R, Haxel B, Große-Thie C, Maschmeyer G, Zipfel M, Martus P, Knoedler M, Keilholz U,	comparator added docetaxel

Klinghammer K. Quality of Life of Patients with Head and Neck Cancer Receiving Cetuximab, Fluorouracil, Cisplatin Comparing to Cetuximab, Fluorouracil, Cisplatin, and Docetaxel within the CEFCID Trial. Oncol Res Treat. 2022;45(6):319-325. doi: 10.1159/000521415. Epub 2021 Dec 10. PMID: 34915492.	
Gogate A, Bennett B, Poonja Z, Stewart G, Medina Colmenero A, Szturz P, Carrington C, Castro C, Gemmen E, Lau A, Carral Maseda A, Winquist E, Arrazubi V, Hao D, Cook A, Martinez Galan J, Ugidos L, Fernández Garay D, Gutierrez Abad D, Metcalf R. Phase 4 Multinational Multicenter Retrospective and Prospective Real-World Study of Nivolumab in Recurrent and Metastatic Squamous Cell Carcinoma of the Head and Neck. Cancers (Basel). 2023 Jul 9;15(14):3552. doi: 10.3390/cancers15143552. PMID: 37509217; PMCID: PMC10377225.	Single arm retrospective, real-world data
Kirtane K, Hoogland AI, Li X, Rodriguez Y, Scheel K, Small BJ, Oswald LB, Muzaffar J, Kish JA, Bonomi M, Bhateja P, Saba NF, Steuer CE, Chung CH, Jim HSL. Patient-reported outcomes in immunotherapy for head and neck cancer. Head Neck. 2023 Jul;45(7):1761-1771. doi: 10.1002/hed.27388. Epub 2023 May 4. PMID: 37141438.	Could not obtain this article full-text. However, a systematic review including this study (https://doi.org/10.1016/j.ctrv.2024.102862) reported that this was a cohort study. Therefore, we excluded this study based on study design.
Mohamed A, Salman B, Shaikh AJ. Evaluating the clinical benefit of pembrolizumab as a first-line agent in advanced solid tumors: A comprehensive review. J Oncol Pharm Pract. 2025 Jun;31(4):616-626. doi: 10.1177/10781552241252100. Epub 2024 May 6. PMID: 38710475.	mixed population
Nuñez-Vera V, Garcia-Perla-Garcia A, Gonzalez-Cardero E, Esteban F, Infante-Cossio P. Impact of Treatment on Quality of Life in Oropharyngeal Cancer Survivors: A 3-Year Prospective Study. Cancers (Basel). 2024 Jul 31;16(15):2724. doi: 10.3390/cancers16152724. PMID: 39123452; PMCID: PMC11311390.	after curative chemoradiation
Singh P, Bennett B, Bailey T, Taylor-Stokes G, Rajkovic I, Contente M, Curtis S, Curtis C. Real-world study of the impact of recurrent/metastatic squamous cell	Wrong study design

carcinoma of the head and neck (R/M SCCHN) on quality of life and productivity in Europe. BMC Cancer. 2021 Jul 24;21(1):854. doi: 10.1186/s12885-021-08557-2. PMID: 34303346; PMCID: PMC8310582.	
Winter A, Schulz SM, Schmitter M, Müller-Richter U, Kübler A, Kasper S, Hartmann S. Comprehensive Geriatric Assessment and Quality of Life Aspects in Patients with Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma (HNSCC). J Clin Med. 2023 Sep 3;12(17):5738. doi: 10.3390/jcm12175738. PMID: 37685806; PMCID: PMC10488489.	Wrong study design
Zou Y, Sun Y, Ravva S, Wagner LI, Zhou J. A Model-Based Meta-Analysis of Pembrolizumab Effects on Patient-Reported Quality of Life: Advancing Patient-Centered Oncology Drug Development. CPT Pharmacometrics Syst Pharmacol. 2026 Feb;15(2):e70106. doi: 10.1002/psp4.70106. Epub 2025 Sep 30. PMID: 41026605; PMCID: PMC12896370.	Mixed population

Literature search strategy

Systematic review search

Embase.com

No.	Query	Results
#1	'head and neck cancer'/mj OR 'ear nose throat cancer'/exp/mj OR 'head and neck carcinoma'/mj OR 'carcinoma of the temporal bone'/exp/mj OR 'ear carcinoma'/exp/mj OR 'face carcinoma'/mj OR 'basal cell carcinoma of the face'/mj OR 'lip carcinoma'/exp/mj OR 'squamous cell carcinoma of the face'/mj OR 'head and neck basal cell carcinoma'/exp/mj OR 'head and neck squamous cell carcinoma'/exp/mj OR 'mouth carcinoma'/exp/mj OR 'branchiogenic carcinoma'/mj OR 'nose carcinoma'/exp/mj OR 'salivary gland carcinoma'/exp/mj OR 'tonsil carcinoma'/exp/mj OR 'head and neck metastasis'/exp/mj OR 'head cancer'/mj OR 'face cancer'/mj OR 'lip cancer'/exp/mj OR 'mouth cancer'/exp/mj OR 'nose cancer'/exp/mj OR 'salivary gland cancer'/exp/mj OR 'scalp cancer'/exp/mj OR 'skull cancer'/exp/mj OR 'metastatic head and neck cancer'/exp/mj OR 'neck cancer'/mj OR 'cervical teratoma'/exp/mj OR 'neck carcinoma'/mj OR 'branchiogenic carcinoma'/exp/mj OR 'larynx carcinoma'/exp/mj OR 'neck hemangioma'/exp/mj OR 'neck metastasis'/exp/mj OR 'neck sarcoma'/exp/mj OR 'parathyroid cancer'/exp/mj OR (((adenoma* OR anticarcinogen* OR blastoma* OR cancer* OR carcinogen* OR carcinom* OR chordoma* OR hemangioma* OR malignan* OR meningioma* OR mesenchymoma* OR metasta* OR neoplas* OR	412538

	neuroma* OR oncogen* OR oncolog* OR paraneoplastic OR plasmacytoma* OR precancerous OR scc OR teratocarcinoma* OR teratoma* OR tumor* OR tumour*) NEAR/6 (aryepiglot* OR arytenoid* OR cranial OR cranium OR ear OR ears OR epiglot* OR facial OR gingiva* OR glottic* OR head OR hypopharyn* OR jaw OR jaws OR larynx OR lip OR lips OR mandib* OR mouth OR nasopharyn* OR neck OR nasal OR nose OR oral* OR oropharyn* OR otorhinolaryn* OR palatal* OR palate OR palatum OR paranasal* OR parathyr* OR paroti* OR pharyn* OR 'postcricoid area' OR salivar* OR scalp OR skull OR sublingual* OR submandib* OR throat OR tonsil* OR uadt OR vallecula)):ti,ab,kw) OR hnscc:ti,ab,kw OR 'hn scc':ti,ab,kw OR lascchn:ti,ab,kw OR scchn:ti,ab,kw	
#2	'metastasis'/exp OR 'advanced cancer'/exp OR 'palliative therapy'/exp OR (((neoplas* OR carcinoma OR cancer* OR malignan* OR tumor* OR tumour*) NEAR/4 (dissemination OR disseminated OR spread OR secondary OR migration OR seed*)):ti,ab,kw) OR metasta*:ti,ab,kw OR micrometasta*:ti,ab,kw OR oligometasta*:ti,ab,kw OR ((advanced NEAR/3 (cancer* OR malignan* OR neoplas* OR tumor* OR tumour* OR hnscc OR 'hn scc' OR lascchn OR scchn)):ti,ab,kw) OR palliat*:ti,ab,kw OR unresect*:ti,ab,kw OR 'un resect*':ti,ab,kw OR nonresect*:ti,ab,kw OR 'non resect*':ti,ab,kw OR inoperable:ti,ab,kw	1795205
#3	'systemic therapy'/exp/mj OR 'cancer immunotherapy'/exp/mj OR 'immunological antineoplastic agent'/exp/mj OR 'cancer hormone therapy'/exp/mj OR 'molecularly targeted therapy'/exp/mj OR 'multimodality cancer therapy'/exp/mj OR 'antineoplastic agent'/exp/mj OR (((hormon* OR endocrin* OR 'combined modalit*' OR multimodal* OR 'multiple modalit*' OR target* OR immun* OR systemic*) NEAR/3 (therap* OR treat*)):ti,ab,kw) OR immunotherap*:ti,ab,kw OR immunetherap*:ti,ab,kw OR 'biologic response modifier therapy':ti,ab,kw OR 'biological response modifier therapy':ti,ab,kw OR 'chemoradiotherapy'/exp/mj OR 'chemoradi*':ti,ab,kw OR 'radiochemo*':ti,ab,kw OR 'chemotherapy'/exp/mj OR chemo:ti,ab,kw OR chemotherap*:ti,ab,kw OR chemoimmuno*:ti,ab,kw OR 'cytostatic agent'/exp/mj OR 'cytostatic*':ti,ab,kw OR 'anthracycline antibiotic agent'/exp/mj OR anthracyclin*:ti,ab,kw OR 'alkylating agent'/exp/mj OR alkylat*:ti,ab,kw	3498984
#4	#1 AND #2 AND #3 NOT ('conference abstract'/it OR 'clinical trial':dtype) NOT (('editorial'/it OR 'letter'/it OR 'note'/it) NOT 'evidence based medicine'/exp) NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp) AND [2015-2025]/py	17243
#5	'meta analysis'/exp OR 'systematic review'/exp OR 'scoping review'/exp OR 'rapid review'/exp OR 'umbrella review'/exp OR 'cochrane database of systematic reviews'/jt OR 'network meta-analysis'/exp OR 'networkmeta analy*':ti,ab,kw OR 'networkmetaanaly*':ti,ab,kw OR metaanaly*:ti,ab,kw OR 'meta analy*':ti,ab,kw OR metanaly*:ti,ab,kw OR prisma:ti,ab,kw OR prospero:ti,ab,kw OR metaanali*:ti,ab,kw OR 'meta anali*':ti,ab,kw	1178732

	OR metanali*:ti,ab,kw OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab,kw) OR (((structured OR systemic*) NEAR/3 (review* OR overview* OR synth*) NEAR/3 literature):ti,ab,kw) OR ((systemic* NEAR/1 review*):ti,ab,kw) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab,kw) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab,kw) OR (((literature NEAR/3 (review* OR overview*)):ti,ab,kw) AND (search*:ti,ab,kw OR database*:ti,ab,kw OR 'data base*':ti,ab,kw)) OR (('data extraction*':ti,ab,kw OR 'data source*':ti,ab,kw) AND ('study selection*':ti,ab,kw OR 'studies selection*':ti,ab,kw)) OR ('search strateg*':ti,ab,kw AND 'selection criteria*':ti,ab,kw) OR ('data source*':ti,ab,kw AND 'data synth*':ti,ab,kw) OR medline*:ti,ab,kw OR pubmed*:ti,ab,kw OR 'pub med*':ti,ab,kw OR embase:ti,ab,kw OR cochrane*:ti,ab,kw OR (((critical* OR rapid*) NEAR/2 (review* OR overview* OR synth*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synth*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynth*:ti,ab,kw OR 'meta synth*':ti,ab,kw OR 'review* of review*':ti,ab,kw	
#6	#4 AND #5	1032

Ovid/Medline

#	Searches	Results
1	"Head and Neck Neoplasms"/ or "Squamous Cell Carcinoma of Head and Neck"/ or Facial Neoplasms/ or exp Mouth Neoplasms/ or exp Otorhinolaryngologic Neoplasms/ or exp Parathyroid Neoplasms/ or ((adenoma* or anticarcinogen* or blastoma* or cancer* or carcinogen* or carcinom* or chordoma* or hemangioma* or malignan* or meningioma* or mesenchymoma* or metasta* or neoplas* or neuroma* or oncogen* or oncolog* or paraneoplastic or plasmacytoma* or precancerous or scc or teratocarcinoma* or teratoma* or tumor* or tumour*) adj6 (aryepiglot* or arytenoid* or cranial or cranium or ear or ears or epiglot* or facial or gingiva* or glottic* or head or hypopharyn* or jaw or jaws or larynx or lip or lips or mandib* or mouth or nasopharyn* or neck or nasal or nose or oral* or oropharyn* or otorhinolaryn* or palatal* or palate or palatum or paranasal* or parathyr* or paroti* or pharyn* or 'postcricoid area' or salivar* or scalp or skull or sublingual* or submandib* or throat or tonsil* or uadt or vallecula)).ti,ab,kf. or hnscc.ti,ab,kf. or 'hn scc'.ti,ab,kf. or lascchn.ti,ab,kf. or scchn.ti,ab,kf.	373221
2	exp Neoplasm Metastasis/ or exp Palliative Care/ or ((neoplas* or carcinoma or cancer* or malignan* or tumor* or tumour*) adj4 (dissemination or disseminated or spread or secondary or migration or seed*)).ti,ab,kf. or metasta*.ti,ab,kf. or micrometasta*.ti,ab,kf. or oligometasta*.ti,ab,kf. or (advanced adj3 (cancer* or malignan* or neoplas* or tumor* or tumour* or hnscc or 'hn scc' or lascchn or scchn)).ti,ab,kf. or palliat*.ti,ab,kf. or unresect*.ti,ab,kf. or 'un resect*'.ti,ab,kf. or nonresect*.ti,ab,kf. or 'non resect*'.ti,ab,kf. or inoperable.ti,ab,kf.	1052921

3	exp Combined Modality Therapy/ or exp Immunotherapy/ or exp Antineoplastic Agents, Immunological/ or exp Antineoplastic Agents/ or ((hormon* or endocrin* or 'combined modalit*' or multimodal* or 'multiple modalit*' or target* or immun* or systemic*) adj3 (therap* or treat*)).ti,ab,kf. or immunotherap*.ti,ab,kf. or immunetherap*.ti,ab,kf. or 'biologic response modifier therapy'.ti,ab,kf. or 'biological response modifier therapy'.ti,ab,kf. or 'chemoradi*'.ti,ab,kf. or 'radiochemo*'.ti,ab,kf. or exp Chemoradiotherapy/ or exp Chemotherapy, Adjuvant/ or exp Consolidation Chemotherapy/ or exp Induction Chemotherapy/ or exp Maintenance Chemotherapy/ or exp Antineoplastic Combined Chemotherapy Protocols/ or chemo.ti,ab,kf. or chemotherap*.ti,ab,kf. or chemoimmuno*.ti,ab,kf. or exp Cytostatic Agents/ or 'cytostatic*'.ti,ab,kf. or exp Anthracyclines/ or anthracyclin*.ti,ab,kf. or exp Antineoplastic Agents, Alkylating/ or alkylat*.ti,ab,kf.	2902517
4	(1 and 2 and 3) not ((exp animals/ or exp models, animal/) not humans/) not ((letter/ or comment/ or editorial/) not (exp Clinical Trial/ or exp Meta-Analysis/ or exp Scoping Review/ or exp Systematic Review/))	27968
5	limit 4 to yr="2015 -Current"	14004
6	exp Meta-Analysis/ or exp Network Meta-Analysis/ or exp Systematic Review/ or (networkmeta analy* or networkmetaanaly* or metaanaly* or meta analy* or metanaly* or prisma or prospero or metaanali* or meta anali* or metanali*).ti,ab,kf. or ((systemati* or scoping or umbrella or structured literature) adj3 (review* or overview*)).ti,ab,kf. or ((structured or systemic*) adj3 (review* or overview* or synth*) adj3 literature).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 (review* or overview*)) and (search* or database* or data base*)).ti,ab,kf. or ((data extraction* or data source*) and (study selection* or studies selection*)).ti,ab,kf. or (search strateg* and selection criteria*).ti,ab,kf. or (data source* and data synth*).ti,ab,kf. or (medline* or pubmed* or pub med* or embase or cochrane*).ti,ab,kf. or cochrane.jw. or ((critical* or rapid*) adj2 (review* or overview* or synth*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synth*)) and (search* or database* or data base*)).ab. or metasynth*.ti,ab,kf. or meta synth*.ti,ab,kf.	873696
7	5 and 6	737

Quality of life search

Embase.com

No.	Query	Results
#1	'head and neck squamous cell carcinoma'/exp OR ((('head and neck' OR 'head neck' OR hn) NEAR/6 ('squamous cell' OR scc)):ti,ab,kw) OR hnscc:ti,ab,kw OR scchn:ti,ab,kw OR lascchn:ti,ab,kw	76269
#2	'pembrolizumab'/exp OR 'pembrolizumab':ti,ab,kw OR 'keytruda':ti,ab,kw OR 'nivolumab'/exp OR 'nivolumab':ti,ab,kw	125742

	OR 'cetuximab'/exp OR 'cetuximab':ti,ab,kw OR 'extreme regimen':ti,ab,kw	
#3	'quality of life'/exp OR qol:ti,ab,kw OR hrqol:ti,ab,kw OR hrql:ti,ab,kw OR qaly*:ti,ab,kw OR ((quality NEAR/2 life*):ti,ab,kw)	1077870
#4	#1 AND #2 AND #3 NOT ('conference abstract'/it OR 'clinical trial':dtype) NOT (('editorial'/it OR 'letter'/it OR 'note'/it) NOT 'evidence based medicine'/exp) NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	493
#5	#4 AND [2005-2026]/py	490
#6	'meta analysis'/exp OR 'systematic review'/exp OR 'scoping review'/exp OR 'rapid review'/exp OR 'umbrella review'/exp OR 'cochrane database of systematic reviews'/jt OR 'network meta-analysis'/exp OR 'networkmeta analy*':ti,ab,kw OR 'networkmetaanaly*':ti,ab,kw OR metaanaly*:ti,ab,kw OR 'meta analy*':ti,ab,kw OR metanaly*:ti,ab,kw OR metaanali*:ti,ab,kw OR 'meta anali*':ti,ab,kw OR metanali*:ti,ab,kw OR prisma:ti,ab OR prospero:ab OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab,kw) OR (((structured OR systemic*) NEAR/3 (review* OR overview* OR synth*) NEAR/3 literature):ti,ab,kw) OR 'systemic* review*':ti,ab,kw OR (((systemati* OR literature OR databases OR 'data bases') NEAR/6 search*):ti,ab,kw) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab,kw) OR (((literature NEAR/3 (review* OR overview*)):ti,ab,kw) AND (search*:ti,ab,kw OR databases:ti,ab,kw OR 'data bases':ti,ab,kw)) OR medline*:ab OR pubmed*:ab OR 'pub med*':ab OR embase:ab OR cochrane*:ab,jt OR psycinfo:ab OR cinahl:ab OR (((critical* OR rapid*) NEAR/2 (review* OR overview* OR synth*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synth*)):ab) AND (search*:ab OR databases:ab OR 'data bases':ab)) OR metasynth*:ti,ab,kw OR 'meta synth*':ti,ab,kw OR 'review of reviews':ti,ab,kw	1216788
#7	'randomized controlled trial'/exp OR 'clinical trial'/exp OR 'randomization'/de OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'triple blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR ((random* NEAR/2 (trial OR study)):ti,ab) OR ((random* NEAR/10 (trial OR trail OR 'clinical trial' OR 'clinical trail' OR 'clinical study' OR 'multicenter study' OR crossover OR 'cross over')):ti) OR ((('single blind*' OR 'double blind*' OR 'triple blind*' OR 'quadruple blind*') NEAR/4 (study OR trial OR trail OR design)):ti,ab) OR ((random* NEAR/3 distribut* NEAR/7 group*):ti,ab) OR (((pragmatic OR practical) NEAR/1 ('clinical trial' OR 'clinical trail')):ti,ab) OR ((('non inferiority' OR noninferiority OR superiority OR equivalence) NEAR/3 (trial OR trail)):ti,ab) OR ((random* NEAR/4 ('cross over*' OR crossover*)):ti,ab) OR ((phase NEAR/5 ('clinical trial' OR 'clinical trail')):ti) OR ((random*	4692635

	NEAR/3 phase NEAR/3 (trial OR trail OR study)):ti,ab) OR randomi*:ti,ab OR rct:ti,ab OR 'random* control*':ti,ab OR placebo*:ti,ab OR randomly*:ti,ab	
#8	#5 AND #6	58
#9	#5 AND #7 NOT #8	199
#10	#8 OR #9	257
#11	#5 NOT #10 AND ('quality of life'/exp/mj OR qol:ti OR hrqol:ti OR hrql:ti OR qaly:ti OR quality:ti)	9

Ovid/Medline

#	Searches	Results
1	exp "Squamous Cell Carcinoma of Head and Neck"/ or (("head and neck" or "head neck" or hn) adj6 ('squamous cell' or scc)).ti,ab,kf. or hnscc.ti,ab,kf. or scchn.ti,ab,kf. or lascchn.ti,ab,kf.	34229
2	('pembrolizumab' or 'keytruda').ti,ab,kf. or exp Nivolumab/ or 'nivolumab'.ti,ab,kf. or exp Cetuximab/ or 'cetuximab'.ti,ab,kf. or 'extreme regimen'.ti,ab,kf.	31702
3	exp "Quality of Life"/ or qol.ti,ab,kf. or hrqol.ti,ab,kf. or hrql.ti,ab,kf. or qaly*.ti,ab,kf. or (quality adj2 life*).ti,ab,kf.	573912
4	(1 and 2 and 3) not ((exp animals/ or exp models, animal/) not humans/) not ((letter/ or comment/ or editorial/) not (exp Clinical Trial/ or exp Meta-Analysis/ or exp Scoping Review/ or exp Systematic Review/))	138
5	limit 4 to yr="2005 -Current"	138
6	exp Meta-Analysis/ or exp Systematic Review/ or exp Scoping Review/ or networkmeta analy*.ti,ab,kf. or networkmetaanaly*.ti,ab,kf. or metaanaly*.ti,ab,kf. or meta analy*.ti,ab,kf. or metanaly*.ti,ab,kf. or metaanali*.ti,ab,kf. or meta anali*.ti,ab,kf. or metanali*.ti,ab,kf. or prisma.ti,ab. or prospero.ab. or ((systemati* or scoping or umbrella or structured literature) adj3 (review* or overview*)).ti,ab,kf. or ((structured or systemic*) adj3 (review* or overview* or synth*) adj3 literature).ti,ab,kf. or systemic* review*.ti,ab,kf. or ((systemati* or literature or databases or data bases) adj6 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 (review* or overview*)) and (search* or databases or data bases)).ti,ab,kf. or medline*.ab. or pubmed*.ab. or pub med*.ab. or embase.ab. or cochrane*.ab,jw. or psycinfo.ab. or cinahl.ab. or ((critical* or rapid*) adj2 (review* or overview* or synth*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synth*)) and (search* or databases or data bases)).ab. or metasynth*.ti,ab,kf. or meta synth*.ti,ab,kf. or 'review of reviews'.ti,ab,kf.	916147
7	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 (random* adj2 study).ti,ab. or (random* adj10 (trial or trail or clinical trial or clinical trail or clinical study or multicenter study or crossover or cross over)).ti,ab,kf. or ((single	2193246

	blind* or double blind* or triple blind* or quadruple blind*) adj4 (study or trial or trail or design)).ti,ab. or (random* adj3 distribut* adj7 group*).ti,ab. or ((pragmatic or practical) adj1 (clinical trial or clinical trail)).ti,ab. or ((non inferiority or noninferiority or superiority or equivalence) adj3 (trial or trail)).ti,ab. or (phase adj5 (clinical trial or clinical trail)).ti. or (random* adj3 phase adj3 (trial or trail or study)).ti,ab. or randomi*.ti,ab. or rct.ti,ab. or random* control*.ti,ab. or placebo*.ti,ab. or randomly*.ti,ab.	
8	5 and 6	11
9	(5 and 7) not 8	53
10	8 or 9	64
11	(5 not 10) and (qol or hrqol or hrql or qaly or quality).ti.	4

Bijlage 3 Verantwoording 2

Voor meer details over de gebruikte richtlijnmethodologie verwijzen wij u naar de Werkwijze. Relevante informatie voor de ontwikkeling/herziening van deze richtlijnmodule is hieronder weergegeven.

Initiatief
Initiatief: Cluster Hoofd-halstumoren

Samenstelling van de werkgroep
Voor het ontwikkelen van de richtlijnmodule is eind 2024 een multidisciplinair cluster ingesteld. Het cluster Hoofd-halstumoren bestaat uit meerdere richtlijnen (zie hier de actuele clusterindeling). De stuurgroep bewaakt het proces van modulair onderhoud binnen het cluster. De expertisegroepsleden brengen hun expertise in, indien nodig. De volgende personen uit het cluster zijn betrokken geweest bij de herziening van deze module:

Clusterstuurgroepleden

- Prof. dr. R. (Remco) de Bree, voorzitter (NVKNO)
- Dr. M. (Mischa) de Ridder (NVRO)
- Dr. L.A. (Lot) Devriese (NIV)
- Prof. dr. M.J.H. (Max) Witjes (NVMKA)
- Dr. H.P.M. (Dirk) Kunst (NVKNO)
- R.A. (Rob) Burdorf (PVHH)

Betrokken clusterexpertisegroepleden

- Dr. C.M. (Caroline) Speksnijder (KNGF/NVOF)
- Dr. D.J.M. (Doke) Buurman (KNMT)

Met ondersteuning van

- Dr. A. (Anja) van der Hout (Kennisinstituut van de Federatie Medisch Specialisten)
- Dr. E. (Eline) Pruijn-de Heus (Kennisinstituut van de Federatie Medisch Specialisten)
- Dr. J. (Jing) de Haan-Du (Kennisinstituut van de Federatie Medisch Specialisten)
- Drs. J. (Joline) Rohof (Kennisinstituut van de Federatie Medisch Specialisten)
- Dr. M.S. (Michiel) Oerbekke (Kennisinstituut van de Federatie Medisch Specialisten)
- Alies Oost (Kennisinstituut van de Federatie Medisch Specialisten)

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

Clusterstuurgroepleden

Tabel 3 Gemelde (neven)functies en belangen stuurgroep

Naam	Hoofdfunctie	Nevenwerkzaamheden	Persoonlijke financiële belangen	Persoonlijke relaties	Extern gefinancierd onderzoek	Intellectuele belangen en reputatie	Overige belangen	Datum	Restrictie
Prof. dr. R. (Remco) de Bree (voorzitter)	KNO-arts / hoofd-halschirurg Hoogleraar /	Onbetaald: Board member Dutch Head	Geen	Geen	KWF. Ultrasound and microbubbles to improve tumor perfusion of head and neck cancers. co-	Geen	Geen	12-12-2024	Restricties ten aanzien van

	afdelingshoofd UMC Utrecht	and Neck Society (NWHHT) Chair Research Steering Committee Dutch Head and Neck Society (NWHHT) Member Clinical Audit Board Dutch Head and Neck Audit (DHNA) Chair committtee Revision Dutch Head and Neck Tumor Guidelines Board member Patient advocacy group Patiëntenvereniging Hoofd-Hals (PVHH) Chair advisory committee research data Dutch registries (PRISMA) Chair Dutch section Collegium Oto-Rhino-Laryngologicum Amicitiae Sacrum (CORLAS) Council Member International Academy of Oral Oncology (IAOO)			applicant ZonMw. Metastatic-directed stereotactic body radiation therapy of oligometastases in head and neck squamous cell carcinoma patients. Projectleider KWF. Personalized follow-up in HPV-related oropharyngeal cancer patients using liquid biopsies. Projectleider Maurits en Anna de Kock Stichting en Vaillantfonds. Fluorescentie geassisteerde reconstructieve chirurgie: beoordeling van vitaliteit van weefsels. Projectleider 1. KWF- FDG-PET/CT to reduce the need for sentinel lymph node biopsy in early stage oral cancer (Projectleider JA) 2. KWF - Ex vivo 7T MRI of resection specimen of oral cancer to improve margin control (Projectleider NEE) 3. KWF - Sentinel lymph node detection in early oral cancer using [68Ga]Ga-tilmanocept PET/CT lymphoscintigra (Projectleider JA) 4. Nutricia - Perioperative nutritional intervention with Fortifit Energy® in combination with excersice verstus standard of care (Projectleider JA) 5. Hanarth Fonds - Triage of Patients with High-risk Oral Squamous cell Carcinoma using Artificial Intelligence (TOSCA) (Projectleider NEE)				besluitvorming betreffende perioperatieve voedingsinterventies. Indien relevant: Vice-voorzitter aan te stellen voor wanneer perioperatieve voedingsinterventies worden besproken.
Dhr. Dr. M. (Mischa) de Ridder	Radiotherapeut-oncoloog UMC Utrecht	Secretaris LPRHHT van de NVRO. Lid METC NED-MED	Geen	Geen	Elekta: To evaluate evidence for eventual transition from PDR treatments to HDR treatments in case of possib (Projectleider JA). Hanarth fonds: Improved response assessment after (chemo)-radiotherapy for locally	Geen	Geen	3-1-2025	Geen restricties.

					advanced head and neck squamous (Projectleider NEE).				
Mevr. Dr. L.A. (Lot) Devriese	Internist UMC Utrecht	Dit project en eerder bij FMS kwaliteits agenda. Werkgroep binnen NVMO, CieOOM, off-label oncologische medicatie (vacatiegelden naar UMC Utrecht). Bestuurslid NWHHT	Geen	Geen	Ja, als lokale PI van studies gesponsord door Farma. Met uitbetaling aan de werkgever, niet aan mij persoonlijk. 1. ISAPharm - Fase 3 onderzoek ISA101b (Projectleider NEE) 2. MERUS - Fase 3 onderzoek petosemtamab (Projectleider NEE) 3. CISLOW studie - Fase 2 IIS gesponsord door ZOnMw (Projectleider NEE)	Geen	Geen	14-11-2024	Geen restricties.
Prof. dr. M.J.H. (Max) Witjes	MKA chirurg-HH oncoloog Universitair Medisch Centrum Groningen	Geen	Geen	Geen	• Fluoguide FG001sponsor initiated trial (2024): Determination of Optimal Dose for Visualization of Inadequate Margins in Oral Squamous Cell Carcinoma Using FG001. Protocol: 2024-514508-14-00. Witjes MJH Voskuil FJ, Fluoguide team. (budget € 378.293) (Projectleider JA) • NIH grant (National Institute of Dental and Craniofacial Research 2023) : Ex vivo intraoperative surgical basal margin analysis in head and neck cancer resection: clinical validation (1R01DE033449-01). Tichauer K, J Broncovic & Witjes MJH, Voskuil FJ.(budget USD 2.5Milj) (Projectleider JA) • SNN Grant (2023) : JTF application for IMPACT-Implants . (Budget € 3.6 Milj) Kraeima J, Witjes MJH, Veldsink JW & Center for Business Development UMCG. (Projectleider NEE) • KWF Kankerbestrijding: RUG 13215 (2021) Witjes MJH, GB Halmos, WM Nagengast. Real-time targeted fluorescence endoscopy in patients for detection of unknown primary cancers of the head and neck area (REFLECT study) (Budget €476.000) (Projectleider JA) • WJ Thijn stichting (2021) : Witjes MJH lichtgevende stoffen helpen de chirurg de tumor beter te	Geen	Geen	16-1-2025	Restricties ten aanzien van besluitvorming betreffende de bepaling van de optimale dosis voor visualisatie van onvoldoende snijmarges bij oraal plaveiselcelcarcinoom.

					verwijderen. (Budget €250.000). (Projectleider JA)				
Dhr. H.P.M. (Dirk) Kunst	KNO-arts; Radboudumc-MUMC+	Voorzitter van het "Radboudumc-MUMC+ Expertisecentrum Schedelbasispathologie" Voorzitter "Academische Alliantie Schedelbasispathologie Radboudumc-MUMC+" Voorzitter "Landelijk Overleg Expertisecentra Schedelbasispathologie" (LOES) President van de "European Skull Base Society" (ESBS) Betrokkenheid patientenverenigingen: Neurofibromatose type 2 patientenvereniging Paragangliomen patientenvereniging	Geen	Geen	Euregio: Hoofd-hals paragangliomen; verschillen management Nederland Duitsland (projectleider JA). TU Eindhoven/Tilburg (aflopende ZonMw studie), over voorspellen van groei obv MRI scans bij brughoektumoren (projectleider NEE).	Geen	Geen	14-2-2025	Geen restricties.
Dhr. R.A. (Rob) Burdorf	Neem niet meer deel aan het arbeidsproces (met pensioen)	Lid wetenschappelijke advies commissie van de PVHH	Geen	Geen	Geen	Geen	Geen	12-11-2024	Geen restricties.

Betrokken clusterexpertisegroepleden

Tabel 4 Gemelde (neven)functies en belangen expertisegroep

Naam	Hoofdfunctie	Nevenwerkzaamheden	Persoonlijke financiële belangen	Persoonlijke relaties	Extern gefinancierd onderzoek	Intellectuele belangen en reputatie	Overige belangen	Datum	Restrictie

Dr. C.M. (Caroline) Speksnijder	Associate professor; UMC Utrecht	Onbetaald:1. Vice-voorzitter International Physiotherapy for HIV/Aids, Oncology, Hospice and Palliative Care (IPT-HOPE; World Physiotherapy) 2. Voorzitter Dutch Association of Supportive Care in Cancer (DASCC; nationale organisatie onder MASCC) Werkgroepen: o FMS Cluster Nazorg bij kanker o FMS Cluster Head and Neck Cancer o Taskforce Cancer Survivorship Care; IKNL en NFK o Research-werkgroep NWHHT o PRISMA, adviesorgaan datagebruik van de cohorten van IKNL, DICA-DHNA en/of PALGA ten behoeve van hoofd-halskanker gerelateerd onderzoek	Geen	Geen	1. Nederlands Fonds Tegen Kanker: "Physical prehabilitation in patients with head and neck cancer scheduled for a laryngectomy; a feasibility study" - Bewegings- en voedingsinterventie (Projectleider JA) 2. Nutricia: "Nutritional and physical prehabilitation in patients with head and neck cancer scheduled for combined approach resection: a pilot study" - Voeding- en bewegingsinterventie	Geen	Geen	11-06-2026	Restricties ten aanzien van besluitvorming betreffende gecombineerde voedings- en bewegingsinterventies als prehabilitatie-interventie
Dr. D.J.M. (Doke) Buurman	Tandarts-Maxillofaciale prothetiek Maastricht UMC+	Lid consilium MFP van NVGPT (onbetaald) Lid klankbordgroep Herziening richtlijn Hoofd-halstumoren Lid werkgroep voor de richtlijn Nazorg/follow-up en ziekte-specifieke revalidatie bij hoofdhalstumoren	Geen	Geen	Geen	Geen	Geen	29-06-2026	Geen restricties

5 Kwalitatieve raming van mogelijke financiële gevolgen in het kader van de Wkkgz

Bij de richtlijnmodule voerden de clusterleden conform de Wet kwaliteit, klachten en geschillen zorg (Wkkgz) een kwalitatieve raming uit om te beoordelen of de aanbevelingen mogelijk leiden tot substantiële financiële gevolgen. Bij het uitvoeren van deze beoordeling is de richtlijnmodule op verschillende domeinen getoetst (zie het stroomschema bij Werkwijze).

Module	Uitkomst raming	Toelichting
Module [naam]	[geen/ mogelijk] financiële gevolgen	[plaatsen desbetreffende uitkomst 1, 2, 3, 4 of 5]

Bijlage 4 Literatuursamenvatting module 2 inclusief alle bijlagen

Introduction

Osteoradionecrosis (ORN) is a rare but impactful complication of radiotherapy. Usually, ORN in the head and neck region is seen in the mandible after radiotherapy for a head and neck cancer. It is caused by tissue damage after radiotherapy with several consequences: hypovascularization, loss of bone-forming cells, fibrosis and accelerated atherosclerosis. Prevention of ORN starts before radiotherapy. For example, the dentist, maxillofacial surgeon and/or oral hygienist, evaluates and sets up a treatment plan including extracting teeth with a poor prognosis (oral foci) before the start of (chemo)radiotherapy ((C)RT) for head and neck cancer, although some controversies exist in the literature. A recent systematic review, supported by moderate-certainty evidence, confirmed that dental extractions should be performed before the start of (C)RT for head and neck cancer to minimize this risk of ORN (Normando, 2022; Almeida-Silva, 2024).

Currently, most Comprehensive Cancer Centers in the Netherlands use a threshold dose of 40 Gy to consider prophylactic removal of teeth with a moderate or poor prognosis to prevent ORN during and after radiotherapy. This practice is based on the findings of Schuurhuis (2018) and Spijkervet (2020). Table 1 presents the definitions and recommended treatment options for identified oral foci prior to the initiation of radiotherapy. The treatment options are categorized according to whether the anticipated cumulative radiotherapy dose is below or above the 40 Gy threshold. Nevertheless, there is insufficient evidence supporting the 40 Gy threshold, and higher threshold doses are commonly used in international practice. Moreover, this relatively low threshold dose may result in the unnecessary extraction of numerous teeth, thereby reducing the number of functional units and impairing masticatory function. A functional unit is a functional tooth, bridge pontic or crown (on implants) capable of making contact with an opposing (prosthetic) tooth. Consequently, a scientifically validated threshold dose for prophylactic tooth extractions is needed.

Currently, it remains unclear which radiotherapy threshold dose for removing dental foci is evidence-based and should be recommended.

Table 1. Assessment and treatment of oral foci within or outside the radiation field
From: Patients with advanced periodontal disease before intensity-modulated radiation therapy are prone to develop bone healing problems: a 2-year prospective follow-up study (Schuurhuis 2018)

Assessed tooth problems	Treatment if cumulative dose > 40 Gy[a]	Treatment if cumulative dose < 40 Gy or outside the radiation portal[a]
Caries profunda	Tooth extraction	Restoration, if necessary combined with endodontic treatment, or tooth extraction
Periapical pathosis (on radiographs) without symptoms and/or additional problems	In teeth *without* root canal filling: endodontic treatment and/or apexification In teeth *with* root canal filling: endodontic re-treatment, apexification, or tooth extraction (needed in case of pre-radiotherapy time limitations)	In teeth *without* root canal filling: endodontic treatment In teeth *with* root canal filling: endodontic re-treatment, apexification, or tooth extraction Treatment can be postponed until after radiotherapy
Extensive periapical pathosis (on radiographs) combined with periodontal disease, in	Tooth extraction	In teeth *without* root canal filling: endodontic treatment combined with initial periodontal treatment

Assessed tooth problems	Treatment if cumulative dose > 40 Gy[a]	Treatment if cumulative dose < 40 Gy or outside the radiation portal[a]
afunctional teeth or *with symptoms*		In teeth *with* root canal filling: endodontic re-treatment, apexification, or tooth extraction depending on the prognosis
Avital pulp *with symptoms* without periapical radiolucency on radiographs	Endodontic treatment or tooth extraction (which might be necessary in case of pre-radiotherapy time limitations)	Endodontic treatment or tooth extraction depending on the prognosis
Avital pulp *without symptoms* and without periapical radiolucency on radiographs	Endodontic treatment or tooth extraction (needed in case of pre-radiotherapy time limitations)	Endodontic treatment (which can be postponed until after radiotherapy)
Periodontal disease with: Pockets 4–5 mm Pockets ≥ 6 mm Gingival recessions ≥ 6 mm	Initial periodontal therapy Tooth extraction Tooth extraction	Initial periodontal therapy Initial periodontal therapy Only recession requires no treatment
Impacted teeth or roots fully covered by bone without radiographic abnormalities	No treatment If problems are expected in the future: tooth extraction	No treatment
Impacted teeth or roots *not fully covered* by bone or with radiographic abnormalities (e.g., cysts, apical radiolucency)	Tooth extraction	No treatment or, in case of symptoms, surgical removal Roots with periapical radiolucency might be worth preserving by endodontic treatment and restoration (which can be postponed until after radiotherapy)
Cysts	Surgical removal	Surgical removal
Internal or external root resorption	Tooth extraction	Endodontic treatment or tooth extraction depending on the prognosis

Search and select

A systematic review of the literature was performed to answer the following questions regarding preventive measures before or after radiotherapy:

- What is the optimal threshold radiation-dose (Gy, cGy) whether tooth extraction is necessary in patients with head and neck cancer before the start of radiotherapy? (PICO 1, table 2)

- What is the effectiveness of measures to prevent osteoradionecrosis in patients who received (chemo)radiotherapy in the head and neck area? (PICO 2, table 2)

Table 2. PICO

	PICO 1 (before radiotherapy)	PICO 2 (after radiotherapy)
Patients	Patients scheduled to receive radiotherapy, with or without a chemotherapy, for head and neck cancer	Patients who received radiotherapy with or without chemotherapy for a head and neck cancer
Intervention	Tooth extraction at a dose of X	Preventive measure for osteoradionecrosis
Control	Tooth extraction at a dose of Y	No preventive measure or an alternative preventive measure

Outcomes	Osteoradionecrosis	Osteoradionecrosis, complications/adverse effects of interventions;
Other selection criteria	Study design: Randomized controlled trials and systematic reviews	Study design: Randomized controlled trials and systematic reviews

Relevant outcome measures

PICO 1 (before radiotherapy)

The guideline development group considered ORN as a critical outcome measure for decision making.

A priori, the guideline development group did not predefine the outcome measure listed above but instead used the definitions of the outcome measure ORN employed in the included studies.

The guideline development group defined a 10% relative difference as the minimal clinically important difference for the outcome measure ORN (ORN present/absent)(RR < 0.9 or > 1.1).

PICO 2 (after radiotherapy)

The guideline development group considered the incidence of osteoradionecrosis as critical outcome measure for decision making and complications/adverse effects as an important outcome.

The working group defined osteoradionecrosis as follows: an area of devitalized and exposed irradiated bone that fails to heal over a period of three to six months in the absence of local neoplastic disease (El-Rabbany 2019). The working group defined complications/adverse effects as follows: hospitalization, morbidity (e.g. pain, loss of sensation, effects on taste), and mortality (El-Rabbany 2019).

The working group was not able to define a minimal clinically relevant difference as the condition is very rare. An incidence varying from 3% (Wahl 2006, in El-Rabbany 2019) to 8-10% (Reuther 2003) has been reported. The true incidence may be higher due to under-reporting of this condition (El-Rabbany 2019). The working group decided that, as osteoradionecrosis may be devastating both in terms of patient health-related quality of life and the burden to the healthcare system, that any indication of a favourable effect of a preventive intervention would be clinically relevant and should be weighed against the risk of complications/adverse effects of the intervention.

Search and select (Methods)

PICO 1 (before radiotherapy)

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms form 2000 until 6th June 2024. The systematic literature search resulted in 192 hits.

Studies were selected based on the following criteria:

- Randomized controlled trials (RCTs), systematic reviews (SRs) or observational studies published after 2000.
- Studies meeting the PICO criteria.

Forty-nine studies were initially selected based on title and abstract screening. After reading the full text, all 49 studies were excluded (see the Table with reasons for exclusion under the tab Methods), and no studies were included.

PICO 2 (after radiotherapy)

The databases Medline (via OVID) and Embase were searched with relevant search terms until May 2021. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 251 hits (86 found with a filter for systematic reviews, 165 found with a filter for RCTs).

First, SRs were selected based on the following criteria: the population consists of patients having received radiotherapy for a tumor in the head and neck area, the study compares one or more preventive treatments, the study is a systematic review (SR) and describes at least the incidence of osteoradionecrosis. One recent SRs was initially selected based on title and abstract screening: the Cochrane review by El-Rabbany (2019). After reading the full text, this SR was included as base for the evidence synthesis for this module.

Based on the SR found, it was decided to select randomized controlled trials (RCTs) based on the following criteria: published in 2019 or later (the search date of El-Rabbany 2019 was November 2019), the population consists (mostly) of patients receiving radiotherapy for a tumor in the head and neck area, the study compares one or more preventive treatments, the study is a RCT and describes at least the incidence of osteoradionecrosis.

Four articles were initially selected based on title and abstract screening. After reading the full text, all studies were excluded.

Summary of literature

PICO 1 (before radiotherapy)

Description of studies

After applying the inclusion criteria of the current guideline's literature review no studies were included.

Results

After applying the inclusion criteria of the current guideline's literature review no studies were included.

Summary of findings

After applying the inclusion criteria of the current guideline's literature review no studies were included (Table 3).

Table 3. Summary of findings for PICO 1 (before radiotherapy)

Osteonecrosis	-	**No GRADE**	-

PICO 2 (after radiotherapy)

Description of studies

The Cochrane Review of El-Rabbany (2019) tried to find out the best way to prevent osteoradionecrosis in people who have had radiotherapy for head and neck cancer. The review looked at any treatment that have been used to prevent osteoradionecrosis. The quality of this review was considered to be of high quality, as it followed standard Cochrane review methodology. For full details of the included studies we refer to El-Rabbany (2019).

Three different ways to prevent osteoradionecrosis were reviewed:

- The use of platelet-rich plasma in bone after removal of healthy teeth prior to radiotherapy.
- Preventing tooth decay, by:
  - Taking out teeth.
  - Using fluoride gel with a toothpaste with a higher level of fluoride than normal.
- Hyperbaric oxygen therapy to improve blood supply, which may help heal damaged tissue.

One study was "awaiting classification" in the Cochrane: Shaw (2019). Anno 2022, we added this study to the evidence synthesis for this module. Table 4 presents all eligible trials.

Table 4. Trials assessing preventive treatments for osteoradionecrosis

Reference, year (trial name)	Intervention and comparison	Study sample size
Batstone 2012	Platelet rich plasma versus no treatment/placebo	44
Horiot 1983	Fluoride gel (450 ppm) versus high-content fluoride toothpaste (1350 ppm)	220
Markx 1985	Hyperbaric oxygen therapy following extractions versus perioperative antibiotic prophylaxis	74
Schoen 2007	Combined hyperbaric oxygen therapy and perioperative antibiotics versus antibiotics alone prior to dental implant therapy	26
Shaw 2019 (HOPON)	Combined hyperbaric oxygen therapy and perioperative antibiotics versus antibiotics alone prior to extractions or dental implant therapy	144

NB: El-Rabbany excluded two clinical trials: Papas (2008) and Toljanic (1996), both of which did not evaluate the incidence of osteoradionecrosis in their patients

Results

Platelet-rich plasma versus no intervention/placebo

This comparison was only made in 1 study, which showed no difference between the 2 interventions: 3/22 sites in the platelet-rich plasma arm developed osteoradionecrosis compared to 1/22 in the control arm (5-year follow-up) (OR 3.32, 95% CI 0.58 to 19.09, P = 0.18) (El-Rabbany, 2019).

Fluoride gel versus high-content fluoride toothpaste

This comparison was only made in 1 study, which showed no difference between the 2 interventions: no patients in either group developed osteoradionecrosis (12 to 36-month follow-up) (El-Rabbany, 2019).

Hyperbaric oxygen therapy versus perioperative antibiotic prophylaxis

This comparison was only made in 1 study, which showed a significantly lower incidence of osteoradionecrosis in the hyperbaric oxygen therapy group (2/37 patients) when compared

to the antibiotic group (11/37 patients) (6-month follow-up) (RR 0.18, 95% CI 0.43 to 0.76, P = 0.01 using Fisher's exact test).
Adverse effects were an outcome of interest in the study conducting this comparison, however no mention was made of the presence or absence of any adverse events.

Combined hyperbaric oxygen therapy and perioperative antibiotics versus antibiotics alone
This comparison was made in 2 studies. Schoen (2007) found no difference between the 2 interventions: 1/13 patients from the hyperbaric oxygen therapy and antibiotics group developed osteoradionecrosis compared to 0/13 in the antibiotics alone group (1-year follow-up) (RR 3.00, 95% CI 0.14 to 65.16, P > 0.05) (El-Rabbany, 2019).

Shaw (2019) analyzed data from 100 of 144 patients and found no difference as well. The incidence of osteoradionecrosis at 6 months was 6.4% and 5.7% for the hyperbaric oxygen therapy group and control groups, respectively (OR 1.13; 95% CI 0.14 to 8.92, P=1).

Summary of findings
The summary of findings for different preventive and management options are presented in Table 5. All the studies had one or more domains assessed to be at significant risk of bias, resulting in an overall high risk of bias designation for all five studies. The lack of patient and operator blinding to the intervention were the most common sources of potential bias (El-Rabbany, 2019; Shaw 2019).

Table 5. *Summary of findings tables for PICO 2 (after radiotherapy), including some preventive options found for the setting before radiotherapy*

Platelet-rich plasma versus no intervention/placebo

Osteonecrosis	OR 3.32, 95% CI 0.58 to 19.09, P = 0.18 **From 1 study**	**Very low GRADE[1]**	We are uncertain whether platelet-rich plasma is effective at reducing the risk of osteoradionecrosis following dental extractions, when compared to placebo. *Sources: El-Rabbany, 2019*
1: The certainty of the evidence was downgraded 3 levels due to high risk of bias and imprecision (only 1 study included with a very small sample size; narrative synthesis conducted, estimates not precise) (El-Rabbany, 2019).			

Fluoride gel versus high-content fluoride toothpaste

Osteonecrosis	no patients in either group developed osteoradionecrosis **From 1 study**	**Very low GRADE[1]**	We are uncertain whether fluoride gel is effective at reducing the risk of osteoradionecrosis when compared to high-content fluoride toothpaste. *Sources: El-Rabbany, 2019*
1: The certainty of the evidence was downgraded 3 levels due to high risk of bias and imprecision (only 1 study included with a small sample size; narrative synthesis conducted, estimates not precise) (El-Rabbany, 2019).			

Hyperbaric oxygen therapy versus perioperative antibiotic prophylaxis

Osteonecrosis	RR 0.18, 95% CI 0.43 to 0.76	**Very low GRADE[1]**	We are uncertain whether hyperbaric oxygen therapy is effective at

	From 1 study		reducing the risk of osteoradionecrosis following dental extractions when compared to perioperative antibiotic prophylaxis. *Sources: El-Rabbany, 2019*
1: The certainty of the evidence was downgraded 3 levels due to high risk of bias and imprecision (only 1 study included with a very small sample size; narrative synthesis conducted, estimates not precise) (El-Rabbany, 2019).			

Combined hyperbaric oxygen therapy and perioperative antibiotics versus antibiotics alone

Osteonecrosis	RR 3.00, 95% CI 0.14 to 65.16 and OR 1.13; 95% CI 0.14 to 8.92 **From 2 studies**	**Very low GRADE[1]**	We are uncertain whether prophylactic antibiotics with hyperbaric oxygen therapy prior to dental implant therapy is effective at reducing the risk of osteoradionecrosis when compared to antibiotics alone. *Sources: El-Rabbany, 2019; Shaw, 2019*
1: The certainty of the evidence was downgraded 3 levels due to high risk of bias and imprecision (only 2 studies included with a small sample size in total (< 2000); narrative synthesis conducted, estimates not precise) (El-Rabbany, 2019).			

Kennisvragen

Tijdens de ontwikkeling van deze module is gebleken dat er binnen deze module nog te weinig bewijs is voor de onderbouwing van de aanbeveling en dus kennisvragen bestaan. De werkgroep meent dat (vervolg)onderzoek wenselijk is om in de toekomst een duidelijker antwoord te kunnen geven op vragen uit de praktijk.

Kennisvragen:

- Zijn aanpassingen in focusonderzoek en extractiebeleid nodig?
- Welke interventie is meest succesvol om ORN te voorkomen na radiotherapie?
- Wat is de drempel-stralingsdosis (Gy, cGy) bij patiënten met hoofd-halskanker om te bepalen of gebitselementen profylactisch verwijderd moeten worden om ORN te voorkomen?
- Bij welke gebitselementen/kaakdelen wordt een stralingsdosis boven de drempeldosis verwacht op basis van de diagnostische beeldvorming?

Toelichting:
Aangezien het bestralingsplan nog niet beschikbaar is op het moment van het focusonderzoek moet er een inschatting worden gemaakt van de te verwachten radiotherapie dosis. Het zou zeer wenselijk zijn als er op basis van de diagnostische beeldvorming met bijvoorbeeld AI een preciezere inschatting kan worden gemaakt van de te verwachten radiotherapie dosis.

Verkeerslichtanalyse en Implementeren- en Agenderen-tabel

Verkeerslichtanalyse (ten behoeve van commentaar- en autorisatiefase)

Kruis aan		
	ROOD	Sterke aanbeveling tegen, geldend voor de gehele populatie, en waar passend bewijs voor is [1]
	ORANJE	Aanbeveling waar geen passend bewijs is voor gehele populatie • Sterke aanbeveling tegen (geen passend bewijs voor gehele populatie en subpopulaties/ condities) • Conditionele aanbeveling (geen passend bewijs voor gehele populatie, maar wel passend bewijs voor een subgroep/-conditie (overweging))
X	**GROEN**	Sterke aanbeveling voor, geldend voor de gehele populatie, en waar passend bewijs voor is [1,2]

[1] Er kan ook sprake zijn van passend bewijs bij een low of very low GRADE; bijvoorbeeld omdat er overwegingen zijn die zwaarwegend zijn in het aanbevolen beleid.

[2] Deze categorie geldt ook indien er passend bewijs is waaruit blijkt dat er geen voorkeur is voor één van de onderzochte interventies/diagnostiekmethoden/verwijspaden, voorbeeld: twee chirurgische technieken zijn even effectief, hebben vergelijkbare complicatierisico's, keuze is afhankelijk van het besluit dat de chirurg samen met de patiënt maakt.

Implementeren-tabel

De implementatietabel brengt in kaart welke factoren de uitvoering van een aanbeveling bevorderen of belemmeren, en welke aanvullende acties nodig zijn voor succesvolle invoering. De adviseur en (cluster)werkgroep vullen de tabel in op basis van gerichte vragen over het onderliggende probleem, relevante randvoorwaarden en mogelijke knelpunten. Op basis hiervan wordt geconcludeerd of een extra implementatie-impuls wenselijk is.

Implementatietabel

Vraag	***Antwoord:*** *Kruis aan en licht toe/ beschrijf*		***Toelichting keuze:***
I1. Wat was het onderliggende probleem om deze uitgangsvraag uit te werken?	**X**	**Ongewenste praktijkvariatie**	Er bestaat variatie tussen centra in de gehanteerde drempeldosis (40 Gy vs. 50 Gy) en in het beleid rondom extracties en preventie van ORN
	X	**Nieuwe evidentie**	**De internationale richtlijn (ISOO-MASCC-ASCO 2024) en recente literatuur geven aanleiding tot heroverweging van drempeldoses en beleid.**
		Anders	
I2. Maak een inschatting over hoeveel patiënten het ongeveer gaat waar de aanbeveling betrekking op heeft?	**X**	**< 1000**	
I3. Is de aanbeveling onderdeel van een bredere set interventies of verwant aan andere richtlijnen of modules? Zo ja, hoe verhoudt zij zich daartoe en moet hiermee rekening worden gehouden bij de implementatie, of kan de aanbeveling als losstaand worden beschouwd?		**Ja**	
	X	**Nee De module adresseert zowel bestaande variatie als nieuwe inzichten, maar benadrukt vooral gebrek aan sterk bewijs en noodzaak tot harmonisatie.** **⍰ ISOO-MASCC-ASCO richtlijn ORN (2024)** **⍰ KIMO richtlijn "Extramurale mondzorg tijdens en na kankerbehandeling"** **⍰ Oncoline / hoofd-hals oncologie richtlijnen**	

I4. Belemmeringen en kansen op verschillende niveaus voor landelijke toepassing van de aanbeveling:		**Belemmerende factoren**	**Bevorderende factoren/ kansen**
Richtlijn/ klinisch traject (innovatie)		**Beperkte evidence, geen duidelijke uniforme drempeldosis**	**Bestaande consensus (40–50 Gy range), sluit aan bij huidige praktijk**
Zorgverleners (artsen en verpleegkundigen)		**Verschillen tussen centra, beperkte kennis over nieuwste inzichten**	**Multidisciplinair overleg is reeds ingeburgerd in centra. Per centrum richten op verbetering.**
Patiënt/ cliënt (naasten)		**Impact van extracties, beperkte tijd voor besluitvorming**	**Gedeelde besluitvorming en betere informatievoorziening**
Sociale context		-	-
Organisatorische context		**Afstemming tussen radiotherapie en mondzorg niet altijd optimaal**	**In veel centra al korte lijnen aanwezig tussen MKA, KNO en radiotherapie**
Financiële en juridische context		**Nazorg (mondzorg) mogelijk niet volledig vergoed**	**Initiële zorg via bijzondere tandheelkunde vergoed**
I5. A) Welke personen/partijen zijn van belang bij het toepassen van de aanbeveling in de praktijk? (kruis aan) **B) Wat is er nodig van deze personen/partijen om de aanbeveling in de praktijk te**		**A**	**B**
	X	Patiënt/ cliënt (naaste)	**Betrokkenheid bij shared decision making** **Begrip van risico's ORN vs. tandbehoud**

kunnen brengen? *Denk aan aanpassingen in gedrag, werkwijzen, beleid, samenwerking of andere randvoorwaarden.*			
	X	Professional	**Afstemmen beleid (40 vs 50 Gy) per centrum** **Multidisciplinair overleg intensiveren** **Uniformeren van focusonderzoek en behandelplanning**
	X	Beroepsvereniging, nl	**Afstemming tussen richtlijnen** **Scholing en disseminatie**
	X	Ziekenhuis (raad van bestuur/UMCNL (voorheen NFU)/NVZ)	**Organiseren MDT-structuur (radiotherapie + mondzorg)** **Faciliteren communicatie**
	X	Zorgverzekeraars/ NZa	**Verduidelijking vergoeding nazorg mondzorg**
		Zorginstituut [duiding nodig]	
		Anders	
I6. Binnen welk tijdsbestek moet de aanbeveling zijn geïmplementeerd?	**X**	< 1 jaar	**Aanbevelingen sluiten grotendeels aan bij bestaande praktijk dus snelle implementatie is mogelijk.**

		binnen 2-3 jaar	
I7. Conclusie: is er extra actie en/of ondersteuning nodig voor implementatie van de aanbeveling? *De reguliere implementatieroutes (publicatie en disseminatie via officiele kanalen, opname in professionele standaarden, scholing en nascholing, gebruik van bestaande ICT systemen, audits en visitaties) van de richtlijnmodule alleen is onvoldoende.*		Ja	
	X	Nee	**Kennis opgedaan vanuit de richtlijn is voldoende om deze te implementeren**
I8. Plaatsing op de Landelijke Implementatieagenda Medisch Specialistische zorg is gewenst. *Het gaat om zorg die (grotendeels) wordt uitgevoerd binnen de ziekenhuismuren. Succesvolle implementatie vraagt om actieve betrokkenheid en samenwerking van meerdere relevante partijen binnen de zorgpraktijk.*		Ja *	
	X	**Nee**	

**Deze aanbeveling komt mogelijk in aanmerking voor plaatsing op de Landelijke Implementatieagenda van het programma Zorg Evaluatie & Gepast Gebruik (ZE&GG), waarin alle betrokken partijen in de medisch-specialistische zorg samenwerken aan de implementatie van bewezen beste zorg. De Federatie levert namens het veld goed onderbouwde aanbevelingen aan, die zijn getoetst op de behoefte aan een implementatie-impuls. De onderwerpen op de Implementatieagenda zijn onderdeel van landelijke zorginkoopafspraken tussen zorgverzekeraars en zorgaanbieders. Voor de beoordeling van aanbevelingen uit richtlijnen wordt gebruikgemaakt van de implementatietabel. Op basis hiervan kunnen we de andere partijen goed informeren en gezamenlijk besluiten of plaatsing op de Implementatieagenda passend is.*

Agenderen-tabel

Kennisvragen zijn vragen over bestaande zorg, die nog onvoldoende zijn onderbouwd met wetenschappelijke literatuur. Het richtlijncluster heeft een belangrijke rol bij het identificeren van kennisvragen bij het ontwikkelen van een richtlijnmodule. De input uit deze Agenderen-tabel wordt gebruikt bij het opstellen van een kennisagenda. Alle geïnventariseerde kennisvragen (vanuit achterban, patiënten en richtlijnen) op het gebied van zorgevaluatie worden beoordeeld door de kennisagenda werkgroep en daarna geprioriteerd door alle relevante partijen tijdens een prioriteringsbijeenkomst. Het is belangrijk om de kennisvraag scherp te formuleren, zodat resultaten van een zorgevaluatie onderzoek daadwerkelijk opgenomen kunnen worden in een richtlijnmodule.

Vraag	***Antwoord*** *Kruis aan*	*Vul in*
A1. Is onderzoek wenselijk om de <u>uitgangsvraag of zoekvraag</u> (met		
	X	Ja :

meer/voldoende zekerheid) te kunnen beantwoorden?		
A2. Wat is de kennisvraag?	Kennis-vraag	Wat is de optimale drempel stralingsdosis (in Gy) voor het indiceren van profylactische tandextracties ter preventie van osteoradionecrose bij patiënten met hoofd-halskanker die radiotherapie ondergaan?
	P	Patiënten met hoofd-halskanker die radiotherapie (± chemotherapie) ondergaan
	I	Profylactische tandextracties gebaseerd op een hogere drempeldosis (bijv. ≥50 Gy)
	C	Profylactische tandextracties gebaseerd op een lagere drempeldosis (bijv. 40 Gy) **O**
	O	Incidentie van osteoradionecrose, functionele uitkomst (kauwfunctie), kwaliteit van leven
A3. Waarom is dit een belangrijke kennisvraag?	Toelichting	Er bestaat momenteel geen evidence-based consensus over de optimale drempeldosis voor profylactische tandextracties. De huidige variatie tussen centra (40 vs. 50 Gy) kan leiden tot zowel overbehandeling (onnodig tandverlies en verminderde kwaliteit van leven) als onderbehandeling (verhoogd risico op ORN). Het beantwoorden van deze vraag is essentieel om zorg te harmoniseren en patiëntuitkomsten te optimaliseren.
A4. Welk onderzoeksdesign is passend om deze kennisvraag te beantwoorden?		RCT
	X	Observationeel onderzoek (CCT)
		Kwaliteitsregistratie
		Anders, namelijk
	Toelichting	Een CCT zou de voorkeur hebben om causale effecten vast te stellen. Grote prospectieve cohortstudies met dosimetrische analyse zijn een realistisch en waardevol alternatief voor een RCT.
A5. Zijn er een andere kennisvragen naar voren gekomen die passen bij het <u>onderwerp van de module</u>, maar niet hetzelfde zijn als		
		Ja

de uitgangs- of zoekvraag en waar *geen* passend bewijs voor is? *Bijvoorbeeld:* het onderwerp van de module is 'Behandeling van aandoening X', waarin behandeling A en behandeling B met elkaar worden vergeleken. De voor- en nadelen van behandeling C ten opzichte van A en/of B is dan nog een openstaande kennisvraag als hier geen passend bewijs voor is. Het past wel bij het onderwerp van deze module en de resultaten van zorgevaluatie onderzoek zouden wel in deze module geduid kunnen worden.		
A6. Wat is de kennisvraag?	Kennis-vraag	Welke preventieve interventies (bijv. hyperbare zuurstoftherapie, PENTO, fluoride-interventies of combinaties daarvan) zijn effectief in het voorkomen van osteoradionecrose bij patiënten na radiotherapie die dento-alveolaire chirurgie ondergaan?
	P	Patiënten die radiotherapie in het hoofd-halsgebied hebben ondergaan en een dento-alveolaire ingreep nodig hebben
	I	Preventieve interventies zoals hyperbare zuurstoftherapie (HBO), pentoxifylline + tocoferol (PENTO), fluoridegebruik
	C	Standaardzorg zonder deze interventies of alternatieve interventies
	O	Incidentie van osteoradionecrose, complicaties, kwaliteit van leven
A7. Waarom is dit een belangrijke kennisvraag?	Toelichting	De huidige literatuur toont zeer lage bewijskracht en inconsistente resultaten voor preventieve interventies zoals HBO en PENTO. Tegelijkertijd worden deze interventies in de praktijk toegepast en zijn zij kostbaar en belastend voor patiënten. Betrouwbaar bewijs is nodig om doelmatige en effectieve zorg te waarborgen en overbehandeling te voorkomen.

A8. Welk onderzoeksdesign is passend om deze kennisvraag te beantwoorden?		RCT
	Toelichting	Gerandomiseerde studies zijn noodzakelijk om de effectiviteit van individuele en gecombineerde preventieve interventies vast te stellen, gezien de huidige onzekerheid en het risico op bias in bestaande studies.

[a)] Formuleer hier de kennisvraag als een onderzoekvraag. Dit kan de zoekvraag zijn, maar kan ook afwijken. Om het juiste onderzoek te doen is het van groot belang dat de kennisvragen scherp geformuleerd worden, in de vorm van een PICO. Uitgangspunt is dat een kennisvraag met één zorgevaluatie onderzoek opgelost kan worden.

5 [b)] Beschrijf in 2 à 3 zinnen waarom dit een relevante kennisvraag is.

Literatuur

Aarup-Kristensen S, Hansen CR, Forner L, Brink C, Eriksen JG, Johansen J. Osteoradionecrosis of the mandible after radiotherapy for head and neck cancer: risk factors and dose-volume correlations. Acta Oncol. 2019;58(10):1373-7. Epub 20190731. doi: 10.1080/0284186X.2019.1643037. PubMed PMID: 31364903.

Brahm CO, Borg C, Malm D, Fridlund B, Lewin F, Zemar A, et al. Patients with head and neck cancer treated with radiotherapy: Their experiences after 6 months of prophylactic tooth extractions and temporary removable dentures. Clin Exp Dent Res. 2021;7(5):894-902. Epub 20210323. doi: 10.1002/cre2.418. PubMed PMID: 33754493; PubMed Central PMCID: PMC8543473.

Bruins HH, Jolly DE, Koole R. Preradiation dental extraction decisions in patients with head and neck cancer. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1999;88(4):406-12. doi: 10.1016/s1079-2104(99)70053-3. PubMed PMID: 10519746.

Bruins HH, Koole R, Jolly DE. Pretherapy dental decisions in patients with head and neck cancer. A proposed model for dental decision support. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1998;86(3):256-67. doi: 10.1016/s1079-2104(98)90169-x. PubMed PMID: 9768412.

Buurman DJM, Willemsen ACH, Speksnijder CM, Baijens LWJ, Hoeben A, Hoebers FJP, et al. Tooth extractions prior to chemoradiation or bioradiation are associated with weight loss during treatment for locally advanced oropharyngeal cancer. Support Care Cancer. 2022;30(6):5329-38. Epub 20220312. doi: 10.1007/s00520-022-06942-6. PubMed PMID: 35278135; PubMed Central PMCID: PMC9046292.

Caparrotti F, Huang SH, Lu L, Bratman SV, Ringash J, Bayley A, et al. Osteoradionecrosis of the mandible in patients with oropharyngeal carcinoma treated with intensity-modulated radiotherapy. Cancer. 2017;123(19):3691-700. Epub 20170613. doi: 10.1002/cncr.30803. PubMed PMID: 28608925.

Chang CT, Liu SP, Muo CH, Liao YF, Chiu KM, Tsai CH, Huang YF. The impact of dental therapy timelines and irradiation dosages on osteoradionecrosis in oral cancer patients: A population-based cohort study. Oral Oncol. 2022;128:105827. Epub 20220329. doi: 10.1016/j.oraloncology.2022.105827. PubMed PMID: 35364549.

Chang DT, Sandow PR, Morris CG, Hollander R, Scarborough L, Amdur RJ, Mendenhall WM. Do pre-irradiation dental extractions reduce the risk of osteoradionecrosis of the mandible? Head Neck. 2007;29(6):528-36. doi: 10.1002/hed.20538. PubMed PMID: 17230555.

Chin D, Mast H, Verduijn GM, Moring M, Petit SF, Rozema FR, et al. Personalizing dental screening and prevention protocols in dentulous patients with oropharyngeal cancer undergoing radiotherapy: A retrospective cohort study. Clin Transl Radiat Oncol. 2024;46:100759. Epub 20240307. doi: 10.1016/j.ctro.2024.100759. PubMed PMID: 38495648; PubMed Central PMCID: PMC10940125.

Chopra S, Kamdar D, Ugur OE, Chen G, Peshek B, Marunick M, et al. Factors predictive of severity of osteoradionecrosis of the mandible. Head Neck. 2011;33(11):1600-5. Epub 20110411. doi: 10.1002/hed.21654. PubMed PMID: 21484922.

Clough S, Burke M, Daly B, Scambler S. The impact of pre-radiotherapy dental extractions on head and neck cancer patients: a qualitative study. Br Dent J. 2018;225(1):28-32. Epub 20180622. doi: 10.1038/sj.bdj.2018.442. PubMed PMID: 29930400.

de Almeida-Silva LA, Lupp JDS, Sobral-Silva LA, Dos Santos LAR, Marques TO, da Silva DBR, et al. The incidence of osteoradionecrosis of the jaws in oral cavity cancer patients treated with intensity-modulated radiotherapy: a systematic review and meta-analysis. Oral Surg Oral Med Oral Pathol Oral Radiol. 2024;138(1):66-78. Epub 20240418. doi: 10.1016/j.oooo.2024.04.008. PubMed PMID: 38772792.

De Felice F, Thomas C, Patel V, Connor S, Michaelidou A, Sproat C, et al. Osteoradionecrosis following treatment for head and neck cancer and the effect of radiotherapy dosimetry: the Guy's and St Thomas' Head and Neck Cancer Unit experience. Oral Surg Oral Med Oral Pathol Oral Radiol. 2016;122(1):28-34. Epub 20160114. doi: 10.1016/j.oooo.2016.01.007. PubMed PMID: 27039003.

de Groot RJ, Wetzels JW, Merkx MAW, Rosenberg A, de Haan AFJ, van der Bilt A, et al. Masticatory function and related factors after oral oncological treatment: A 5-year prospective study. Head Neck. 2019;41(1):216-24. Epub 20181215. doi: 10.1002/hed.25445. PubMed PMID: 30552819; PubMed Central PMCID: PMC6590803.

Dekker H, Bravenboer N, van Dijk D, Bloemena E, Rietveld DHF, Ten Bruggenkate CM, Schulten E. The irradiated human mandible: A quantitative study on bone vascularity. Oral Oncol. 2018;87:126-30. Epub 20181102. doi: 10.1016/j.oraloncology.2018.10.030. PubMed PMID: 30527227.

Dekker H, Schulten E, van Ruijven L, van Essen HW, Blom GJ, Bloemena E, et al. Bone microarchitecture and turnover in the irradiated human mandible. J Craniomaxillofac Surg. 2020;48(8):733-40. Epub 20200609. doi: 10.1016/j.jcms.2020.05.015. PubMed PMID: 32591131.

DeLuke D, Carrico C, Ray C, Stilianoudakis S, Holler S, Padilla L, Song S. Is Dose Volume a Better Predictor of Osteoradionecrosis Risk Than Total Dose for Patients Who Have Received Head and Neck Radiation? J Oral Maxillofac Surg. 2022;80(9):1557-63. Epub 20220425. doi: 10.1016/j.joms.2022.04.009. PubMed PMID: 35594907.

Dumoulin S, van Maanen A, Magremanne M. Dental prevention of maxillo-mandibular osteoradionecrosis: A ten-year retrospective study. J Stomatol Oral Maxillofac Surg. 2021 Apr;122(2):127-134. doi: 10.1016/j.jormas.2020.05.022. Epub 2020 Jun 11. PMID: 32535252.

El-Rabbany M, Duchnay M, Raziee HR, Zych M, Tenenbaum H, Shah PS, et al. Interventions for preventing osteoradionecrosis of the jaws in adults receiving head and neck radiotherapy. Cochrane Database Syst Rev. 2019 Nov 20;2019(11):CD011559. doi: 10.1002/14651858.CD011559.pub2. PMID: 31745986; PMCID: PMC6953365.

Forner LE, Dieleman FJ, Shaw RJ, Kanatas A, Butterworth CJ, Kjeller G, et al. Hyperbaric oxygen treatment of mandibular osteoradionecrosis: Combined data from the two randomized clinical trials DAHANCA-21 and NWHHT2009-1. Radiother Oncol. 2022 Jan;166:137-144. doi: 10.1016/j.radonc.2021.11.021. Epub 2021 Nov 26. PMID: 34843843.

Frankart AJ, Frankart MJ, Cervenka B, Tang AL, Krishnan DG, Takiar V. Osteoradionecrosis: Exposing the Evidence Not the Bone. Int J Radiat Oncol Biol Phys. 2021 Apr 1;109(5):1206-1218. doi: 10.1016/j.ijrobp.2020.12.043. Epub 2021 Jan 4. PMID: 33412258.

Gomes-Silva W, Morais-Faria K, Rivera C, Najas GF, Marta GN, da Conceicao Vasconcelos KGM, et al. Impact of radiation on tooth loss in patients with head and neck cancer: a retrospective dosimetric-based study. Oral Surg Oral Med Oral Pathol Oral Radiol. 2021;132(4):409-17. Epub 20210710. doi: 10.1016/j.oooo.2021.06.021. PubMed PMID: 34366269.

Iqbal Z, Kyzas P. Analysis of the critical dose of radiation therapy in the incidence of Osteoradionecrosis in head and neck cancer patients: a case series. BDJ Open. 2020;6:18. Epub 20200924. doi: 10.1038/s41405-020-00044-3. PubMed PMID: 33042578; PubMed Central PMCID: PMC7515872.

Kanatas A, Ghazali N, Lowe D, Udberg M, Heseltine J, O'Mahony E, Rogers SN. Issues patients would like to discuss at their review consultation: variation by early and late stage oral, oropharyngeal and laryngeal subsites. Eur Arch Otorhinolaryngol. 2013;270(3):1067-74. Epub 20120629. doi: 10.1007/s00405-012-2092-6. PubMed PMID: 22743645.

Kojima Y, Yanamoto S, Umeda M, Kawashita Y, Saito I, Hasegawa T, et al. Relationship between dental status and development of osteoradionecrosis of the jaw: a multicenter retrospective study. Oral Surg Oral Med Oral Pathol Oral Radiol. 2017;124(2):139-45. Epub 20170504. doi: 10.1016/j.oooo.2017.04.012. PubMed PMID: 28606831.

Kubota H, Miyawaki D, Mukumoto N, Ishihara T, Matsumura M, Hasegawa T, et al. Risk factors for osteoradionecrosis of the jaw in patients with head and neck squamous cell carcinoma. Radiat Oncol. 2021;16(1):1. Epub 20210105. doi: 10.1186/s13014-020-01701-5. PubMed PMID: 33402192; PubMed Central PMCID: PMC7786900.

Lee CT, Litwin S, Yao C, Liu JC, Ridge JA, Galloway TJ. Osteoradionecrosis rate in oropharynx cancer treated with dose volume histogram based constraints. Radiother Oncol. 2022;176:215-21. Epub 20221015. doi: 10.1016/j.radonc.2022.10.011. PubMed PMID: 36252636.

Liao PH, Lin C, Huang JY, Lin HM, Kuo TJ. Association between tooth extraction during radiotherapy and the risk of osteoradionecrosis in patients with head and neck cancers. Eur Arch Otorhinolaryngol. 2023;280(6):2945-52. Epub 20230309. doi: 10.1007/s00405-023-07885-2. PubMed PMID: 36892614.

Matsuo K, Fujishima I. Textural Changes by Mastication and Proper Food Texture for Patients with Oropharyngeal Dysphagia. Nutrients. 2020;12(6). Epub 20200530. doi: 10.3390/nu12061613. PubMed PMID: 32486264; PubMed Central PMCID: PMC7352363.

NKI. Nederlandse werkgroep Hoofd-Hals tumoren. Hypofarynxcarcinoom, landelijke richtlijn versie: 2.0 2010 [04-11-2024]. Available from: http://www.med-info.nl/Richtlijnen/Oncologie/Hoofdhalstumoren/Hypofarynxcarcinoom.pdf.

NKI. Nederlandse werkgroep Hoofd-Hals tumoren. Larynxcarcinoom, landelijke richtlijn versie: 3.0 2010 [04-11-2024]. Available from: http://www.med-info.nl/Richtlijnen/Oncologie/Hoofdhalstumoren/Larynxcarcinoom.pdf.

NKI. Nederlandse werkgroep Hoofd-Hals tumoren. Mondholte- en orofarynxcarcinoom, landelijke richtlijn versie: 1.4 2004 [04-11-2024]. Available from: http://www.med-info.nl/Richtlijnen/Oncologie/Hoofdhalstumoren/Mondholte-%20en%20orofarynxcarcinoom.pdf.

Normando AGC, Perez-de-Oliveira ME, Guerra ENS, Lopes MA, Rocha AC, Brandao TB, et al. To extract or not extract teeth prior to head and neck radiotherapy? A systematic review and meta-analysis. Support Care Cancer. 2022;30(11):8745-59. Epub 20220617. doi: 10.1007/s00520-022-07215-y. PubMed PMID: 35713725.

Owosho AA, Tsai CJ, Lee RS, Freymiller H, Kadempour A, Varthis S, et al. The prevalence and risk factors associated with osteoradionecrosis of the jaw in oral and oropharyngeal cancer patients treated with intensity-modulated radiation therapy (IMRT): The Memorial Sloan Kettering Cancer Center experience. Oral Oncol. 2017;64:44-51. Epub 20161203. doi: 10.1016/j.oraloncology.2016.11.015. PubMed PMID: 28024723; PubMed Central PMCID: PMC5560021.

Parahoo RS, Semple CJ, Killough S, McCaughan E. The experience among patients with multiple dental loss as a consequence of treatment for head and neck cancer: A qualitative study. J Dent. 2019;82:30-7. Epub 20190130. doi: 10.1016/j.jdent.2019.01.010. PubMed PMID: 30710651.

Patel V, Di Silvio L, Kwok J, Burns M, Henley Smith R, Thavaraj S, Veschini L. The impact of intensity-modulated radiation treatment on dento-alveolar microvasculature in pharyngeal cancer implant patients. J Oral Rehabil. 2020;47(11):1411-21. Epub 20200907. doi: 10.1111/joor.13084. PubMed PMID: 32841377.

Peterson DE, Koyfman SA, Yarom N, Lynggaard CD, Ismaila N, Forner LE, et al. Prevention and Management of Osteoradionecrosis in Patients With Head and Neck Cancer Treated With Radiation Therapy: ISOO-MASCC-ASCO Guideline. J Clin Oncol. 2024;42(16):1975-96. Epub 20240501. doi: 10.1200/JCO.23.02750. PubMed PMID: 38691821.

Reuther T, Schuster T, Mende U, Kübler A. Osteoradionecrosis of the jaws as a side effect of radiotherapy of head and neck tumour patients--a report of a thirty year retrospective review. Int J Oral Maxillofac Surg. 2003 Jun;32(3):289-95. doi: 10.1054/ijom.2002.0332. PMID: 12767877.

Rogers SN, Alvear A, Anesi A, Babin E, Balik A, Batstone M, et al. Variations in concerns reported on the patient concerns inventory in patients with head and neck cancer from different health settings across the world. Head Neck. 2020;42(3):498-512. Epub 20191213. doi: 10.1002/hed.26027. PubMed PMID: 31833121; PubMed Central PMCID: PMC7079080.

Samani M, Beheshti S, Cheng H, Sproat C, Kwok J, Patel V. Prophylactic pentoxifylline and vitamin E use for dental extractions in irradiated patients with head and neck cancer. Oral Surg Oral Med Oral Pathol Oral Radiol. 2022 Mar;133(3):e63-e71. doi: 10.1016/j.oooo.2021.08.007. Epub 2021 Aug 21. PMID: 34753695.

Saunders D, Koyfman SA, Ismaila N, Futran ND, Mowery YM, Watson E, et al. Prevention and Management of Osteoradionecrosis in Patients With Head and Neck Cancer Treated With Radiation Therapy: ISOO-MASCC-ASCO Guideline Clinical Insights. JCO Oncol Pract. 2024:OP2400182. Epub 20240501. doi: 10.1200/OP.24.00182. PubMed PMID: 38691818.

Schuurhuis JM, Stokman MA, Witjes MJH, Reintsema H, Langendijk JA, Vissink A, Spijkervet FKL. Patients with advanced periodontal disease before intensity-modulated radiation therapy are prone to develop bone healing problems: a 2-year prospective follow-up study. Support Care Cancer. 2018;26(4):1133-42. Epub 20171031. doi: 10.1007/s00520-017-3934-y. PubMed PMID: 29090383; PubMed Central PMCID: PMC5847027.

Shaw R, Tesfaye B, Bickerstaff M, Silcocks P, Butterworth C. Refining the definition of mandibular osteoradionecrosis in clinical trials: The cancer research UK HOPON trial (Hyperbaric Oxygen for the Prevention of Osteoradionecrosis). Oral Oncol. 2017 Jan;64:73-77. doi: 10.1016/j.oraloncology.2016.12.002. Epub 2016 Dec 10. PMID: 28024727.

Shaw RJ, Butterworth CJ, Silcocks P, Tesfaye BT, Bickerstaff M, Jackson R, et al. HOPON (Hyperbaric Oxygen for the Prevention of Osteoradionecrosis): A Randomized Controlled Trial of Hyperbaric Oxygen to Prevent Osteoradionecrosis of the Irradiated Mandible After Dentoalveolar Surgery. Int J Radiat Oncol Biol Phys. 2019 Jul 1;104(3):530-539. doi: 10.1016/j.ijrobp.2019.02.044. Epub 2019 Mar 7. PMID: 30851351.

Spijkervet FKL, Brennan MT, Peterson DE, Witjes MJH, Vissink A. Research Frontiers in Oral Toxicities of Cancer Therapies: Osteoradionecrosis of the Jaws. J Natl Cancer Inst Monogr. 2019;2019(53). doi: 10.1093/jncimonographs/lgz006. PubMed PMID: 31425599.

Spijkervet FKL, Schuurhuis JM, Stokman MA, Witjes MJH, Vissink A. Should oral foci of infection be removed before the onset of radiotherapy or chemotherapy? Oral Dis. 2021;27(1):7-13. Epub 20200601. doi: 10.1111/odi.13329. PubMed PMID: 32166855; PubMed Central PMCID: PMC7818265.

Studer G, Gratz KW, Glanzmann C. Osteoradionecrosis of the mandibula in patients treated with different fractionations. Strahlenther Onkol. 2004;180(4):233-40. doi: 10.1007/s00066-004-1171-z. PubMed PMID: 15057434.

Tonosaki K (a), Yonenaga K, Ono S, Itai S, Oyama S, Mizuno T, et al. Swallowing evaluation by the Kuchikara Taberu Balance Chart and videoendscopic examination reveals that respiratory conditions, chewing, and position are strongly related to dysphagia. Odontology. 2021;109(2):448-52. Epub 20201027. doi: 10.1007/s10266-020-00561-5. PubMed PMID: 33108554.

Tonosaki K (b), Yonenaga K, Ono S, Itai S, Oyama S, Mizuno T, et al. Correction to: Swallowing evaluation by the Kuchikara Taberu Balance Chart and videoendscopic examination reveals that respiratory conditions, chewing, and position are strongly related to dysphagia. Odontology. 2021;109(2):453-4. doi: 10.1007/s10266-020-00575-z. PubMed PMID: 33346895.

Treister NS, Brennan MT, Sollecito TP, Schmidt BL, Patton LL, Mitchell R, et al. Exposed bone in patients with head and neck cancer treated with radiation therapy: An analysis of the Observational Study of Dental Outcomes in Head and Neck Cancer Patients (OraRad). Cancer. 2022;128(3):487-96. Epub 20211019. doi: 10.1002/cncr.33948. PubMed PMID: 34665873; PubMed Central PMCID: PMC8776577.

Tsai CJ, Hofstede TM, Sturgis EM, Garden AS, Lindberg ME, Wei Q, et al. Osteoradionecrosis and radiation dose to the mandible in patients with oropharyngeal cancer. Int J Radiat Oncol Biol Phys. 2013;85(2):415-20. Epub 20120712. doi: 10.1016/j.ijrobp.2012.05.032. PubMed PMID: 2275804.

van Dijk LV, Abusaif AA, Rigert J, Naser MA, Hutcheson KA, Lai SY, et al. Normal Tissue Complication Probability (NTCP) Prediction Model for Osteoradionecrosis of the Mandible in Patients With Head and Neck Cancer After Radiation Therapy: Large-Scale Observational Cohort. Int J Radiat Oncol Biol Phys. 2021;111(2):549-58. Epub 20210610. doi: 10.1016/j.ijrobp.2021.04.042. PubMed PMID: 33965514; PubMed Central PMCID: PMC8906058.

Willemsen ACH, Hoeben A, Lalisang RI, Van Helvoort A, Wesseling FWR, Hoebers F, et al. Disease-induced and treatment-induced alterations in body composition in locally advanced head and neck squamous cell carcinoma. J Cachexia Sarcopenia Muscle. 2020;11(1):145-59. Epub 20190919. doi: 10.1002/jcsm.12487. PubMed PMID: 31536685; PubMed Central PMCID: PMC7015232.

Yang Y, Muller OM, Shiraishi S, Harper M, Amundson AC, Wong WW, et al. Empirical Relative Biological Effectiveness (RBE) for Mandible Osteoradionecrosis (ORN) in Head and Neck Cancer Patients Treated With Pencil-Beam-Scanning Proton Therapy (PBSPT): A Retrospective, Case-Matched Cohort Study. Front Oncol. 2022;12:843175. Epub 20220303. doi: 10.3389/fonc.2022.843175. PubMed PMID: 35311159; PubMed Central PMCID: PMC8928456.

Table 1. Assessment and treatment of oral foci within or outside the radiation field
From: Patients with advanced periodontal disease before intensity-modulated radiation therapy are prone to develop bone healing problems: a 2-year prospective follow-up study (Schuurhuis 2018)

Assessed tooth problems	Treatment if cumulative dose > 40 Gy[a]	Treatment if cumulative dose < 40 Gy or outside the radiation portal[a]
Caries profunda	Tooth extraction	Restoration, if necessary combined with endodontic treatment, or tooth extraction
Periapical pathosis (on radiographs) without symptoms and/or additional problems	In teeth *without* root canal filling: endodontic treatment and/or apexification In teeth *with* root canal filling: endodontic re-treatment, apexification, or tooth extraction (needed in case of pre-radiotherapy time limitations)	In teeth *without* root canal filling: endodontic treatment In teeth *with* root canal filling: endodontic re-treatment, apexification, or tooth extraction Treatment can be postponed until after radiotherapy
Extensive periapical pathosis (on radiographs) combined with periodontal disease, in afunctional teeth or *with symptoms*	Tooth extraction	In teeth *without* root canal filling: endodontic treatment combined with initial periodontal treatment In teeth *with* root canal filling: endodontic re-treatment, apexification, or tooth extraction depending on the prognosis
Avital pulp *with symptoms* without periapical radiolucency on radiographs	Endodontic treatment or tooth extraction (which might be necessary in case of pre-radiotherapy time limitations)	Endodontic treatment or tooth extraction depending on the prognosis
Avital pulp *without symptoms* and without periapical radiolucency on radiographs	Endodontic treatment or tooth extraction (needed in case of pre-radiotherapy time limitations)	Endodontic treatment (which can be postponed until after radiotherapy)
Periodontal disease with: Pockets 4–5 mm Pockets ≥ 6 mm Gingival recessions ≥ 6 mm	Initial periodontal therapy Tooth extraction Tooth extraction	Initial periodontal therapy Initial periodontal therapy Only recession requires no treatment
Impacted teeth or roots fully covered by bone without radiographic abnormalities	No treatment If problems are expected in the future: tooth extraction	No treatment
Impacted teeth or roots *not fully covered* by bone or with radiographic abnormalities (e.g., cysts, apical radiolucency)	Tooth extraction	No treatment or, in case of symptoms, surgical removal Roots with periapical radiolucency might be worth preserving by endodontic treatment and restoration (which can be postponed until after radiotherapy)
Cysts	Surgical removal	Surgical removal

Assessed tooth problems	Treatment if cumulative dose > 40 Gy[a]	Treatment if cumulative dose < 40 Gy or outside the radiation portal[a]
Internal or external root resorption	Tooth extraction	Endodontic treatment or tooth extraction depending on the prognosis

Table of excluded studies (PICO 1)

Reference	Reason for exclusion
Berger A, Bensadoun RJ. Dose de tolérance des tissus sains: la mandibule [Normal tissue tolerance to external beam radiation therapy: the mandible]. Cancer Radiother. 2010 Jul;14(4-5):295-300. French. doi: 10.1016/j.canrad.2010.03.011. Epub 2010 Jul 1. PMID: 20594892.	Article in French
de Almeida-Silva LA, Lupp JDS, Sobral-Silva LA, Dos Santos LAR, Marques TO, da Silva DBR, Caneppele TMF, Bianchi-de-Moraes M. The incidence of osteoradionecrosis of the jaws in oral cavity cancer patients treated with intensity-modulated radiotherapy: a systematic review and meta-analysis. Oral Surg Oral Med Oral Pathol Oral Radiol. 2024 Jul;138(1):66-78. doi: 10.1016/j.oooo.2024.04.008. Epub 2024 Apr 18. PMID: 38772792.	Wrong I/C (does not compare tooth extraction in combination with different radiation doses)
Nabil S, Samman N. Incidence and prevention of osteoradionecrosis after dental extraction in irradiated patients: a systematic review. Int J Oral Maxillofac Surg. 2011 Mar;40(3):229-43. doi: 10.1016/j.ijom.2010.10.005. Epub 2010 Nov 5. PMID: 21115324.	Wrong I/C (does not compare tooth extraction in combination with different radiation doses)
Dekker H, Bravenboer N, van Dijk D, Bloemena E, Rietveld DHF, Ten Bruggenkate CM, Schulten EAJM. The irradiated human mandible: A quantitative study on bone vascularity. Oral Oncol. 2018 Dec;87:126-130. doi: 10.1016/j.oraloncology.2018.10.030. Epub 2018 Nov 2. PMID: 30527227.	Wrong I/C
Kojima Y, Yanamoto S, Umeda M, Kawashita Y, Saito I, Hasegawa T, Komori T, Ueda N, Kirita T, Yamada SI, Kurita H, Senga Y, Shibuya Y, Iwai H. Relationship between dental status and development of osteoradionecrosis of the jaw: a multicenter retrospective study. Oral Surg Oral Med Oral Pathol Oral Radiol. 2017 Aug;124(2):139-145. doi: 10.1016/j.oooo.2017.04.012. Epub 2017 May 4. PMID: 28606831.	Wrong I/C (does not compare tooth extraction at different dosages)
van Dijk LV, Abusaif AA, Rigert J, Naser MA, Hutcheson KA, Lai SY, Fuller CD, Mohamed ASR; on behalf on the MD Anderson Symptom Working Group. Normal Tissue Complication Probability (NTCP) Prediction Model for Osteoradionecrosis of the Mandible in Patients With Head and Neck Cancer After Radiation Therapy: Large-Scale Observational Cohort. Int J Radiat Oncol Biol Phys. 2021 Oct 1;111(2):549-558. doi: 10.1016/j.ijrobp.2021.04.042. Epub 2021 Jun 10. PMID: 33965514; PMCID: PMC8906058.	Wrong study type (prediction model)
Verdonck HW, de Jong JM, Granzier ME, Nieman FH, de Baat C, Stoelinga PJ. Intensity-modulated radiation therapy for oropharyngeal cancer: radiation dosage constraint at the anterior mandible. Oral Oncol. 2009 Jun;45(6):511-4. doi: 10.1016/j.oraloncology.2008.07.007. Epub 2008 Sep 18. PMID: 18804413.	Wrong I/C (does not compare different dosages)
Aarup-Kristensen S, Hansen CR, Forner L, Brink C, Eriksen JG, Johansen J. Osteoradionecrosis of the mandible after radiotherapy for head and neck cancer: risk factors and dose-volume correlations. Acta Oncol. 2019 Oct;58(10):1373-1377. doi: 10.1080/0284186X.2019.1643037. Epub 2019 Jul 31. PMID: 31364903.	Wrong I/C (no comparison between tooth extraction at different doses)
Ben-David MA, Diamante M, Radawski JD, Vineberg KA, Stroup C, Murdoch-Kinch CA, Zwetchkenbaum SR, Eisbruch A. Lack of osteoradionecrosis of the mandible after intensity-modulated radiotherapy for head and neck cancer: likely contributions of both dental care and improved dose distributions. Int J Radiat Oncol Biol Phys. 2007 Jun 1;68(2):396-402. doi: 10.1016/j.ijrobp.2006.11.059. Epub 2007 Feb 22. PMID: 17321069; PMCID: PMC2702207.	Wrong I/C (no comparison between tooth extraction at different doses)
Caparrotti F, Huang SH, Lu L, Bratman SV, Ringash J, Bayley A, Cho J, Giuliani M, Kim J, Waldron J, Hansen A, Tong L, Xu W, O'Sullivan B, Wood R, Goldstein D, Hope A. Osteoradionecrosis of the mandible in patients with oropharyngeal carcinoma treated with intensity-modulated radiotherapy. Cancer. 2017 Oct 1;123(19):3691-3700. doi: 10.1002/cncr.30803. Epub 2017 Jun 13. PMID: 28608925.	Wrong I/C (no comparison between tooth extraction at different doses)
Chang CT, Liu SP, Muo CH, Liao YF, Chiu KM, Tsai CH, Huang YF. The impact of dental therapy timelines and irradiation dosages on osteoradionecrosis in oral cancer patients: A population-based cohort study. Oral Oncol. 2022 May;128:105827. doi: 10.1016/j.oraloncology.2022.105827. Epub 2022 Mar 29. PMID: 35364549.	Wrong I/ C (bundles tooth extraction pre- and post RT)

Chang DT, Sandow PR, Morris CG, Hollander R, Scarborough L, Amdur RJ, Mendenhall WM. Do pre-irradiation dental extractions reduce the risk of osteoradionecrosis of the mandible? Head Neck. 2007 Jun;29(6):528-36. doi: 10.1002/hed.20538. PMID: 17230555.	Wrong I/C (no comparison between tooth extraction at different doses)
Chin D, Mast H, Verduijn GM, Möring M, Petit SF, Rozema FR, Wolvius EB, Jonker BP, Heemsbergen WD. Personalizing dental screening and prevention protocols in dentulous patients with oropharyngeal cancer undergoing radiotherapy: A retrospective cohort study. Clin Transl Radiat Oncol. 2024 Mar 7;46:100759. doi: 10.1016/j.ctro.2024.100759. PMID: 38495648; PMCID: PMC10940125.	Wrong I/C (no comparison between tooth extraction at different doses)
Chopra S, Kamdar D, Ugur OE, Chen G, Peshek B, Marunick M, Kim H, Lin HS, Jacobs J. Factors predictive of severity of osteoradionecrosis of the mandible. Head Neck. 2011 Nov;33(11):1600-5. doi: 10.1002/hed.21654. Epub 2011 Apr 11. PMID: 21484922.	Wrong I/C (no comparison between tooth extraction at different doses)
De Felice F, Thomas C, Patel V, Connor S, Michaelidou A, Sproat C, Kwok J, Burke M, Reilly D, McGurk M, Simo R, Lyons A, Oakley R, Jeannon JP, Lei M, Urbano TG. Osteoradionecrosis following treatment for head and neck cancer and the effect of radiotherapy dosimetry: the Guy's and St Thomas' Head and Neck Cancer Unit experience. Oral Surg Oral Med Oral Pathol Oral Radiol. 2016 Jul;122(1):28-34. doi: 10.1016/j.oooo.2016.01.007. Epub 2016 Jan 14. PMID: 27039003.	Wrong I/C (no comparison between tooth extraction at different doses)
Dekker H, Schulten EAJM, van Ruijven L, van Essen HW, Blom GJ, Bloemena E, Ten Bruggenkate CM, Kullaa AM, Bravenboer N. Bone microarchitecture and turnover in the irradiated human mandible. J Craniomaxillofac Surg. 2020 Aug;48(8):733-740. doi: 10.1016/j.jcms.2020.05.015. Epub 2020 Jun 9. PMID: 32591131.	Wrong I/C (no comparison between tooth extraction at different doses)
Delpon G, Renouf M, Langé M, Blery P, Dupas C, Longis J, Thariat J, Doré M. Systematic dosimetric evaluation of risk of osteoradionecrosis (DERO): First results of dose reporting for preventing teeth osteoradionecrosis after head and neck irradiation. Cancer Radiother. 2023 Apr;27(2):103-108. doi: 10.1016/j.canrad.2022.08.003. Epub 2023 Feb 3. PMID: 36739196.	Wrong study type (builds a model)
DeLuke D, Carrico C, Ray C, Stilianoudakis S, Holler S, Padilla L, Song S. Is Dose Volume a Better Predictor of Osteoradionecrosis Risk Than Total Dose for Patients Who Have Received Head and Neck Radiation? J Oral Maxillofac Surg. 2022 Sep;80(9):1557-1563. doi: 10.1016/j.joms.2022.04.009. Epub 2022 Apr 25. PMID: 35594907.	Wrong I/C (tooth extraction after RT)
Dziegielewski PT, Bernard S, Mendenhall WM, Hitchock KE, Parker Gibbs C, Wang J, Amdur RJ, Silver NL, Hardeman J, Seikaly H, Reschly WJ, Danan D, Sawhney R. Osteoradionecrosis in osseous free flap reconstruction: Risk factors and treatment. Head Neck. 2020 Aug;42(8):1928-1938. doi: 10.1002/hed.26118. Epub 2020 Mar 5. PMID: 32134160.	Wrong I/C (no comparison between tooth extraction at different doses)
Embring A, Onjukka E, Mercke C, Lax I, Berglund A, Bornedal S, Wennberg B, Dalqvist E, Friesland S. Re-Irradiation for Head and Neck Cancer: Cumulative Dose to Organs at Risk and Late Side Effects. Cancers (Basel). 2021 Jun 25;13(13):3173. doi: 10.3390/cancers13133173. PMID: 34202135; PMCID: PMC8269009.	Wrong I/C (no comparison between tooth extraction at different doses)
Glas HH, Kraeima J, Tribius S, Leusink FKJ, Rendenbach C, Heiland M, Stromberger C, Rashad A, Fuller CD, Mohamed ASR, Lai SY, Witjes MJH. Three-Dimensional Evaluation of Isodose Radiation Volumes in Cases of Severe Mandibular Osteoradionecrosis for the Prediction of Recurrence after Segmental Resection. J Pers Med. 2022 May 20;12(5):834. doi: 10.3390/jpm12050834. PMID: 35629256; PMCID: PMC9143211.	Wrong I/C (no comparison between tooth extraction at different doses)
Gomes-Silva W, Morais-Faria K, Rivera C, Najas GF, Marta GN, da Conceição Vasconcelos KGM, de Andrade Carvalho H, de Castro G Jr, Brandão TB, Epstein JB, Santos-Silva AR. Impact of radiation on tooth loss in patients with head and neck cancer: a retrospective dosimetric-based study. Oral Surg Oral Med Oral Pathol Oral Radiol. 2021 Oct;132(4):409-417. doi: 10.1016/j.oooo.2021.06.021. Epub 2021 Jul 10. PMID: 34366269.	Wrong I/C (post-radiation extracted teeth)
Gomez DR, Estilo CL, Wolden SL, Zelefsky MJ, Kraus DH, Wong RJ, Shaha AR, Shah JP, Mechalakos JG, Lee NY. Correlation of osteoradionecrosis and dental events with dosimetric parameters in intensity-modulated radiation therapy for head-and-neck cancer. Int J Radiat Oncol Biol Phys. 2011 Nov 15;81(4):e207-13. doi: 10.1016/j.ijrobp.2011.02.003. Epub 2011 May 11. PMID: 21570202.	Wrong I/C (no comparison between tooth extraction at different doses)
Hentz C, Diaz AZ, Borrowdale RW, Emami B, Kase M, Choi M. Establishing a targeted plan for prophylactic dental extractions in patients with laryngeal cancer receiving adjuvant radiotherapy. Oral Surg Oral Med Oral Pathol Oral Radiol. 2016 Jul;122(1):43-9. doi: 10.1016/j.oooo.2016.01.021. Epub 2016 Feb 13. PMID: 27068679.	Wrong I/C (no comparison between tooth extraction at different doses)
Iqbal Z, Kyzas P. Analysis of the critical dose of radiation therapy in the incidence of Osteoradionecrosis in head and neck cancer patients: a case series. BDJ Open. 2020 Sep 24;6:18. doi: 10.1038/s41405-020-00044-3. PMID: 33042578; PMCID: PMC7515872.	Wrong I/C (no comparison between tooth extraction at different doses)

Jumeau R, Nguyen-Tan PF, Bahig H, Liem X, Lambert L, Schmittbuhl M, Simard D, Filion E. Pre-irradiation dental care: Ready-to-use templates for oropharyngeal cancers. Rep Pract Oncol Radiother. 2018 Jul-Aug;23(4):270-275. doi: 10.1016/j.rpor.2018.06.007. Epub 2018 Jul 26. PMID: 30090026; PMCID: PMC6078107.	Wrong I/C (no comparison between tooth extraction at different doses)
Karaca Y, Beauvois S, Paesmans M, Mokhtari Z, Dequanter D, Wardi CA, Evrard L, Van Gestel D. Retrospective study evaluating dental side effects of radiotherapy in patients treated for head and neck cancer. J Stomatol Oral Maxillofac Surg. 2024 Jun;125(3S):101858. doi: 10.1016/j.jormas.2024.101858. Epub 2024 Mar 30. PMID: 38556165.	Wrong study type (prediction model)
Kovarik PDE, Patil R, Cvek J, Kelly C, Jackson M, Mackenzie L, West N, Willis N, Kovarik JP, Banks R, Kennedy M, Adams J, Iqbal MS. Extra-mandibular Osteoradionecrosis after the Treatment of Head and Neck Cancer. Clin Oncol (R Coll Radiol). 2023 Sep;35(9):e498-e505. doi: 10.1016/j.clon.2023.06.013. Epub 2023 Jun 27. PMID: 37433701.	Wrong I/C (no comparison between tooth extraction at different doses)
Kubota H, Miyawaki D, Mukumoto N, Ishihara T, Matsumura M, Hasegawa T, Akashi M, Kiyota N, Shinomiya H, Teshima M, Nibu KI, Sasaki R. Risk factors for osteoradionecrosis of the jaw in patients with head and neck squamous cell carcinoma. Radiat Oncol. 2021 Jan 5;16(1):1. doi: 10.1186/s13014-020-01701-5. PMID: 33402192; PMCID: PMC7786900.	Wrong I/C (no comparison between tooth extraction at different doses)
Lang K, Held T, Meixner E, Tonndorf-Martini E, Ristow O, Moratin J, Bougatf N, Freudlsperger C, Debus J, Adeberg S. Frequency of osteoradionecrosis of the lower jaw after radiotherapy of oral cancer patients correlated with dosimetric parameters and other risk factors. Head Face Med. 2022 Feb 26;18(1):7. doi: 10.1186/s13005-022-00311-8. PMID: 35219324; PMCID: PMC8881856.	Wrong I/C (no comparison between tooth extraction at different doses)
Lee CT, Litwin S, Yao CMKL, Liu JC, Ridge JA, Galloway TJ. Osteoradionecrosis rate in oropharynx cancer treated with dose volume histogram based constraints. Radiother Oncol. 2022 Nov;176:215-221. doi: 10.1016/j.radonc.2022.10.011. Epub 2022 Oct 15. PMID: 36252636.	Wrong study type (prediction model)
Lee IJ, Koom WS, Lee CG, Kim YB, Yoo SW, Keum KC, Kim GE, Choi EC, Cha IH. Risk factors and dose-effect relationship for mandibular osteoradionecrosis in oral and oropharyngeal cancer patients. Int J Radiat Oncol Biol Phys. 2009 Nov 15;75(4):1084-91. doi: 10.1016/j.ijrobp.2008.12.052. Epub 2009 Mar 26. PMID: 19327914.	Wrong I/C (no comparison between tooth extraction at different doses)
Liao PH, Lin C, Huang JY, Lin HM, Kuo TJ. Association between tooth extraction during radiotherapy and the risk of osteoradionecrosis in patients with head and neck cancers. Eur Arch Otorhinolaryngol. 2023 Jun;280(6):2945-2952. doi: 10.1007/s00405-023-07885-2. Epub 2023 Mar 9. PMID: 36892614.	Wrong I (tooth extraction during radiotherapy)
MD Anderson Head and Neck Cancer Symptom Working Group. Dose-volume correlates of mandibular osteoradionecrosis in Oropharynx cancer patients receiving intensity-modulated radiotherapy: Results from a case-matched comparison. Radiother Oncol. 2017 Aug;124(2):232-239. doi: 10.1016/j.radonc.2017.06.026. Epub 2017 Jul 18. PMID: 28733053; PMCID: PMC5572506.	Wrong I/C (no comparison between tooth extraction at different doses)
Musha A, Shimada H, Kubo N, Kawamura H, Okano N, Sato H, Kaminuma T, Okada K, Anakura M, Adachi A, Shirai K, Saitoh JI, Yokoo S, Chikamatsu K, Ohno T. Clinical features and dosimetric evaluation of carbon ion radiation-induced osteoradionecrosis of mandible in head and neck tumors. Radiother Oncol. 2021 Aug;161:205-210. doi: 10.1016/j.radonc.2021.06.022. Epub 2021 Jun 18. PMID: 34147522.	Wrong I/C (no comparison between tooth extraction at different doses)
Naseer A, Goode F, Doyle T. Osteoradionecrosis - an old problem with new consequences. Curr Opin Support Palliat Care. 2024 Mar 1;18(1):39-46. doi: 10.1097/SPC.0000000000000690. Epub 2024 Dec 22. PMID: 38170197.	Wrong study type (review but not systematic)
Patel V, Di Silvio L, Kwok J, Burns M, Henley Smith R, Thavaraj S, Veschini L. The impact of intensity-modulated radiation treatment on dento-alveolar microvasculature in pharyngeal cancer implant patients. J Oral Rehabil. 2020 Nov;47(11):1411-1421. doi: 10.1111/joor.13084. Epub 2020 Sep 7. PMID: 32841377.	Wrong I/C (no comparison between tooth extraction at different doses)
Patel V, Humbert-Vidan L, Thomas C, Sassoon I, McGurk M, Fenlon M, Urbano TG. Dentoalveolar radiation dose following IMRT in oropharyngeal cancer-An observational study. Spec Care Dentist. 2021 May;41(3):319-326. doi: 10.1111/scd.12578. Epub 2021 Feb 12. PMID: 33576541.	Wrong I/C (no comparison between tooth extraction at different doses)
Saito I, Hasegawa T, Kawashita Y, Kato S, Yamada SI, Kojima Y, Ueda N, Umeda M, Shibuya Y, Kurita H, Kirita T, Akashi M. Association between dental extraction after radiotherapy and osteoradionecrosis: A multi-centre retrospective study. Oral Dis. 2022 May;28(4):1181-1187. doi: 10.1111/odi.13826. Epub 2021 Mar 14. PMID: 33650256.	Wrong I/c (tooth extraction after RT)
Sasahara G, Koto M, Ikawa H, Hasegawa A, Takagi R, Okamoto Y, Kamada T. Effects of the dose-volume relationship on and risk factors for maxillary osteoradionecrosis after carbon ion radiotherapy. Radiat Oncol. 2014 Apr 3;9(1):92. doi: 10.1186/1748-717X-9-92. PMID: 24708583; PMCID: PMC3992144.	Wrong I/C (Carbon ion RT)

Sijtsema ND, Verduijn GM, Nasserinejad K, van Norden Y, Mast H, van der Lugt A, Hoogeman MS, Petit SF. Development of a local dose-response relationship for osteoradionecrosis within the mandible. Radiother Oncol. 2023 Sep;186:109736. doi: 10.1016/j.radonc.2023.109736. Epub 2023 Jun 12. PMID: 37315578.	Wrong I/c (tooth extraction after RT)
Studer G, Grätz KW, Glanzmann C. Osteoradionecrosis of the mandibula in patients treated with different fractionations. Strahlenther Onkol. 2004 Apr;180(4):233-40. doi: 10.1007/s00066-004-1171-z. PMID: 15057434.	Wrong I/C (no comparison between tooth extraction at different doses); Wrong study type (prediction model)
Treister NS, Brennan MT, Sollecito TP, Schmidt BL, Patton LL, Mitchell R, Haddad RI, Tishler RB, Lin A, Shadick R, Hodges JS, Lalla RV. Exposed bone in patients with head and neck cancer treated with radiation therapy: An analysis of the Observational Study of Dental Outcomes in Head and Neck Cancer Patients (OraRad). Cancer. 2022 Feb 1;128(3):487-496. doi: 10.1002/cncr.33948. Epub 2021 Oct 19. PMID: 34665873; PMCID: PMC8776577.	Wrong I/C (no comparison between tooth extraction at different doses)
Tsai CJ, Hofstede TM, Sturgis EM, Garden AS, Lindberg ME, Wei Q, Tucker SL, Dong L. Osteoradionecrosis and radiation dose to the mandible in patients with oropharyngeal cancer. Int J Radiat Oncol Biol Phys. 2013 Feb 1;85(2):415-20. doi: 10.1016/j.ijrobp.2012.05.032. Epub 2012 Jul 12. PMID: 22795804.	Wrong I/C (no comparison between tooth extraction at different doses)
Vischioni B, Russo S, Meuli M, Bonora M, Ronchi S, Ingargiola R, Camarda AM, Imparato S, Preda L, Ciocca M, Molinelli S, Orlandi E. Dosimetric and Clinical Risk Factors for the Development of Maxillary Osteoradionecrosis in Adenoid Cystic Carcinoma (ACC) Patients Treated With Carbon Ion Radiotherapy. Front Oncol. 2022 Mar 2;12:829502. doi: 10.3389/fonc.2022.829502. PMID: 35311095; PMCID: PMC8924362.	Wrong I/C (no comparison between tooth extraction at different doses)
Yang Y, Muller OM, Shiraishi S, Harper M, Amundson AC, Wong WW, McGee LA, Rwigema JM, Schild SE, Bues M, Fatyga M, Anderson JD, Patel SH, Foote RL, Liu W. Empirical Relative Biological Effectiveness (RBE) for Mandible Osteoradionecrosis (ORN) in Head and Neck Cancer Patients Treated With Pencil-Beam-Scanning Proton Therapy (PBSPT): A Retrospective, Case-Matched Cohort Study. Front Oncol. 2022 Mar 3;12:843175. doi: 10.3389/fonc.2022.843175. PMID: 35311159; PMCID: PMC8928456.	Wrong I/C (Photon versus proton)
Yilmaz B, Somay E, Topkan E, Kucuk A, Pehlivan B, Selek U. The predictive value of pretreatment hemoglobin-to-platelet ratio on osteoradionecrosis incidence rates of locally advanced nasopharyngeal cancer patients managed with concurrent chemoradiotherapy. BMC Oral Health. 2023 Apr 20;23(1):231. doi: 10.1186/s12903-023-02937-9. PMID: 37081475; PMCID: PMC10116666.	Wrong I/C (no comparison between tooth extraction at different doses)
Zhang W, Zhang X, Yang P, Blanchard P, Garden AS, Gunn B, Fuller CD, Chambers M, Hutcheson KA, Ye R, Lai SY, Radwan MAS, Zhu XR, Frank SJ. Intensity-modulated proton therapy and osteoradionecrosis in oropharyngeal cancer. Radiother Oncol. 2017 Jun;123(3):401-405. doi: 10.1016/j.radonc.2017.05.006. Epub 2017 May 23. PMID: 28549794; PMCID: PMC5779856.	Wrong I/C (no comparison between tooth extraction at different doses)

Table of excluded studies (PICO 2)

Author and year	Reason for exclusion
Muraki 2019	Not a RCT or quasi-RCT
Sandhu 2020	Not a RCT or quasi-RCT
Van Dijk 2021	Not a RCT or quasi-RCT
Zhonghua 2021	Article in Chinese

Literature search strategy (PICO 1)

Embase.com

No.	Query	Results
#17	#16 NOT (#13 OR #11)	**123**
#16	#9 AND #15	**136**
#15	'case control study'/de OR 'comparative study'/exp OR 'control group'/de OR 'controlled study'/de OR 'controlled clinical trial'/de OR 'crossover procedure'/de OR 'double blind procedure'/de OR 'phase 2 clinical trial'/de OR 'phase 3 clinical trial'/de OR 'phase 4 clinical trial'/de OR 'pretest posttest design'/de OR 'pretest posttest control group design'/de OR 'quasi experimental study'/de OR 'single blind procedure'/de OR 'triple blind procedure'/de OR (((control OR controlled) NEAR/6 trial):ti,ab,kw) OR (((control OR controlled) NEAR/6 (study OR studies)):ti,ab,kw) OR (((control OR controlled) NEAR/1 active):ti,ab,kw) OR 'open label*':ti,ab,kw OR (((double OR two OR three OR multi OR trial) NEAR/1 (arm OR arms)):ti,ab,kw) OR ((allocat* NEAR/10 (arm OR arms)):ti,ab,kw) OR placebo*:ti,ab,kw OR 'sham-control*':ti,ab,kw OR (((single OR double OR triple OR assessor) NEAR/1 (blind* OR masked)):ti,ab,kw) OR nonrandom*:ti,ab,kw OR 'non-random*':ti,ab,kw OR 'quasi-experiment*':ti,ab,kw OR crossover:ti,ab,kw OR 'cross over':ti,ab,kw OR 'parallel group*':ti,ab,kw OR 'factorial trial':ti,ab,kw OR ((phase NEAR/5 (study OR trial)):ti,ab,kw) OR ((case* NEAR/6 (matched OR control*)):ti,ab,kw) OR ((match* NEAR/6 (pair OR pairs OR cohort* OR control* OR group* OR healthy OR age OR sex OR gender OR patient* OR subject* OR participant*)):ti,ab,kw) OR ((propensity NEAR/6 (scor* OR match*)):ti,ab,kw) OR versus:ti OR vs:ti OR compar*:ti OR ((compar* NEAR/1 study):ti,ab,kw) OR (('major clinical study'/de OR 'clinical study'/de OR 'cohort analysis'/de OR 'observational study'/de OR 'cross-sectional study'/de OR 'multicenter study'/de OR 'correlational study'/de OR 'follow up'/de OR cohort*:ti,ab,kw OR 'follow up':ti,ab,kw OR followup:ti,ab,kw OR longitudinal*:ti,ab,kw OR prospective*:ti,ab,kw OR retrospective*:ti,ab,kw OR observational*:ti,ab,kw OR 'cross sectional*':ti,ab,kw OR cross?ectional*:ti,ab,kw OR multicent*:ti,ab,kw OR 'multi-cent*':ti,ab,kw OR consecutive*:ti,ab,kw) AND (group:ti,ab,kw OR groups:ti,ab,kw OR subgroup*:ti,ab,kw OR versus:ti,ab,kw OR vs:ti,ab,kw OR compar*:ti,ab,kw OR 'odds ratio*':ab OR 'relative odds':ab OR 'risk ratio*':ab OR 'relative risk*':ab OR 'rate ratio':ab OR aor:ab OR arr:ab OR rrr:ab OR ((('or' OR 'rr') NEAR/6 ci):ab)))	**15138557**
#14	#13 NOT #11	**14**
#13	#9 AND #12	**15**
#12	'randomized controlled trial'/exp OR random*:ti,ab OR (((pragmatic OR practical) NEAR/1 'clinical trial*'):ti,ab) OR ((('non inferiority' OR noninferiority OR superiority OR equivalence) NEAR/3 trial*):ti,ab) OR rct:ti,ab,kw	**2205867**
#11	#9 AND #10	**8**
#10	'meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab	**1033991**
#9	#7 NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp) AND [2000-2024]/py	**219**
#8	#7 NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	**253**

#7	#6 NOT (('adolescent'/exp OR 'child'/exp) NOT ('adult'/exp OR 'aged'/exp OR 'middle aged'/exp))	**435**
#6	#3 AND #4 AND #5	**440**
#5	#1 OR #2	**664871**
#4	'osteoradionecrosis'/exp OR 'tooth extraction'/exp OR osteoradionecro*:ti,ab,kw OR radioosteonecro*:ti,ab,kw OR orn:ti,ab,kw OR (((tooth OR teeth OR molar* OR dental*) NEAR/3 extract*):ti,ab,kw)	**51647**
#3	('radiation dose'/de OR 'radiation dose response'/exp OR 'radiotherapy dosage'/de OR dose:ti,ab,kw OR doses:ti,ab,kw OR threshold:ti,ab,kw OR cutoff*:ti,ab,kw OR 'cut off*':ti,ab,kw OR dosimetr*:ti,ab,kw) AND (cgy:ti,ab,kw OR gy:ti,ab,kw OR 'gray unit*':ti,ab,kw OR centigray*:ti,ab,kw OR 'centi gray*':ti,ab,kw)	**115893**
#2	'head and neck tumor'/exp 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 (aryepiglot* OR arytenoid* OR epiglot* OR gingiva* OR glottic* 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 'postcricoid area' OR salivar* OR sublingual* OR submandib* OR tongue OR tonsil* OR uadt OR vallecula)):ti,ab,kw)	**664622**
#1	'head and neck squamous cell carcinoma'/exp OR 'hn-scc':ti,ab,kw OR 'hnscc':ti,ab,kw OR 'head and neck squamous cell carcinoma':ti,ab,kw OR 'head neck squamous cell carcinoma':ti,ab,kw OR 'squamous cell carcinoma of head and neck':ti,ab,kw OR lascchn:ti,ab,kw	**54769**

Ovid/Medline

Ovid MEDLINE(R) ALL <1946 to June 05, 2024>

1	(exp Squamous Cell Carcinoma of Head/ and Neck/) or hn-scc.ti,ab,kf. or hnscc.ti,ab,kf. or lascchn.ti,ab,kf. or (squamous cell carcinoma adj2 (head adj1 neck)).ti,ab,kf.	**12686**
2	exp "Head and Neck 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 (aryepiglot* or arytenoid* or epiglot* or gingiva* or glottic* 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 'postcricoid area' or salivar* or sublingual* or submandib* or tongue or tonsil* or uadt or vallecula)).ti,ab,kf.	**448424**
3	1 or 2	**448525**
4	(exp "Radiation Dosage"/ or "Radiotherapy Dosage"/ or dose.ti,ab,kf. or doses.ti,ab,kf. or threshold.ti,ab,kf. or cutoff*.ti,ab,kf. or cut-off*.ti,ab,kf. or dosimetr*.ti,ab,kf.) and (cgy or gy or gray-unit* or centigray* or centi-gray*).ti,ab,kf.	**65460**
5	exp "Osteoradionecrosis"/ or exp "Tooth Extraction"/ or osteoradionecro*.ti,ab,kf. or radioosteonecro*.ti,ab,kf. or orn.ti,ab,kf. or ((tooth or teeth or molar* or dental*) adj3 extract*).ti,ab,kf.	**44722**
6	3 and 4 and 5	**226**
7	6 not ((exp "Adolescent"/ or exp "Child"/ or exp "Infant"/) not exp "Adult"/)	**225**
8	limit 7 to yr="2000 -Current"	**182**
9	meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or scoping or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data extraction" or "data source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid)	**751105**

	adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.	
10	8 and 9	**5**
11	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$3)).tw. or Placebos/ or placebo*.tw.	**2734630**
12	8 and 11	**28**
13	12 not 10	**27**
14	epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case-control.tw. or cohort.tw. or cohort-analy$.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/	**4743770**
15	8 and 14	**122**
16	15 not (12 or 10)	**103**

Literature search strategy (PICO 2)

Embase

No.	Query	Results
#14	#13 NOT #12 RCT	159
#13	#9 AND #11	206
#12	#8 AND #11 SR	86
#11	#7 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)	790
#10	'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)	6513548
#9	('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	2500470
#8	('meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab) NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp) NOT ('conference abstract'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it)	533576
#7	#5 AND #6	987

#6	'prevention study'/exp OR 'prevention'/exp OR prevent*:ab,ti,kw OR prophyla*:ti,ab,kw OR 'intraoral stent*':ti,ab,kw	3201075
#5	#3 OR #4	5432
#4	'osteoradionecrosis'/exp OR 'bone radionecrosis':ti,ab,kw OR 'osteo-radio-necro*':ti,ab,kw OR 'osteo-radionecro*':ti,ab,kw OR 'osteoradionecro*':ti,ab,kw OR ((radiation NEAR/2 osteonecro*):ti,ab,kw) OR 'radiation bone necro*':ti,ab,kw OR 'radio-osteonecro*':ti,ab,kw	2445
#3	#1 AND #2	4573
#2	'bone necrosis'/exp OR 'bone necro*':ti,ab,kw OR 'osteonecro*':ti,ab,kw	43307
#1	'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	1097794

Ovid/Medline

#	Searches	Results
13	12 not 11RCT	36
12	8 and 10	57
11	8 and 9 SR	45
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/)	2121059
9	(meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or scoping or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data extraction" or "data source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.) not (comment/ or editorial/ or letter/ or ((exp animals/ or exp models, animal/) not humans/))	497543
8	7 not ((exp animals/ or exp models, animal/) not humans/) not (letter/ or comment/ or editorial/)	399
7	5 and 6	421
6	exp Primary Prevention/ or exp Secondary Prevention/ or Tertiary Prevention/ or prevent*.ti,ab,kf. or prophyla*.ti,ab,kf.	1783322
5	3 or 4	2456
4	(bone radionecrosis or osteo-radio-necrosis or osteo-radionecrosis or osteoradionecrosis or (radiation adj2 osteonecro*) or radiation bone necrosis or radio-osteonecrosis).ti,ab,kf.	1861
3	1 and 2	748
2	Osteonecrosis/ or bone necro*.ti,ab,kf. or osteonecro*.ti,ab,kf.	15577
1	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.	732292

Evidence tables (PICO 1)

Evidence table for intervention studies (randomized controlled trials)

Research question: What is the effectiveness of preventive measures to prevent osteoradionecrosis in patients receiving radiotherapy for a tumor in the head and neck area?

For full details of the included studies Batstone (2012); Horiot, (1983); Markx, (1985) and Schoen, (2007). We refer to El-Rabbany (2019)

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Shaw 2019 (HOPON)	RCT	Men and women aged ≥18 years with an indication for surgery to the mandible and prior radiation therapy to the mandible of at least 50 Gy. Indications for surgery included extraction of premolar or molar teeth or the placement of osseointegrated dental implants	Chlorhexidine mouthwash and orally administered antibiotics comprised amoxicillin 3 g 1 hour preoperatively, or 1 g administered intravenously, and 250 mg 3 times daily for 5 days postoperatively. Hyperbaric oxygen (HBO) was administered at 2.4 atmospheres absolute for 80 to 90 minutes in 30 daily treatments (20 immediately before and 10 after surgery).	Chlorhexidine mouthwash and orally administered antibiotics comprised amoxicillin 3 g 1 hour preoperatively, or 1 g administered intravenously, and 250 mg 3 times daily for 5 days postoperatively.	6 and 12 months	**Incidence osteoradionecrosis at 6 months:** Intervention: 3 of 47 patients (6.4%) Comparison: 3 of 53 patients (5.7%) Effect size: OR 1.13 (95% CI, 0.14-8.92) No new cases of ORN developed between 6 and 12 months. **Adverse events:** "Patients in the hyperbaric arm had fewer acute symptoms but no significant differences in late pain or quality of life." **"**There were no significant differences in death, hospital admission, incapacitation, or further surgery between the 2 arms."	Dropout after randomization but before treatment was higher in the HBO arm, at 17 of 72 patients (24%) compared with 6 of 72 patients (8%) in the non-HBO arm. Despite the differences in dropout rate, the baseline characteristics were similar whether the comparison was made on patients randomized, per protocol, or those analyzed for the primary endpoint

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

Research question: What is the effectiveness of preventive measures to prevent osteoradionecrosis in patients receiving radiotherapy for a tumor in the head and neck area?
For full details of the included studies Batstone (2012); Horiot, (1983); Markx, (1985) and Schoen, (2007). We refer to El-Rabbany (2019)

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)
Shaw 2019	Unclear Eligible patients were randomly assigned (1:1) to receive or not receive Hyperbaric oxygen (HBO).	Likely Allocation of treatment was unblinded to site investigators and patients.	Likely Allocation of treatment was unblinded to site investigators and patients.	Likely Allocation of treatment was unblinded to site investigators and patients (We assume care providers were also aware of the HBO treatment)	Unlikely Assessment of the primary endpoint was blinded and remotely assessed by a blinded expert panel of investigators.	Unlikely Protocol published,	Unlikely No substantial differences between treatment arms.	Unlikely

5

Bijlage 5 Verantwoording 3

Voor meer details over de gebruikte richtlijnmethodologie verwijzen wij u naar de Werkwijze. Relevante informatie voor de ontwikkeling/herziening van deze richtlijnmodule is hieronder weergegeven.

Initiatief
Initiatief: Cluster Hoofd-halstumoren

Samenstelling van de werkgroep
Voor het ontwikkelen van de richtlijnmodule is eind 2024 een multidisciplinair cluster ingesteld. Het cluster Hoofd-halstumoren bestaat uit meerdere richtlijnen (zie hier de actuele clusterindeling). De stuurgroep bewaakt het proces van modulair onderhoud binnen het cluster. De expertisegroepsleden brengen hun expertise in, indien nodig. De volgende personen uit het cluster zijn betrokken geweest bij de herziening van deze module:

Clusterstuurgroepleden

- Prof. dr. R. (Remco) de Bree, voorzitter (NVKNO)
- Dr. M. (Mischa) de Ridder (NVRO)
- Dr. L.A. (Lot) Devriese (NIV)
- Prof. dr. M.J.H. (Max) Witjes (NVMKA)
- Dr. H.P.M. (Dirk) Kunst (NVKNO)
- R.A. (Rob) Burdorf (PVHH)

Betrokken clusterexpertisegroepleden

- Drs. A.J.M. (Xander) van Bemmel (NVKNO)
- Dr. E.V. (Elisabeth) Sjögren (NVKNO)

Met ondersteuning van

- Dr. A. (Anja) van der Hout (Kennisinstituut van de Federatie Medisch Specialisten)
- Dr. E. (Eline) Pruijn-de Heus (Kennisinstituut van de Federatie Medisch Specialisten)
- Dr. J. (Jing) de Haan-Du (Kennisinstituut van de Federatie Medisch Specialisten)
- Drs. J. (Joline) Rohof (Kennisinstituut van de Federatie Medisch Specialisten)
- Dr. M.S. (Michiel) Oerbekke (Kennisinstituut van de Federatie Medisch Specialisten)
- Alies Oost (Kennisinstituut van de Federatie Medisch Specialisten)

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

Clusterstuurgroepleden

Tabel 5 Gemelde (neven)functies en belangen stuurgroep

Naam	Hoofdfunctie	Nevenwerkzaamheden	Persoonlijke financiële belangen	Persoonlijke relaties	Extern gefinancierd onderzoek	Intellectuele belangen en reputatie	Overige belangen	Datum	Restrictie
Prof. dr. R. (Remco) de Bree (voorzitter)	KNO-arts / hoofd-halschirurg Hoogleraar /	Onbetaald: Board member Dutch Head	Geen	Geen	KWF. Ultrasound and microbubbles to improve tumor perfusion of head and neck cancers. co-	Geen	Geen	12-12-2024	Restricties ten aanzien van

	afdelingshoofd UMC Utrecht	and Neck Society (NWHHT) Chair Research Steering Committee Dutch Head and Neck Society (NWHHT) Member Clinical Audit Board Dutch Head and Neck Audit (DHNA) Chair committtee Revision Dutch Head and Neck Tumor Guidelines Board member Patient advocacy group Patiëntenvereniging Hoofd-Hals (PVHH) Chair advisory committee research data Dutch registries (PRISMA) Chair Dutch section Collegium Oto-Rhino-Laryngologicum Amicitiae Sacrum (CORLAS) Council Member International Academy of Oral Oncology (IAOO)			applicant ZonMw. Metastatic-directed stereotactic body radiation therapy of oligometastases in head and neck squamous cell carcinoma patients. Projectleider KWF. Personalized follow-up in HPV-related oropharyngeal cancer patients using liquid biopsies. Projectleider Maurits en Anna de Kock Stichting en Vaillantfonds. Fluorescentie geassisteerde reconstructieve chirurgie: beoordeling van vitaliteit van weefsels. Projectleider 1. KWF- FDG-PET/CT to reduce the need for sentinel lymph node biopsy in early stage oral cancer (Projectleider JA) 2. KWF - Ex vivo 7T MRI of resection specimen of oral cancer to improve margin control (Projectleider NEE) 3. KWF - Sentinel lymph node detection in early oral cancer using [68Ga]Ga-tilmanocept PET/CT lymphoscintigra (Projectleider JA) 4. Nutricia - Perioperative nutritional intervention with Fortifit Energy® in combination with excersice verstus standard of care (Projectleider JA) 5. Hanarth Fonds - Triage of Patients with High-risk Oral Squamous cell Carcinoma using Artificial Intelligence (TOSCA) (Projectleider NEE)				besluitvorming betreffende perioperatieve voedingsinterventies. Indien relevant: Vice-voorzitter aan te stellen voor wanneer perioperatieve voedingsinterventies worden besproken.
Dhr. Dr. M. (Mischa) de Ridder	Radiotherapeut-oncoloog UMC Utrecht	Secretaris LPRHHT van de NVRO. Lid METC NED-MED	Geen	Geen	Elekta: To evaluate evidence for eventual transition from PDR treatments to HDR treatments in case of possib (Projectleider JA). Hanarth fonds: Improved response assessment after (chemo)-radiotherapy for locally	Geen	Geen	3-1-2025	Geen restricties.

					advanced head and neck squamous (Projectleider NEE).				
Mevr. Dr. L.A. (Lot) Devriese	Internist UMC Utrecht	Dit project en eerder bij FMS kwaliteits agenda. Werkgroep binnen NVMO, CieOOM, off-label oncologische medicatie (vacatiegelden naar UMC Utrecht). Bestuurslid NWHHT	Geen	Geen	Ja, als lokale PI van studies gesponsord door Farma. Met uitbetaling aan de werkgever, niet aan mij persoonlijk. 1. ISAPharm - Fase 3 onderzoek ISA101b (Projectleider NEE) 2. MERUS - Fase 3 onderzoek petosemtamab (Projectleider NEE) 3. CISLOW studie - Fase 2 IIS gesponsord door ZOnMw (Projectleider NEE)	Geen	Geen	14-11-2024	Geen restricties.
Prof. dr. M.J.H. (Max) Witjes	MKA chirurg-HH oncoloog Universitair Medisch Centrum Groningen	Geen	Geen	Geen	• Fluoguide FG001sponsor initiated trial (2024): Determination of Optimal Dose for Visualization of Inadequate Margins in Oral Squamous Cell Carcinoma Using FG001. Protocol: 2024-514508-14-00. Witjes MJH Voskuil FJ, Fluoguide team. (budget € 378.293) (Projectleider JA) • NIH grant (National Institute of Dental and Craniofacial Research 2023) : Ex vivo intraoperative surgical basal margin analysis in head and neck cancer resection: clinical validation (1R01DE033449-01). Tichauer K, J Broncovic & Witjes MJH, Voskuil FJ.(budget USD 2.5Milj) (Projectleider JA) • SNN Grant (2023) : JTF application for IMPACT-Implants . (Budget € 3.6 Milj) Kraeima J, Witjes MJH, Veldsink JW & Center for Business Development UMCG. (Projectleider NEE) • KWF Kankerbestrijding: RUG 13215 (2021) Witjes MJH, GB Halmos, WM Nagengast. Real-time targeted fluorescence endoscopy in patients for detection of unknown primary cancers of the head and neck area (REFLECT study) (Budget €476.000) (Projectleider JA) • WJ Thijn stichting (2021) : Witjes MJH lichtgevende stoffen helpen de chirurg de tumor beter te	Geen	Geen	16-1-2025	Restricties ten aanzien van besluitvorming betreffende de bepaling van de optimale dosis voor visualisatie van onvoldoende snijmarges bij oraal plaveiselcelcarcinoom.

					verwijderen. (Budget €250.000). (Projectleider JA)				
Dhr. H.P.M. (Dirk) Kunst	KNO-arts; Radboudumc-MUMC+	Voorzitter van het "Radboudumc-MUMC+ Expertisecentrum Schedelbasispathologie" Voorzitter "Academische Alliantie Schedelbasispathologie Radboudumc-MUMC+" Voorzitter "Landelijk Overleg Expertisecentra Schedelbasispathologie" (LOES) President van de "European Skull Base Society" (ESBS) Betrokkenheid patientenverenigingen: Neurofibromatose type 2 patientenvereniging Paragangliomen patientenvereniging	Geen	Geen	Euregio: Hoofd-hals paragangliomen; verschillen management Nederland Duitsland (projectleider JA). TU Eindhoven/Tilburg (aflopende ZonMw studie), over voorspellen van groei obv MRI scans bij brughoektumoren (projectleider NEE).	Geen	Geen	14-2-2025	Geen restricties.
Dhr. R.A. (Rob) Burdorf	Neem niet meer deel aan het arbeidsproces (met pensioen)	Lid wetenschappelijke advies commissie van de PVHH	Geen	Geen	Geen	Geen	Geen	12-11-2024	12-11-2024

Betrokken clusterexpertisegroepleden

Tabel 6 Gemelde (neven)functies en belangen expertisegroep

Naam	Hoofdfunctie	Nevenwerkzaam-heden	Persoonlijke financiële belangen	Persoonlijke Relaties	Extern gefinancierd onderzoek	Intellectuele belangen en reputatie	Overige belangen	Datum	Actie

Xander van Bemmel (NVKNO)	Kno arts Hoofd Hals chirurg (Medisch Spectrum Twente)	Geen	Geen	Geen	Geen	Geen	Geen	22-06-2026	Geen restricties.
Elisabeth Sjögren (NVKNO)	Medisch Specialist, LUMC	Onbetaalde bestuursfuncties bij: - European Laryngological Society - Confederation of European ORL-HNS	Geen	Geen	Geen	Geen	Geen	20-05-2026	Voorstel: geen restricties

Kwalitatieve raming van mogelijke financiële gevolgen in het kader van de Wkkgz

Bij de richtlijnmodule voerden de clusterleden conform de Wet kwaliteit, klachten en geschillen zorg (Wkkgz) een kwalitatieve raming uit om te beoordelen of de aanbevelingen mogelijk leiden tot substantiële financiële gevolgen. Bij het uitvoeren van deze beoordeling is de richtlijnmodule op verschillende domeinen getoetst (zie het stroomschema bij Werkwijze).

Module	Uitkomst raming	Toelichting
Module [naam]	[geen/ mogelijk] financiële gevolgen	[plaatsen desbetreffende uitkomst 1, 2, 3, 4 of 5]

Bijlage 6 Literatuursamenvatting module 3 inclusief alle bijlagen

Introduction (English)

In the Netherlands, the standard treatment for patients with a cT2 laryngeal carcinoma without distant metastases (M0) is radiotherapy. However, surgical treatment options, such as (endoscopic) partial laryngeal surgery, are also described in the literature. To date, the role of surgical treatment options in the Netherlands compared to radiotherapy remains insufficiently clear.

Search and select

A systematic review of the literature was performed to answer the following question: What are the (un)beneficial effects of endoscopic surgery or partial laryngectomy on ≥2-year overall survival, ≥2-year disease specific survival, ≥2-year laryngectomy-free survival, ≥2-year locoregional control, voice outcomes, overall quality of life, dysphagia outcomes (including feeding tube, swallowing), airway outcomes (including breathing, dyspnea, tracheotomy), and patient decisional regret in patients with a supraglottic, glottic, or subglottic T2M0 larynx carcinoma (regardless of N-stage) when compared to intensity modulated radiotherapy or volumetric modulated arc therapy?

Table 1. PICO

Patients	Patients with a supraglottic, glottic, or subglottic T2M0 larynx carcinoma, regardless of N-stage
Intervention	Endoscopic surgery (including transoral laser microsurgery [TLM], transoral robotic surgery [TORS]) or partial laryngectomy (including both horizontal and vertical procedures)
Control	Intensity Modulated Radiotherapy (IMRT) or Volumetric Modulated Arc Therapy (VMAT)
Outcomes	≥2-year overall survival, ≥2-year disease specific survival, ≥2-year laryngectomy-free survival, ≥2-year locoregional control, voice outcomes, overall quality of life, dysphagia outcomes (including feeding tube, swallowing), airway outcomes (including breathing, dyspnea, tracheotomy), and patient decisional regret
Other selection criteria	Study design: systematic reviews, randomized controlled trials and other comparative research

<u>Relevant outcome measures</u>

The guideline panel considered ≥2-year overall survival, ≥2-year disease specific survival, ≥2 year laryngectomy-free survival, and ≥2-year locoregional control as **critical outcome measures** for decision making**;** and voice outcomes, overall quality of life, dysphagia outcomes (including feeding tube, swallowing), airway outcomes (including breathing, dyspnea, tracheotomy), and patient decisional regret as **important outcome measures** for decision making.

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

The guideline panel defined the following thresholds as a minimal clinically (patient) important difference. All minimal clinically relevant differences were defined at a minimum of a median follow-up period of three years (in line with "NVMO-commissie ter Beoordeling van Oncologische Middelen (BOM)"):

- Survival
  - Overall survival: > 5% difference, or > 3% and HR< 0.7.
  - Relapse-free survival: HR< 0.7.
- Change in voice quality (see Table 2)
- Dysphagia (see Table 2)
- Breathing: a difference of 10% (RR <0.91 or >1.10; RD 0.10)
- 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.

Table 2. Minimallic clinical important differences for voice quality and dysphagia

Voice quality	Voice-specific questionnaire	VHI	Unclear - a change of 25% in the VHI total score	
	Audio-perceptual analysis	GBRAS Likert scale	Unclear - a change of 25% in the subscale scores	
		Patient self-ratings of voice function/acceptability: -Likert scale (0-3) -Questions on a 100-mm visual analogue scale	Unclear - a change of 25% in the scores	
	Acoustical analysis	F0	Unclear - a change of 25% in the score	
		Jitter (%)	Unclear - a change of 25% in the score	
		Shimmer (dB)	Unclear - a change of 25% in the score	
		HNR	Unclear - a change of 25% in the score	
		CPPS	Unclear - a change of 25% in the score	
	Aerodynamic analysis	MPT	Unclear - a change of 25% in the score	
Dysphagia	Patient-reported outcome (PROM)	Sydney Swallowing Questionnaire (SSQ) (Wallace 2000)	Range of scores (1-1700)	Unclear - a change of 25% in the score
		MD Anderson Dysphagia Inventory (MDADI) – physical (Chen 2001)	Four subscales (0-100)	A change of 10 points in total score (Hutcheson 2016)
		Eating Assessment Tool-10 (EAT-10) (Belafsky 2008)	Range of scores (0-40)	Unclear - a change of 25% in the score
		Swallowing quality of life questionnaire (SWAL-QOL) (Rinkel 2009; Rinkel 2014)	Range of scores (0-100)	A change of 12 points in total score (Rinkel 2014)
	Clinician-reported outcome (CROM)	Functional Oral Intake Scale (FOIS) (Crary 2005)	Ordinal scale (1-7)	A change of 1 point in total score (Messing 2017)
		Performance Status Scale-Head and Neck Cancer (PSS-H&N) (List 1990)		A change of 10 points (Berg 2015)

		Normalcy of Food Intake Scale for Head and Neck Logopedic Part (NFIS-HN-L) (Kalf 2012; Van den Berg 2012)		Unclear - a change of 25% in the score
		Danish Head and Neck Cancer Group (DAHANCA) morbidity scoring system for dysphagia (DAHANCA 2012; Mortensen 2013)	Ordinal scale (0-4)	Unclear - a change of 25% in the score

Search and select (Methods)

A systematic literature search was performed by a medical information specialist using the following bibliographic databases: Embase.com and Ovid/Medline all. Both databases were searched from 2005 to August 18th 2025 for systematic reviews, RCTs and observational studies. Systematic searches were completed using a combination of controlled vocabulary and natural language keywords. The overall search strategy was derived from the following primary search concepts: (1) larynx carcinoma (supraglottic, glottic or subglottic); (2) endoscopic surgery or partial laryngectomy. Duplicates were removed using EndNote software. After deduplication a total of 674 records were imported for title/abstract screening.

Initially, 64 studies were selected based on title and abstract screening. Studies were selected when: the sample consisted of patients with a T2M0 (supraglottic, glottic, subglottic) laryngeal carcinoma, endoscopic surgery or partial laryngectomy was compared to intensity modulated radiotherapy or volumetric modulated arc therapy, an outcome of interest was reported, and the study was a randomized controlled trial or a systematic review of randomized controlled trials. After reading the full text, all studies were excluded (see the exclusion table under the tab 'Evidence tabellen'), and no single study or systematic review could be included.

Summary of literature

Description of studies

No single study or systematic review could be included in the analysis of the literature for patients with a T2M0 laryngeal carcinoma.

Results

No single study or systematic review could be included in the analysis of the literature for patients with a T2M0 laryngeal carcinoma.

Summary of Findings

No single study or systematic review could be included in the analysis of the literature for patients with a T2M0 laryngeal carcinoma.

Kennisvragen

Tijdens de ontwikkeling van deze module is gebleken dat er binnen deze module nog te weinig bewijs is voor de onderbouwing van de aanbeveling en dus kennisvragen bestaan. De werkgroep meent dat (vervolg)onderzoek wenselijk is om in de toekomst een duidelijker antwoord te kunnen geven op vragen uit de praktijk.

Kennisvragen:

- Is de locoregionale controle na partiele larynxchirurgie gelijkwaardig aan locoregionale radiotherapie voor cT2 glottisch larynxcarcinoom?
- Hoe is de subjectieve stemkwaliteit gemeten met PROMs voor patiënten met een cT2 glottisch larynxcarcinoom die partiele larynxchirurgie ondergaan vergeleken met patiënten die locoregionale radiotherapie ondergaan?
- Hoe is de slikfunctie gemeten met PROMs voor patiënten met een cT2 glottisch larynxcarcinoom die partiele larynxchirurgie ondergaan vergeleken met patiënten die locoregionale radiotherapie ondergaan?

Toelichting:

De eerste vraag die beantwoord moet worden is of de oncologische en functionele uitkomsten van partiële larynxchirurgie voor cT2 glottisch larynxcarcinoom patiënten gelijk zijn aan die van radiotherapie in een brede Nederlandse setting. Uit meerdere single center ervaringen lijken hier wel aanwijzingen voor te zijn, maar vergelijkende studies met de huidige standaardbehandeling (locoregionale radiotherapie) zijn niet voorhanden. Redenen om partiele larynxchirurgie toe te passen zijn mogelijk voordelen ten aanzien van (lange termijn) toxiciteit, waaronder stemkwaliteit en slikfunctie.

Verkeerslichtanalyse en Implementeren- en Agenderen-tabel

Verkeerslichtanalyse (ten behoeve van commentaar- en autorisatiefase)

Kruis aan		
	ROOD	Sterke aanbeveling tegen, geldend voor de gehele populatie, en waar passend bewijs voor is [1]
X	**ORANJE**	Aanbeveling waar geen passend bewijs is voor gehele populatie • Sterke aanbeveling tegen (geen passend bewijs voor gehele populatie en subpopulaties/ condities) • Conditionele aanbeveling (geen passend bewijs voor gehele populatie, maar wel passend bewijs voor een subgroep/-conditie (overweging))
	GROEN	Sterke aanbeveling voor, geldend voor de gehele populatie, en waar passend bewijs voor is [1,2]

[1] Er kan ook sprake zijn van passend bewijs bij een low of very low GRADE; bijvoorbeeld omdat er overwegingen zijn die zwaarwegend zijn in het aanbevolen beleid.

[2] Deze categorie geldt ook indien er passend bewijs is waaruit blijkt dat er geen voorkeur is voor één van de onderzochte interventies/diagnostiekmethoden/verwijspaden, voorbeeld: twee chirurgische technieken zijn even effectief, hebben vergelijkbare complicatierisico's, keuze is afhankelijk van het besluit dat de chirurg samen met de patiënt maakt.

Implementeren-tabel

Vraag	***Antwoord:*** *Kruis aan en licht toe/ beschrijf*	***Toelichting keuze:***

I1. Wat was het onderliggende probleem om deze uitgangsvraag uit te werken?		**Ongewenste praktijkvariatie**	
		Nieuwe evidentie	
	X	**Beoordelen welke behandelmethode voor het T2 larynxcarcinoom als gouden standaard zou moeten gelden: radiotherapie of partiele larynxchirurgie**	
I2. Maak een inschatting over hoeveel patiënten het ongeveer gaat waar de aanbeveling betrekking op heeft?		**< 1000**	
I3. Is de aanbeveling onderdeel van een bredere set interventies of verwant aan andere richtlijnen of modules? Zo ja, hoe verhoudt zij zich daartoe en moet hiermee rekening worden gehouden bij de implementatie, of kan de aanbeveling als losstaand worden beschouwd?	**X**	**Ja, behandelrichtlijnen HH kanker, kan echter losstaand worden beschouwd**	
I4. Belemmeringen en kansen op verschillende niveaus voor landelijke toepassing van de aanbeveling:		**Belemmerende factoren**	**Bevorderende factoren/ kansen**
Richtlijn/ klinisch traject (innovatie)			
Zorgverleners (artsen en verpleegkundigen)	**X**	**Expertise mbt larynxsparende chirurgische behandelingen**	
Patiënt/ cliënt (naasten)	**X**	**Wens tot een operatie vs wens tot radiotherapie**	
Sociale context			
Organisatorische context			
Financiële en juridische context			
I5. A) Welke personen/partijen zijn van belang bij het toepassen van de aanbeveling in de praktijk? (kruis aan)		**A**	**B**
	x	Patiënt/ cliënt (naaste)	
	x	Professional	

B) Wat is er nodig van deze personen/partijen om de aanbeveling in de praktijk te kunnen brengen? *Denk aan aanpassingen in gedrag, werkwijzen, beleid, samenwerking of andere randvoorwaarden.*		Beroepsvereniging, nl	
		Ziekenhuis (raad van bestuur/UMCNL (voorheen NFU)/NVZ)	
		Zorgverzekeraars/ NZa	
		Zorginstituut [duiding nodig]	
		Anders	
I6. Binnen welk tijdsbestek moet de aanbeveling zijn geïmplementeerd?	**x**	< 1 jaar	**Let op: geen verandering van huidige werkwijze**
		binnen 2-3 jaar	
I7. Conclusie: is er extra actie en/of ondersteuning nodig voor implementatie van de aanbeveling? *De reguliere implementatieroutes (publicatie en disseminatie via officiele kanalen, opname in professionele standaarden, scholing en nascholing, gebruik van bestaande ICT systemen, audits en visitaties) van de richtlijnmodule alleen is onvoldoende.*		Ja	
	x	Nee	
I8. Plaatsing op de Landelijke Implementatieagenda Medisch Specialistische zorg is gewenst. *Het gaat om zorg die (grotendeels) wordt uitgevoerd binnen de ziekenhuismuren. Succesvolle implementatie vraagt om actieve betrokkenheid en samenwerking van meerdere relevante partijen binnen de zorgpraktijk.*	**x**	Ja *	
		Nee	

**Deze aanbeveling komt mogelijk in aanmerking voor plaatsing op de Landelijke Implementatieagenda van het programma Zorg Evaluatie & Gepast Gebruik (ZE&GG), waarin alle betrokken partijen in de medisch-specialistische zorg samenwerken aan de implementatie van bewezen beste zorg. De Federatie levert namens het veld goed onderbouwde aanbevelingen aan, die zijn getoetst op de behoefte aan een implementatie-impuls. De onderwerpen op de Implementatieagenda zijn onderdeel van landelijke zorginkoopafspraken tussen zorgverzekeraars en zorgaanbieders. Voor de beoordeling van aanbevelingen uit richtlijnen wordt gebruikgemaakt van de implementatietabel. Op basis hiervan kunnen we de andere partijen goed informeren en gezamenlijk besluiten of plaatsing op de Implementatieagenda passend is.*

Agenderen-tabel

Vraag	***Antwoord*** *Kruis aan*	 *Vul in*
A1. Is onderzoek wenselijk om de <u>uitgangsvraag of zoekvraag</u> (met meer/voldoende zekerheid) te kunnen beantwoorden?	**X**	Nee. *Tijdens de ontwikkeling van deze module is gebleken dat er volgens het cluster sprake is van passend bewijs voor de uitgangsvraag en zoekvraag.*
		Ja
A2. Wat is de kennisvraag?	Kennis-vraag	[tekst] [a)]
	P	[tekst]
	I	[tekst]
	C	[tekst]
	O	[tekst]
A3. Waarom is dit een belangrijke kennisvraag?	Toelichting	[tekst] [b)]
A4. Welk onderzoeksdesign is passend om deze kennisvraag te beantwoorden?		RCT
		Observationeel onderzoek
		Kwaliteitsregistratie
		Anders, namelijk
	Toelichting	[tekst]
A5. Zijn er een andere kennisvragen naar voren gekomen die passen bij het <u>onderwerp van de module</u>, maar niet hetzelfde zijn als de uitgangs- of zoekvraag en waar *geen* passend bewijs voor is? *Bijvoorbeeld:* het onderwerp van de module is 'Behandeling van aandoening X', waarin behandeling A en behandeling B met elkaar worden vergeleken. De voor- en nadelen van behandeling C ten opzichte van A en/of B is dan nog een openstaande kennisvraag als hier geen passend bewijs voor is. Het past wel bij het onderwerp van deze module en de resultaten van zorgevaluatie onderzoek zouden wel in deze module geduid kunnen worden.	X	Nee
		Ja
A6. Wat is de kennisvraag?	Kennis-vraag	[tekst] [a)]
	P	[tekst]
	I	[tekst]
	C	[tekst]

	O	[tekst]
A7. Waarom is dit een belangrijke kennisvraag?	Toelichting	[tekst] [b)]
A8. Welk onderzoeksdesign is passend om deze kennisvraag te beantwoorden?		RCT
		Observationeel onderzoek
		Kwaliteitsregistratie
		Anders, namelijk:
	Toelichting	[tekst]

[a)] Formuleer hier de kennisvraag als een onderzoekvraag. Dit kan de zoekvraag zijn, maar kan ook afwijken. Om het juiste onderzoek te doen is het van groot belang dat de kennisvragen scherp geformuleerd worden, in de vorm van een PICO. Uitgangspunt is dat een kennisvraag met één zorgevaluatie onderzoek opgelost kan worden.

[b)] Beschrijf in 2 à 3 zinnen waarom dit een relevante kennisvraag is.

Literatuur

Er zijn geen referenties gebruikt

Bijlage 7 Verantwoording 4

Voor meer details over de gebruikte richtlijnmethodologie verwijzen wij u naar de Werkwijze. Relevante informatie voor de ontwikkeling/herziening van deze richtlijnmodule is hieronder weergegeven.

Initiatief
Initiatief: Cluster Hoofd-halstumoren

Samenstelling van de werkgroep
Voor het ontwikkelen van de richtlijnmodule is eind 2024 een multidisciplinair cluster ingesteld. Het cluster Hoofd-halstumoren bestaat uit meerdere richtlijnen (zie hier de actuele clusterindeling). De stuurgroep bewaakt het proces van modulair onderhoud binnen het cluster. De expertisegroepsleden brengen hun expertise in, indien nodig. De volgende personen uit het cluster zijn betrokken geweest bij de herziening van deze module:

Clusterstuurgroepleden

- Prof. dr. R. (Remco) de Bree, voorzitter (NVKNO)
- Dr. M. (Mischa) de Ridder (NVRO)
- Dr. L.A. (Lot) Devriese (NIV)
- Prof. dr. M.J.H. (Max) Witjes (NVMKA)
- Dr. H.P.M. (Dirk) Kunst (NVKNO)
- R.A. (Rob) Burdorf (PVHH)

Betrokken clusterexpertisegroepleden

- Prof. dr. J.C. (Jeroen) Jansen (NVKNO)
- Drs. D.P.S. (Djenghiz) Samlal (NVKNO)
- W. (Willie) van Delft (NVPG)

Met ondersteuning van

- Dr. A. (Anja) van der Hout (Kennisinstituut van de Federatie Medisch Specialisten)
- Dr. E. (Eline) Pruijn-de Heus (Kennisinstituut van de Federatie Medisch Specialisten)
- Dr. J. (Jing) de Haan-Du (Kennisinstituut van de Federatie Medisch Specialisten)
- Drs. J. (Joline) Rohof (Kennisinstituut van de Federatie Medisch Specialisten)
- Dr. M.S. (Michiel) Oerbekke (Kennisinstituut van de Federatie Medisch Specialisten)
- Alies Oost (Kennisinstituut van de Federatie Medisch Specialisten)

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

Clusterstuurgroepleden

Tabel 7 Gemelde (neven)functies en belangen stuurgroep

Naam	Hoofdfunctie	Nevenwerkzaamheden	Persoonlijke financiële belangen	Persoonlijke relaties	Extern gefinancierd onderzoek	Intellectuele belangen en reputatie	Overige belangen	Datum	Restrictie
Prof. dr. R. (Remco) de Bree	KNO-arts / hoofd-halschirurg	Onbetaald: Board member	Geen	Geen	KWF. Ultrasound and microbubbles to improve tumor perfusion of head	Geen	Geen	12-12-2024	Restricties ten aanzien

(voorzitter)	Hoogleraar / afdelingshoofd UMC Utrecht	Dutch Head and Neck Society (NWHHT) Chair Research Steering Committee Dutch Head and Neck Society (NWHHT) Member Clinical Audit Board Dutch Head and Neck Audit (DHNA) Chair committtee Revision Dutch Head and Neck Tumor Guidelines Board member Patient advocacy group Patiëntenvereniging Hoofd-Hals (PVHH) Chair advisory committee research data Dutch registries (PRISMA) Chair Dutch section Collegium Oto-Rhino-Laryngologicum Amicitiae Sacrum (CORLAS) Council Member International Academy of Oral Oncology (IAOO)			and neck cancers. co-applicant ZonMw. Metastatic-directed stereotactic body radiation therapy of oligometastases in head and neck squamous cell carcinoma patients. Projectleider KWF. Personalized follow-up in HPV-related oropharyngeal cancer patients using liquid biopsies. Projectleider Maurits en Anna de Kock Stichting en Vaillantfonds. Fluorescentie geassisteerde reconstructieve chirurgie: beoordeling van vitaliteit van weefsels. Projectleider 1. KWF- FDG-PET/CT to reduce the need for sentinel lymph node biopsy in early stage oral cancer (Projectleider JA) 2. KWF - Ex vivo 7T MRI of resection specimen of oral cancer to improve margin control (Projectleider NEE) 3. KWF - Sentinel lymph node detection in early oral cancer using [68Ga]Ga-tilmanocept PET/CT lymphoscintigra (Projectleider JA) 4. Nutricia - Perioperative nutritional intervention with Fortifit Energy® in combination with excersice verstus standard of care (Projectleider JA) 5. Hanarth Fonds - Triage of Patients with High-risk Oral Squamous cell Carcinoma using Artificial Intelligence (TOSCA) (Projectleider NEE)				van besluitvorming betreffende perioperatieve voedingsinterventies. Indien relevant: Vice-voorzitter aan te stellen voor wanneer perioperatieve voedingsinterventies worden besproken.
Dhr. Dr. M. (Mischa) de Ridder	Radiotherapeut-oncoloog UMC Utrecht	Secretaris LPRHHT van de NVRO. Lid METC NED-MED	Geen	Geen	Elekta: To evaluate evidence for eventual transition from PDR treatments to HDR treatments in case of possib (Projectleider JA). Hanarth fonds: Improved response assessment after (chemo)-	Geen	Geen	3-1-2025	Geen restricties.

					radiotherapy for locally advanced head and neck squamous (Projectleider NEE).				
Mevr. Dr. L.A. (Lot) Devriese	Internist UMC Utrecht	Dit project en eerder bij FMS kwaliteits agenda. Werkgroep binnen NVMO, CieOOM, off-label oncologische medicatie (vacatiegelden naar UMC Utrecht). Bestuurslid NWHHT	Geen	Geen	Ja, als lokale PI van studies gesponsord door Farma. Met uitbetaling aan de werkgever, niet aan mij persoonlijk. 1. ISAPharm - Fase 3 onderzoek ISA101b (Projectleider NEE) 2. MERUS - Fase 3 onderzoek petosemtamab (Projectleider NEE) 3. CISLOW studie - Fase 2 IIS gesponsord door ZOnMw (Projectleider NEE)	Geen	Geen	14-11-2024	Geen restricties.
Prof. dr. M.J.H. (Max) Witjes	MKA chirurg-HH oncoloog Universitair Medisch Centrum Groningen	Geen	Geen	Geen	• Fluoguide FG001sponsor initiated trial (2024): Determination of Optimal Dose for Visualization of Inadequate Margins in Oral Squamous Cell Carcinoma Using FG001. Protocol: 2024-514508-14-00. Witjes MJH Voskuil FJ, Fluoguide team. (budget € 378.293) (Projectleider JA) • NIH grant (National Institute of Dental and Craniofacial Research 2023) : Ex vivo intraoperative surgical basal margin analysis in head and neck cancer resection: clinical validation (1R01DE033449-01). Tichauer K, J Broncovic & Witjes MJH, Voskuil FJ.(budget USD 2.5Milj) (Projectleider JA) • SNN Grant (2023) : JTF application for IMPACT-Implants . (Budget € 3.6 Milj) Kraeima J, Witjes MJH, Veldsink JW & Center for Business Development UMCG. (Projectleider NEE) • KWF Kankerbestrijding: RUG 13215 (2021) Witjes MJH, GB Halmos, WM Nagengast. Real-time targeted fluorescence endoscopy in patients for detection of unknown primary cancers of the head and neck area (REFLECT study) (Budget €476.000) (Projectleider JA) • WJ Thijn stichting (2021) : Witjes MJH lichtgevende stoffen helpen de chirurg	Geen	Geen	16-1-2025	Restricties ten aanzien van besluitvorming betreffende de bepaling van de optimale dosis voor visualisatie van onvoldoende snijmarges bij oraal plaveiselcelcarcinoom.

					de tumor beter te verwijderen. (Budget €250.000). (Projectleider JA)				
Dhr. H.P.M. (Dirk) Kunst	KNO-arts; Radboudumc-MUMC+	Voorzitter van het "Radboudumc-MUMC+ Expertisecentrum Schedelbasispathologie" Voorzitter "Academische Alliantie Schedelbasispathologie Radboudumc-MUMC+" Voorzitter "Landelijk Overleg Expertisecentra Schedelbasispathologie" (LOES) President van de "European Skull Base Society" (ESBS) Betrokkenheid patientenverenigingen: Neurofibromatose type 2 patientenvereniging Paragangliomen patientenvereniging	Geen	Geen	Euregio: Hoofd-hals paragangliomen; verschillen management Nederland Duitsland (projectleider JA). TU Eindhoven/Tilburg (aflopende ZonMw studie), over voorspellen van groei obv MRI scans bij brughoektumoren (projectleider NEE).	Geen	Geen	14-2-2025	Geen restricties.
Dhr. R.A. (Rob) Burdorf	Neem niet meer deel aan het arbeidsproces (met pensioen)	Lid wetenschappelijke advies commissie van de PVHH	Geen	Geen	Geen	Geen	Geen	12-11-2024	12-11-2024

Betrokken clusterexpertisegroepleden

Tabel 8 Gemelde (neven)functies en belangen expertisegroep

Naam	Hoofdfunctie	Nevenwerkzaam-heden	Persoonlijke financiële belangen	Persoonlijke Relaties	Extern gefinancierd onderzoek	Intellectuele belangen en reputatie	Overige belangen	Datum	Actie

Jeroen Jansen (NVKNO)	Medisch specialist, Kno arts (LUMC)	Geen	Geen	Geen	1. KWF: Pectoralis, chirurgisch oncologisch operatietechniek (projectleider NEE) 2. EU: TRUST-AI, predictiemodellen AI (projectleider NEE) 3. Gieskes Strijbisfonds: Uitlegbare Kunstmatige Intelligentie, predictiemodellen AI (projectleider NEE) 4. DICA: Mond-holtecarcinoom, uitkomstanalyse (projectleider NEE) 5. KWF: FLUID, HPV in bloed bij kanker (projectleider NEE)	Geen	Geen	22-06-2026	Geen restricties.
Willie van Delft (NVPG)	Bestuur NVPG	Geen	Geen	Geen	Geen	Geen	Geen	22-06-2026	Geen restricties.
Djenghiz Samlal (NVKNO)	Arts promovendus schedelbasispathologie Radboud universitair medisch centrum.	Geen	Geen	Geen	Bij European Union (EFRE / EFRO) en Provincie Gelderland en Ministry of Economics, Industry, Climate Protection and Energy of the state of North Rhine Westphali: GrenszGlo, hoofdhals paragangliomen.	Geen	Geen	05-02-2026	Geen restricties

Kwalitatieve raming van mogelijke financiële gevolgen in het kader van de Wkkgz

Bij de richtlijnmodule voerden de clusterleden conform de Wet kwaliteit, klachten en geschillen zorg (Wkkgz) een kwalitatieve raming uit om te beoordelen of de aanbevelingen mogelijk leiden tot substantiële financiële gevolgen. Bij het uitvoeren van deze beoordeling is de richtlijnmodule op verschillende domeinen getoetst (zie het stroomschema bij Werkwijze).

Module	Uitkomst raming	Toelichting
Module [naam]	[geen/ mogelijk] financiële gevolgen	[plaatsen desbetreffende uitkomst 1, 2, 3, 4 of 5]

Bijlage 8 Literatuursamenvatting module 4 inclusief alle bijlagen

Introduction

In toenemende mate is er aandacht voor de kwaliteit van leven (KvL) van patiënten met hoofdhalsparagangliomen (HNPGL), omdat de behandeling hiervan een grote impact kan hebben op het dagelijks functioneren terwijl het natuurlijk beloop vaak mild is. Uit eerder HNPGL onderzoek is gebleken dat de KvL door HNGPL verminderd kan zijn. In de hedendaagse praktijk wordt echter vooral gevaren op verwachtte uitval als proxy van KvL. Dit kan leiden tot keuzes die niet goed aansluiten bij de voorkeuren of het welzijn van de patiënt. Het beter in kaart brengen van KvL kan bijdragen aan meer passende en patiëntgerichte zorg.

A systematic review of the literature was performed to answer the following question(s):
What aspects of quality of life are impacted by head and neck paragangliomas (including jugulotympanic, carotid body, vagal, and multiple head and neck paragangliomas) on patients' quality of life, patient-reported outcomes, and psychosocial functioning?

PICO

Patients	Patients with head and neck paraganglioma
Intervention	Jugulotympanic paraganglioma, carotid body paraganglioma, vagal paraganglioma, multiple head and neck paraganglioma
Control	N.A.
Outcomes	Quality of life, QoL, patient-reported outcome, psychosocial functioning
Other selection criteria	Study design: systematic reviews and randomized controlled trials

Relevant outcome measures

The guideline panel considered **quality of life** as a **critical** outcome measure for decision making; and **psychosocial functioning** as an **important** outcome measure for decision making.

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

Search and select (Methods)

A systematic literature search was performed by a medical information specialist using the following bibliographic databases: Embase.com and Ovid/Medline all. Both databases were searched from 2005 to August 25th 2025 for systematic reviews, observational and other studies. Systematic searches were completed using a combination of controlled vocabulary and natural language keywords. The overall search strategy was derived from the following primary search concepts: (1) head and neck paraganglioma; (2) quality of life, patient-reported outcome, psychosocial functioning. Duplicates were removed using EndNote software. After deduplication a total of 722 records were imported for title/abstract screening. Initially, 35 studies were selected based on title and abstract screening. After reading the full text, 23 studies were excluded (see the exclusion table under the tab 'Evidence tabellen'), and 12 studies were included.

Summary of literature

Description of studies

A total of 12 studies were included in the analysis of the literature. Important study characteristics and results are summarized in table 1. Because the research question does

not include a control group and is observational in nature, a risk-of-bias assessment and GRADE evaluation are not applicable.

Table 1. Characteristics of included studies

Study	Participants	Measurement of QoL	Comments
Canu, 2025	Patients diagnosed with head and neck paragangliomas (HNPGLs) between January 2000 and May 2022. **Inclusion criteria**: occurrence of one or more HNPGLs and consent to being interviewed. **Exclusion criteria** were pre-existing neurological disorders or lesions, end of the post-surgery follow-up in patients surgically treated, and head and neck surgery due to reasons other than HNPGL. **N** at baseline: N=72 Surgery: N=49 Wait and see: N=23 **Age** (mean, SD) at diagnosis: 47.2 ± 16.2 Surgery: 44.2 ± 15.2 Wait and see: 53.6 ± 16.9 **Sex**: 25 (34.7%) male. Surgery: 15 (30.6%) male Wait and see: 10 (43.5%) male	1. Voice Handicap Index (VHI): a self-administered tool assessing the severity of speech disorders in three domains: functional, emotional, and physical. In every domain, the answers to different items were scored using a 0–4 Likert scale. 2. M.D. Anderson Dysphagia Inventory (MDAD): a self-administered questionnaire assessing the impact of dysphagia on the QoL of patients affected by head and neck tumors. This questionnaire assesses global, functional, physical, and emotional areas. The answers to every item were given a score between 1 and 5. 3. Deglutition Handicap Index (DHI): a self-administered questionnaire consisting of 30 items on deglutition-related aspects of daily life (5-point rating scale). It is subdivided into three domains of 10 items: physical (symptoms), functional (nutritional and respiratory consequences), and emotional (psychosocial consequences). 4. EORTC QLQ-H&N35: a questionnaire dedicated to patients affected by head and neck tumors, evaluating different QoL aspects of daily life related to head and neck symptomatology.	**Funding:** supported by the Italian Association for Cancer Research (AIRC, under IG 2020-ID 24820 project for Mario Maggi). **Conflicts:** No conflicts of interest was declared.

De Bresser, 2025	Patients with a confirmed paragangliomas and pheochromocytomas (PPGL) diagnosis at any point in time with a specific focus on head and neck paragangliomas (HNPGLs) and those with a hereditary cause of PPGLs, enrolled between July 2022 and December 2023. **N** at baseline: N=100 Sporadic: N=16 Hereditary: N=84 **Age** (mean, SD) at questionnaire completion: 52.5 ± 16.4 Sporadic: 59.7 ± 14.7 Hereditary: 51.1 ± 16.4 **Sex**: 45% male. Sporadic: 31% male Hereditary: 48% male Other characteristics: **Age** (mean, SD) at PPGL diagnosis: 42.5 ± 15.7 Sporadic: 53.8 ± 15.4 Hereditary: 40.4 ± 14.9	1. Hospital Anxiety and Depression Scale (HADS) 2. Modified Fatigue Impact Scale (MFIS) 3. EuroQol 5D-5L (EQ-5D-5L) 4. European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) 5. Cancer Worry Scale (CWS)	**Funding**: no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. **Conflicts**: No conflicts of interest was declared.
Molina-Romero, 2024	Patients with glomus jugulare tumor treated with Gamma Knife Perfexion between June 2020 and December 2022 in a single center in Latin America. **N** at baseline: N=77 **Age** (mean, SD) at 53.2 years **Sex**: not reported <u>Other characteristics:</u> De median hospital stay was 4.92 hours.	Short Form-36 scale Measure moment: considering the prior and after-treatment state.	**Funding**: Nil. **Conflicts:** No conflicts of interest was declared.
Ehret, 2020	Patients with glomus jugulare tumor treated with single-session image-guided robotic radiosurgery (RRS) between July 2005 and November 2018 in a single center in Germany. **N** at baseline: N=53	12-item health survey questionnaire SF12v2 Measure moment: before treatment delivery and during follow-up visits.	**Funding**: Munich Medical Research School, Ludwig-Maximilians-University Munich **Conflicts:**

	Age (median, range) at 54.5 (27-83.4) years **Sex:** male 20 (37.7%) <u>Other characteristics:</u> Tumor volume (median, range): 4.3 (0.1 - 31.6) cc. Radiation dosage (median, range): 16.5 (13.5 - 18.0) Gy		Not reported in the article.

Hebb, 2020	Patients with glomus jugulare tumors registered in the Maritime Lateral Skull Base Clinic in Canada.
	
	N at baseline: N=23
	
	Age (median, range) at treatment: conservatively managed: 44 (not reported) years; stereotactic radiotherapy (SRT): 59 (40-75); a combination of SRT and surgery: 51 (39-73).
	
	Sex: male 20 (37.7%)
	
	<u>Other characteristics:</u>
	Treatment:
	conservatively managed: n=5;
	stereotactic radiotherapy (SRT): n=15;
	a combination of SRT and surgery: n=3.
		Short-Form 12 Health Survey (SF-12)	**Funding:**
			Not reported.
			
			Conflicts:
			No conflicts of interest was declared.

García-Alva, 2019	Patients with established carotid body tumors (CBT) diagnosis (prior to resection) recruited in a tertiary referral center for CBTs in Mexico between January 2017 and December 2018. **N** at baseline: N=23 Control group: N=23 paired by age and gender **Age** (mean, sd) at 55 (15.14) years **Sex**: male 4 (17%) <u>Other characteristics:</u> 95% percent of the patients were as asymptomatic. Shamblin classification was estimated:	Short Form (SF-36) Measure moment: prior to resection.	**Funding:** No funding was received. **Conflicts:** No conflicts of interest was declared.

	Shamblin I in 9%; Shamblin II in 52%; Shamblin III in 39%.		
Patel, 2019	Patients with jugular paraganglioma treated with stereotactic radiosurgery (SRS) at Mayo Clinic in America. **N** at baseline: N=26 **Age** (median, range) at 53 (38-58) years **Sex**: male 10 (39%) <u>Other characteristics:</u> Tumor volume (median, IQR): 7090 (4618–9513 cubic mm). Radiation dose (median, IQR): 16 (15–16 Gy). Time from SRS to the date the survey (median, IQR): 97 (33–155 mo, range 12–226 mo).	Overall HRQoL: • Short Form 36 (SF-36) Health Survey • Patient-Reported Outcomes Measurement Information System-10 (PROMIS-10). To evaluate specific effects on lower cranial nerve function: • Eating Assessment Tool-10 (EAT-10) • Voice Handicap Index (VHI) The effect of voice on QoL • Voice Related Quality of Life (VRQOL) To characterize the effect of SRS: • Glasgow Benefit Inventory (GBI)	**Funding:** Internal departmental funding was used without commercial sponsorship or support. **Conflicts:** No conflicts of interest was declared.
Galland-Girodet, 2014	Patients diagnosed with paragangliomas (PGL) receiving radiation therapy as a component of their treatment between 1987 and 2010. **N** at baseline: N=21 **Age** (mean, range): 62 (23-90) years **Sex**: male 10 (47.6%) Control: the QoL of 2,929 patients treated for squamous cell carcinoma with a range for age of 50–59 year old, and a male majority. <u>Other characteristics:</u> Radiation dose (median, range): 52.2 (45–55.8) Gy. Time from SRS to the date the survey (median, range): 102 (12–228) mo	• EORTC QLQ-C30 • QLQ-H&N35: The Head and Neck-specific module EORTC QLQ-H&N 35 contains 35 items evaluated 18 symptoms.	**Funding:** Not reported. **Conflicts:** No conflicts of interest was declared.
Van Hulsteijn, 2013	Patients with paragangliomas, as well as asymptomatic SDH mutation carriers	• Hospital Anxiety and Depression Scale	**Funding:** No specific grant from any funding

	recruited from the outpatient clinic in a tertiary referral center for paragangliomas in the Netherlands. The patients were requested to provide a **control group** with similar socioeconomic status from the same geographical area, with similar age and sex. **N** at baseline: N=174 Control: N=100 **Age** (mean, range): 52.2±13.5 years Control: 49.3±12.9 years **Sex:** male 70 (40.2%) Control: male 38/77 due to 13 control persons did not fill in their sex (43.7%).	• Multidimensional Fatigue Index 20 • Short Form 36	agency in the public, commercial or not-for-profit sector. **Conflicts:** No conflicts of interest was declared.
Havekes, 2012	Patients with head and neck paragangliomas (HNPGL) recruited from the outpatient clinic in a tertiary referral center for HNPGL in the Netherlands. The patients were requested to provide a **control person** with similar age and sex. **N** at baseline: N=74 Own controls: N=41 Leiden controls: N=74 **Age** (mean, sd) in years: 49.1±12.2 Own Control: 45.0±11.4 Leiden control: 52.2±8.9 **Sex**: male 39 (53%) Own control: male 18 (43.9%) Leiden control: male 39 (52.7%)	• Epworth Sleepiness Scale The ESS is a validated self-administered questionnaire that has been proposed as a method for measuring daytime sleepiness in adults. • St. George Respiratory Questionnaire The SGRQ is a validated self-administered questionnaire that has been proposed as a method for measuring health-related quality of life in chronic respiratory patients.	**Funding:** Not reported. **Conflicts:** Not reported.
Havekes, 2008	Patients with head-and-neck paragangliomas in the outpatient clinic in a tertiary referral center in the Netherlands. The patients were requested to provide a **control person** of comparable age and sex with a comparable socioeconomic status from the same geographical area.	• HADS • MFI-20 • Nottingham Health Profile (NHP) The NHP survey consists of 38 yes/no questions. These are subdivided into six scales	**Funding:** Not reported. **Conflicts:** Not reported.

	N at baseline: N=82/105 Control: N=44/105 Leiden Control: N=168 **Age** (mean, range): 48.8±12.0 years Own Control: 47.2±10.9 years Leiden Control: 49.4±12.6 years **Sex**: male 42 (51.2%) Control: male 20 (50%, 4 missing) Leiden Control: 86 (51.2%)	assessing impairments: pain (eight items), energy level (three items), sleep (five items), emotional reactions (nine items), social isolation (five items), and disability/functioning (eight items). • Short Form-36 (SF-36)	
Henzel, 2007	Patients with Glomus Jugulare Tumors treated with SRT in the Department of Radiation Oncology, Philipps University of Marburg, and the Department of Stereotactic Neurosurgery and Radiosurgery, HELIOS Klinikum Erfurt in Germany between 1999-2005. **N** at baseline: N=17 **Age** (median, range): 65 (30-82) years **Sex:** male 2 (11.8%)	Short Form-36 (SF-36) Measure moment: 12 months after SRT	**Funding:** Not reported. **Conflicts:** Not reported.

Results

Table 2. Overview of reported quality of life data among patients with head and neck paraganglioma

<table>
<tr><th>Study</th><th>Patients</th><th>Questionnaire and scoring</th><th>Response rate</th><th>Main findings related with quality of life</th></tr>
<tr><td>Canu, 2025</td><td>Patients diagnosed with head and neck paragangliomas</td><td>Voice Handicap Index (VHI)
The sum of the scores defines the speech disability as mild (<20 points), moderate (21–30 points), and severe (>30 points).

M.D. Anderson Dysphagia Inventory (MDAD)
The sum of the scores defines the deglutition function of the patients as unsatisfactory (<41 points), moderately (41–70 points), and highly satisfactory (>70 points).

Deglutition Handicap Index (DHI):
A score between 0 and 4 was given to every item of this questionnaire; the sum of the scores defines the deglutition disability as mild (<20 points), moderate (21–30 points), and severe (>30 points).</td><td>72.2%</td><td>
<table>
<tr><th>Questionnaire</th><th>Undergoing surgery (N=34) Median (quartiles)</th><th>Wait and see (N=18) Median (quartiles)</th><th></th></tr>
<tr><td>MDADI</td><td>92.0 (79.2-96.0)</td><td>96.0 (77.0-96.0)</td><td>p=0.391</td></tr>
<tr><td>VHI</td><td>8.0 (0.0-32.0)</td><td>0.0 (0.0-2.0)</td><td>p=0.001</td></tr>
<tr><td>DHI</td><td>3.0 (1.0-13.5)</td><td>0.5 (0.0-4.0)</td><td>p=0.020</td></tr>
</table>
</td></tr>
</table>

<table>
<tr>
<td></td>
<td></td>
<td>EORTC QLQ-H&N35: Evaluating different QoL aspects of daily life related to head and neck symptomatology.</td>
<td>39.0%</td>
<td>
<table>
<tr><th>Symptoms</th><th>Undergoing surgery (%) N=25</th><th>Wait and see (%) N=7</th></tr>
<tr><td>Pain</td><td>8.3 (0-16.7)</td><td>8.3 (0-16.7)</td></tr>
<tr><td>Swallowing</td><td>0 (0-16.7)</td><td>0 (0-8.3)</td></tr>
<tr><td>Senses</td><td>0 (0-0)</td><td>0 (0-0)</td></tr>
<tr><td>Speech</td><td>11.1 (0-16.6)</td><td>0 (0-11.1)</td></tr>
<tr><td>Social eating</td><td>0 (0-0)</td><td>0 (0-0)</td></tr>
<tr><td>Social contact</td><td>0 (0-0)</td><td>0 (0-0)</td></tr>
<tr><td>Sexuality</td><td>0 (0-25.0)</td><td>0 (0-0)</td></tr>
<tr><td>Teeth</td><td>0 (0-16.7)</td><td>0 (0-0)</td></tr>
<tr><td>Opening mouth</td><td>0 (0-0)</td><td>0 (0-0)</td></tr>
<tr><td>Dry mouth</td><td>0 (0-0)</td><td>0 (0-33.3)</td></tr>
<tr><td>Sticky saliva</td><td>0 (0-0)</td><td>0 (0-33.3)</td></tr>
<tr><td>Coughed</td><td>0 (0-33.3)</td><td>33.3 (0-33.3)</td></tr>
<tr><td>Felt ill</td><td>0 (0-16.7)</td><td>0 (0-0)</td></tr>
<tr><td>Pain killers</td><td>0 (0-100.0)</td><td>0 (0-0)</td></tr>
<tr><td>Nutritional supplements</td><td>0 (0-0)</td><td>0 (0-0)</td></tr>
<tr><td>Feeding tube</td><td>0 (0-0)</td><td>0 (0-0)</td></tr>
<tr><td>Weight loss</td><td>0 (0-0)</td><td>0 (0-0)</td></tr>
<tr><td>Weight gain</td><td>0 (0-0)</td><td>0 (0-0)</td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr>
<td>Bresser, 2025</td>
<td>Both newly diagnosed and with an existing paragangliomas and pheochromocytomas diagnosis</td>
<td>HADS:
no anxiety and/or depression (0-7),
possible anxiety and/or depression (8-10),
plausible anxiety and/or depression (11-21)</td>
<td>83%</td>
<td>
<table>
<tr><th></th><th>Anxiety Mean score</th><th>Depression Mean score</th><th>Any sign of anxiety or depression</th></tr>
<tr><td>Overall (n=83)</td><td>3.9 ± 3.9</td><td>3.1 ± 3.7</td><td>Anxiety: n=16/83, 19%. Depression: n=9/83, 13%</td></tr>
<tr><td>Sporadic (n=14)</td><td>3.3 ± 3.5</td><td>4.0 ± 3.9</td><td>n=6/14, 43%</td></tr>
<tr><td>Hereditary (n=69)</td><td>4.1 ± 4.4</td><td>2.8 ± 3.5</td><td>n=21/69, 30%</td></tr>
</table>
</td>
</tr>
<tr>
<td></td>
<td>EQ-5D-5L:
using a 5-point scale ranging from 1 to 5.</td>
<td>86%</td>
<td>

Significant difference between hereditary and sporadic PPGLs was seen in the dimension of usual activities (P = .039).
Overall, patients with sporadic PPGL exhibited more severe outcomes across all 5 dimensions
When stratifying the results for presymptomatic and symptomatic patients, no differences were found between the 2 groups across all dimensions.

</td>
</tr>
<tr>
<td></td>
<td>Visual analogue scale (VAS):
ranges from 0 to 100 (with 100 being the best imaginable health).</td>
<td>86%</td>
<td>
<table>
<tr><th></th><th>median EQ VAS score</th><th>mean EQ VAS of the Dutch tariff</th></tr>
<tr><td>Overall</td><td>81 ± 17</td><td>82.0</td></tr>
<tr><td>Sporadic</td><td>80.0 ± 21.8</td><td>82.0</td></tr>
<tr><td>Hereditary</td><td>85 ± 17</td><td>82.0</td></tr>
<tr><td>presymptomatic</td><td>85 ± 15.0</td><td>82.0</td></tr>
<tr><td>symptomatic</td><td>80 ± 17.5</td><td>82.0</td></tr>
</table>
The sample size (N) for the specific group that responded to this questionnaire is not reported.
</td>
</tr>
</table>

		EORTC QLQ-C30: Scores range from 0 to 100, with higher scores on functional scales and lower scores on the symptoms scale indicating better QoL.	85%	

	Overall (N=85) Median (IQR)	Hereditary (N not reported) Median (IQR)	Sporadic (N not reported) Median (IQR)
Global health status/QoL	83.3 (75.0-100.0)	83.3 (75.0-100.0)	75.0 (66.7-89.9)
Physical functioning	100.0 (86.7-100.0)	100.0 (93.3-100.0)	93.3 (73.3-100.0)
Role functioning	100.0 (83.3-100.0)	100.0 (83.3-100.0)	100.0 (70.8-100.0)
Emotional functioning	91.7 (66.7-100.0)	91.7 (66.7-100.0)	91.7 (66.7-100.0)
Cognitive functioning	100.0 (83.3-100.0)	100.0 (83.3-100.0)	100.0 (70.8-100.0)
Social functioning	100.0 (83.3-100.0)	100.0 (83.3-100.0)	100.0 (66.7-100.0)
Fatigue	22.2 (0-33.3)	11.1 (0-33.3)	33.3 (11.1-41.7)
Nausea and vomiting	0 (0-0)	0 (0-0)	0 (0-12.5)
Pain	0 (0-16.7)	0 (0-16.7)	0 (0-16.7)
Dyspnea	0 (0-0)	0 (0-0)	0 (0-33.3)
Insomnia	33.3 (0-33.3)	0 (0-33.3)	33.3 (0-66.7)
Appetite loss	0 (0-0)	0 (0-0)	0 (0-0)
Constipation	0 (0-0)	0 (0-0)	0 (0-0)
Diarrhea	0 (0-0)	0 (0-0)	0 (0-0)
Financial difficulties	0 (0-0)	0 (0-0)	0 (0-0)

When comparing our data with the EORTC QLQ-C30 reference values for patients with all stages of head and neck cancer, the overall cohort, whether

<table>
<tr><td></td><td></td><td></td><td></td><td>stratified for hereditary or sporadic PPGLs or (pre)symptomatic status, showed higher median outcomes for the QoL and functional scales and lower values for the symptomatic scales compared to the reference Values.</td></tr>
<tr><td></td><td></td><td>MFIS:
Scores ≥38 denote PPGL-related tiredness exerting a substantial influence on daily activities.</td><td>85%</td><td>
<table>
<tr><td></td><td>MFIS mean total score</td><td>Any sign of PPGL-related tiredness</td></tr>
<tr><td>Overall</td><td>18.7 ± 17.1</td><td>n=14/85, 16%.</td></tr>
<tr><td>Sporadic</td><td>24.9± 18.8</td><td>n=3/14, 21%</td></tr>
<tr><td>Hereditary</td><td>17.6 ± 16.6</td><td>n=11/71, 15%</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><td></td><td></td><td></td><td></td><td>The cohort in this study showed no overall signs of PPGL-related tiredness, compared to a cohort of women with breast cancer.</td></tr>
<tr><td></td><td></td><td>CWS:
Scores ranging from 8 to 32. Higher scores indicate more frequent worries about cancer. A diagnostic cut-off score of 14 or higher indicates severe Fear of cancer occurrence or recurrence.</td><td>82%</td><td>
<table>
<tr><td></td><td>CWS mean total score</td><td>Description in the article.</td></tr>
<tr><td>Overall</td><td>12.5 ± 4.0</td><td>ranged from 8 to 30, representing a moderate degree of fear, when compared to other hereditary tumor syndromes.</td></tr>
<tr><td>Sporadic</td><td>10.8 ± 3.0</td><td rowspan="2">indicating a slight elevation in cancer-related concerns among hereditary PPGLs.</td></tr>
<tr><td>Hereditary</td><td>12.8 ± 4.1</td></tr>
</table>
The sample size (N) for the specific group that responded to this questionnaire is not reported.
</td></tr>
<tr><td>Molina-Romero, 2024</td><td>Patients with glomus jugulare tumor tumors treated with Gamma Knife Perfexion</td><td>The Short Form-36 scale: range is 0 to 100, where a higher score indicates better health. Results are standardized to a mean of 50 and a standard deviation of 10 in the US general population</td><td>Not clearly reported</td><td>
<table>
<tr><td>Domains</td><td>Pre-treatment Mean (%)*</td><td>Post-treatment Mean (%)*</td><td>95% confidence interval of the difference</td></tr>
<tr><td>Physical functioning</td><td>84.7</td><td>88.9</td><td>(-20, 5)</td></tr>
<tr><td>Role limitations due to physical health</td><td>48.8</td><td>78.5</td><td>(-87.5, -25)</td></tr>
<tr><td>Role limitations due to emotional problems</td><td>57.9</td><td>84.1</td><td>(-83, -50)</td></tr>
<tr><td>Energy/Fatigue</td><td>60.7</td><td>72.9</td><td>(-17.8, -6.6)</td></tr>
<tr><td>Emotional well-being</td><td>66</td><td>78</td><td>(-22, -8)</td></tr>
<tr><td>Social functioning</td><td>75</td><td>83</td><td>(-37.5, 5.4)</td></tr>
<tr><td>Pain</td><td>69.9</td><td>78.6</td><td>(-32.5, 5)</td></tr>
<tr><td>General health</td><td>44.6</td><td>63.9</td><td>(-30, -10)</td></tr>
</table>
</td></tr>
</table>

				<table><tr><td>General change</td><td>37.5</td><td>66</td><td>(-39.5, -17.6)</td></tr></table> *As presented in the original article. It is not clear how was the 'Mean (%)' calculated. The measurement post-treatment was also not clear how long after the treatment. The sample sizes (N) before and after the treatment respectively, are not reported.
Ehret, 2020	Patients with glomus jugulare tumor tumors treated with single-session image-guided robotic radiosurgery	Health survey questionnaire SF12v2: The received answers were transformed into a standardized continuous scale ranging from 0 to 100, with 50 being the mean. Higher SF12v2 scores indicate a better Qol and better overall function. Only patients who answered all questions were included in the analysis.	88.6%/66.0%/66.0% (before treatment /6 months after treatment/ last follow-up (after a median of 38 months)	Analysis of the data showed no significant decline in any of the eight Qol health concepts. The health concept bodily pain (BP) significantly improved compared with the baseline (P = .04), whereas mental health (MH) showed a trend toward post-treatment improvement without reaching significance (P = .08). During the last follow-up, the results do not show any decrease in the measured Qol areas. All mean differences were at least zero or positive while no statistically significant improvement was identified.

Hebb, 2020	Patients with glomus jugulare tumor tumors treated with: 1) conservatively managed; 2) stereotactic radiotherapy (SRT): 3) combination of SRT and surgery.	The Short Form-36 scale: range is 0 to 100, where a higher score indicates better health.	Not reported.	Statistical analysis of SF-12 categorical data scores were not performed because of the intrinsic nature of the data including many questions with zero respondents. Q1: Positive responses of all groups of patients were evident that none of the patients reported their general health as poor. Conservatively treated patients were more often to report their general health as excellent and post-SRT treatment was associated with a report of fair health in 20% of patients. Q2 and 3: Limitations in daily activities were minimal with no group report that health prohibited a lot of their activities- with the majority of patients in each group falling in the not at all category. Questions 4, 5, 6 and 7: SRT patients seemed to have poorer outcomes in the hearing domains which is in keeping with reports of worse subjective measures of physical and emotional health. Q8: Pain was reported as extremely interfering with normal work patterns in a minority of conservative and post-SRT patients. There were no reports of pain interfering with work and housework moderately, quite a bit, or extremely, and most patients reported that pain did not interfere at all. Q9 and Q11: Patients were more likely to report tranquility in ratings of calm and peaceful than depression as indicated by rating as down and blue. SRT was associated with increased depressive and decreased tranquility ratings. Q10: Conservative patients appeared to have the highest energy reserve. Post-SRT patients were more likely to report diminished energy levels. None of the patients in any of the treatment groups reported having energy all of the time, and no patients reported having energy none of the time.

<table>
<tr><td></td><td></td><td></td><td></td><td>Q12: Physical and emotional health did not impact social activities. In 100% of both conservative and pre-SRT and 80% post-SRT patient’s social activities were resilient to the influence of either physical or emotional factors.</td></tr>
<tr><td>García-Alva, 2019</td><td>Patients diagnosed with carotid body tumors (CBT) prior to resection</td><td>The Short Form-36 scale: range is 0 to 100, where a higher score indicates better health.

Measure moment: prior to resection.

Patients who do not answered completely the questionnaires or were unable to answer it were excluded (n=1).</td><td>95.7%</td><td>
<table>
<tr><th>Domains</th><th>Control (N=22) Median (IQR)</th><th>CBT (N=22) Median (IQR)</th><th>P value*</th></tr>
<tr><td>Physical function</td><td>100 (75-100)</td><td>80 (20-100)</td><td><0.001*</td></tr>
<tr><td>Role-physical</td><td>100 (90-100)</td><td>75 (0-100)</td><td><0.001*</td></tr>
<tr><td>Body pain</td><td>100 (61-100)</td><td>72 (22-100)</td><td><0.001*</td></tr>
<tr><td>General health</td><td>82 (56-100)</td><td>56 (10-86)</td><td><0.001*</td></tr>
<tr><td>Vitality</td><td>80 (50-100)</td><td>60 (20-100)</td><td>0.006*</td></tr>
<tr><td>Social functioning</td><td>90 (50-100)</td><td>75 (37-100)</td><td>0.002*</td></tr>
<tr><td>Role emotional</td><td>100 (66-100)</td><td>66 (0-100)</td><td><0.001*</td></tr>
<tr><td>Mental health</td><td>82 (32-100)</td><td>60 (20-92)</td><td><0.001*</td></tr>
<tr><td colspan="4">*Generated using Mann-Whitney U test.</td></tr>
</table>
<table>
<tr><th>Domains</th><th>Shamblin I (N=2) Median (IQR)</th><th>Shamblin II (N=12) Median (IQR)</th><th>Shamblin III (N=9) Median (IQR)</th><th>P value*</th></tr>
<tr><td>Physical function</td><td>85 (85-85)</td><td>75 (20-90)</td><td>95 (70-100)</td><td>0.047</td></tr>
<tr><td>Role-physical</td><td>100 (100-100)</td><td>25 (0-100)</td><td>100 (50-100)</td><td>0.030</td></tr>
<tr><td>Body pain</td><td>78 (72-84)</td><td>74 (22-100)</td><td>72 (41-100)</td><td>0.655</td></tr>
<tr><td>General health</td><td>61 (40-82)</td><td>63(10-82)</td><td>56 (40-100)</td><td>0.941</td></tr>
<tr><td>Vitality</td><td>70 (55-85)</td><td>57 (20-95)</td><td>60 (50-100)</td><td>0.446</td></tr>
<tr><td>Social functioning</td><td>75 (50-100)</td><td>75 (37-100)</td><td>75 (50-100)</td><td>0.947</td></tr>
<tr><td>Role emotional</td><td>66 (33-100)</td><td>49 (0-100)</td><td>66 (33-100)</td><td>0.528</td></tr>
</table>
</td></tr>
</table>

				Mental health	64 (52-76)	58 (20-88)	64 (44-92)	0.444
				*Generated using Kruskal–Wallis test.				

<table>
<tr>
<td>Patel, 2019</td>
<td>patients with jugular paraganglioma treated with stereotactic radiosurgery (SRS)</td>
<td>The SF36 physical /mental component subscore (T score) is a norm-based score with a standard range that has a mean of 50 and a standard deviation of 10. The T-score typically ranges from approximately 15 to 61, with scores above 50 indicating better physical /mental health compared to the general population.

The PROMIS-10: physical/mental (T score) uses a T-score metric with a mean of 50 and a standard deviation of 10, meaning a higher score indicates worse physical /mental function.

Eating Assessment Tool-10 (EAT-10): ranges from 0 to 40, with a score of 3 or higher indicating a potential risk for dysphagia (swallowing difficulty)

Voice Handicap Index (VHI) ranges 0 to 120, where higher</td>
<td>30.6%</td>
<td>
<table>
<tr><th>Questionnaires</th><th>Primary or Staged SRS (N=19)
(Median, IQR)</th><th>SRS for recurrent JP (N=7)
Median (IQR)</th></tr>
<tr><td>SF36 physical component subscore</td><td>53.2 (44.3–56.4)</td><td>55.7 (48.8–57.5)</td></tr>
<tr><td>SF36 mental component subscore</td><td>55.0 (51.4–57.4)</td><td>56.0 (49.6–62.2)</td></tr>
<tr><td>PROMIS-10 physical</td><td>39.8 (37.4–42.3)</td><td>39.8 (37.4–42.3)</td></tr>
<tr><td>PROMIS-10 mental</td><td>41.1 (36.3–41.1)</td><td>36.3 (33.8–43.5)</td></tr>
<tr><td>GBI</td><td>2.8 (-2.8–19.4)</td><td>13.9 (0–16.7)</td></tr>
<tr><td>VHI</td><td>2 (0–10)</td><td>6 (0–70)</td></tr>
<tr><td>EAT-10</td><td>0 (0–1)</td><td>7 (0–21)</td></tr>
<tr><td>VRQoL</td><td>100 (95-100)</td><td>100 (67.5-100)</td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr><td></td><td></td><td>scores indicate a greater voice-related handicap.

Voice Related Quality of Life (VRQOL) (Normalized score) ranges 0 to 100, with a higher scores indicate beter quality of life with less impact from a voice disorder.

Glasgow Benefit Inventory (GBI): range is -100 to +100. A score of +100 indicates the maximum possible benefit from an intervention, while a score of −100 indicates the maximum possible harm.</td><td></td><td></td></tr>
<tr><td>Galland-Girodet, 2014</td><td>patients diagnosed with paragangliomas (PGL) receiving radiation therapy as a component of their treatment.</td><td><u>EORTC QLQ-C30:</u>
Scored from 0 to 100. For the functional scales and global QoL, a score of 100 represents a perfect QoL (absence of burden), whereas for the symptom scales, a score of 100 indicates heavy burden.

<u>QLQ-H&N35:</u></td><td>70%</td><td><table><tr><th>Subscales in EORTC QLQ-C30</th><th>PGL (N=20) Mean (SD)</th><th>EORTC database Control (N=2929) Mean (SD)</th></tr><tr><td>Physical functioning</td><td>76.1±22.4</td><td>81.2 ± 20.4</td></tr><tr><td>Role functioning</td><td>77.2 ± 29.5</td><td>78.9 ± 28.1</td></tr><tr><td>Emotional functioning</td><td>65.4 ± 36.5</td><td>72.5 ± 24.1</td></tr><tr><td>Cognitive functioning</td><td>70.2 ± 29.2</td><td>85.9 ±19.7</td></tr><tr><td>Social functioning</td><td>60.5 ± 36.5</td><td>82.6 ± 24.7</td></tr><tr><td>Total score mean</td><td>69.9 ± 30.8</td><td>80.2 ± 23.4</td></tr></table></td></tr>
</table>

		The Head and Neck-specific module Patients were required to have completed radiation at least 12 months prior to the quality of life assessment.		Symptoms in QLQ-H&N35	H&N PGL treated with radiotherapy alone (N=9) Mean (SD)	H&N PGL treated with combined treatment (N=11) Mean (SD)
				Pain in the mouth	10.2±12.3	17.5±14.9
				Swallowing	13.9±25.7	31.7±28.0
				Senses	18.5±25.6	21.7±24.9
				Speech	6.2±9.8	34.4±19.9
				Social eating	11.1±18.6	17.5±24.4
				Social contact	17.8±22.1	24.7±27.9
				Sexuality	30±41.5	33.3±47.1
				Dental issues	33.3±40.8	26.7±43.9
				Trismus	0±0	40±34.4
				Dry mouth	29.6±30.9	50.0±39.3
				Sticky saliva	18.5±29.4	30.0±24.6
				Cough	18.5±33.8	50.0±42.3
				Asthenia	11.1±23.6	30.0±36.7
				Painkillers	44.4±52.7	44.4±52.7
				Nutritional supplements	11.1±33.3	10.0±31.6
				Feeding tube	0±0	0±0
				Weight loss	11.1±33.3	30.0±48.3
				Weight gain	44.4±52.7	50.0±52.7
				Total score mean	18.3±13.2	30.1±13.8

<table>
<tr>
<td>Van Hulsteijn, 2013</td>
<td>Patients with paragangliomas, as well as asymptomatic SDH mutation carriers</td>
<td>HADS:
Scores range from 0 to 21 for each subscale and from 0 to 42 for the total score. A higher score indicates a higher level of anxiety and depression

MFI-20:
Items are scored on a five-point scale and subscales range from 4 to 20. Higher scores are associated with a higher feeling of fatigue.

SF-36:
Scores are expressed on a 0–100 scale, with higher scores indicating a better QoL.</td>
<td>58%</td>
<td>
<table>
<tr><th></th><th>Patients (n=174) Mean (SD)</th><th>Controls (n=100) Mean (SD)</th><th>Age-adjusted reference values (literature based) Mean (SD)</th></tr>
<tr><td>HADS</td><td></td><td></td><td></td></tr>
<tr><td>Anxiety</td><td>5.9±3.8</td><td>5.0±3.2</td><td>4.9±3.6</td></tr>
<tr><td>Depression</td><td>4.0 ±3.7</td><td>3.0±2.7</td><td>3.6±3.3</td></tr>
<tr><td>Total</td><td>9.9±6.9</td><td>8.1±5.3</td><td>8.4±6.3</td></tr>
<tr><td>MFI-20</td><td></td><td></td><td></td></tr>
<tr><td>General fatigue</td><td>11.3±4.8</td><td>9.3±4.1</td><td>9.9±5.2</td></tr>
<tr><td>Physical fatigue</td><td>9.9±4.6</td><td>7.7±3.6</td><td>8.8±4.9</td></tr>
<tr><td>Reduced activity</td><td>9.3±4.0</td><td>7.6±3.7</td><td>8.7±4.6</td></tr>
<tr><td>Reduced motivation</td><td>9.2±4.0</td><td>7.8±3.4</td><td>8.2±4.0</td></tr>
<tr><td>Mental fatigue</td><td>10.0±4.3</td><td>8.9±4.2</td><td>8.3±4.8</td></tr>
<tr><td>SF-36</td><td></td><td></td><td></td></tr>
<tr><td>Physical functioning</td><td>84.0±18.9</td><td>89.4±14.3</td><td>78.4±22.2</td></tr>
<tr><td>Social functioning</td><td>78.0±24.3</td><td>87.0±17.9</td><td>86.0±20.9</td></tr>
<tr><td>Role limitation physical</td><td>68.5±41.0</td><td>86.5±33.8</td><td>77.6±36.7</td></tr>
<tr><td>Role limitation-emotional</td><td>79.7±35.4</td><td>86.3±33.2</td><td>84.9±31.3</td></tr>
<tr><td>Mental health</td><td>72.0±17.6</td><td>77.1±15.4</td><td>76.8±18.5</td></tr>
<tr><td>Vitality</td><td>60.9±20.2</td><td>66.7±17.5</td><td>66.8±20.5</td></tr>
<tr><td>Bodily pain</td><td>82.6±21.8</td><td>87.0±18.6</td><td>79.0±25.2</td></tr>
<tr><td>General health</td><td>62.7±22.9</td><td>74.5±16.9</td><td>68.7±22.1</td></tr>
<tr><td>Health change</td><td>50.6±20.3</td><td>52.0±16.7</td><td>51.0±18.3</td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr>
<td>Havekes, 2012</td>
<td>Consecutive patients with head and neck paragangliomas
In the Netherlands</td>
<td><u>Epworth Sleepiness Scale</u>
The normal range of ESS scores is 2–10 with a normal distribution. A score of 10 or more is considered increased.

<u>St. George Respiratory Questionnaire</u>
The SGRQ scores range from 0 to 100, 0 score indicating no impairment of quality of life. A four-point change in SGRQ is considered a clinically significant difference.</td>
<td>70%</td>
<td>
<table>
<tr><th></th><th>Patients (n=74)
Mean (SD)</th><th>Controls (n=41)
Mean (SD)</th><th>Leiden controls (n=74)
Mean (SD)</th></tr>
<tr><td>ESS</td><td></td><td></td><td></td></tr>
<tr><td>Total score</td><td>6.1±4.1</td><td>5.7±3.9</td><td>5.1±3.5</td></tr>
<tr><td>Total score ≥10</td><td>21%</td><td>20%</td><td>12%</td></tr>
<tr><td>SGRQ</td><td></td><td></td><td></td></tr>
<tr><td>Symptoms score</td><td>17.1±19.3</td><td>12.2±13.5</td><td>Not reported</td></tr>
<tr><td>Activity score</td><td>15.4±18.5</td><td>7.2±9.9</td><td>Not reported</td></tr>
<tr><td>Disturbance of psychosocial function</td><td>5.3±10.5</td><td>1.2±2.6</td><td>Not reported</td></tr>
<tr><td>Total score</td><td>10.4±12.9</td><td>5.0±4.8</td><td>Not reported</td></tr>
</table>
<table>
<tr><th></th><th>Patients without CBT (n=10)
Mean (SD)</th><th>Patients with single CBT (n=35)
Mean (SD)</th><th>Patients with bilateral CBT (n=26)
Mean (SD)</th><th>Patients with CBT (n=61)
Mean (SD)</th></tr>
<tr><td>ESS</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Total score</td><td>2.6±2.0</td><td>6.6±4.2</td><td>6.7±4.0</td><td>6.6±4.1</td></tr>
<tr><td>Total score ≥10</td><td>0%</td><td>20%</td><td>26.9%</td><td>23%</td></tr>
</table>
CBT: Carotid body tumor.
</td>
</tr>
</table>

	Single CBT without surgery (n=10) Mean (SD)	Single CBT with surgery (n=11) Mean (SD)
ESS		
Total score	5.8±4.7	7.7±4.6

<table>
<tr><td></td><td></td><td></td><td></td><td>
<table>
<tr><td>Total score ≥10</td><td>20%</td><td>27%</td></tr>
</table>
</td></tr>
<tr><td>Havekes, 2008</td><td>Patients with head and neck paragangliomas in the outpatient clinic in a tertiary referral center in the Netherlands.</td><td>HADS:
Scores range from 0 to 21 for each subscale and from 0 to 42 for the total score. A higher score indicates a higher level of anxiety and depression

MFI-20:
Items are scored on a five-point scale and subscales range from 4 to 20. Higher scores are associated with a higher feeling of fatigue.

Nottingham Health Profile (NHP):
Subscale scores are calculated as a weighted mean of the associated items and are expressed as a value ranging from 0 to 100.</td><td>78.1%</td><td>
<table>
<tr><td></td><td>Patients (n=82)
Mean (SD)</td><td>Controls (n=44)
Mean (SD)</td><td>Leiden controls (n=168)
Mean (SD)</td></tr>
<tr><td>SF-36</td><td></td><td></td><td></td></tr>
<tr><td>Physical functioning</td><td>86.7±17.2</td><td>94.4±10.3</td><td>91.0±14.7</td></tr>
<tr><td>Social functioning</td><td>82.8±23.1</td><td>89.6±15.4</td><td>92.4±15.3</td></tr>
<tr><td>Role limitation physical</td><td>73.2±36.8</td><td>89.5±25.1</td><td>89.2±26.3</td></tr>
<tr><td>Role limitation-emotional</td><td>81.7±34.8</td><td>91.5±24.2</td><td>90.1±25.9</td></tr>
<tr><td>Bodily pain</td><td>83.1±19.5</td><td>90.7±15.3</td><td>87.9±16.3</td></tr>
<tr><td>General health perception</td><td>66.8±21.8</td><td>76.5±18.5</td><td>75.7±17.2</td></tr>
<tr><td>Health change</td><td>51.5±19.4</td><td>51.2±13.3</td><td>55.0±18.3</td></tr>
<tr><td>NHP</td><td></td><td></td><td></td></tr>
<tr><td>Energy</td><td>16.2±31.1</td><td>3.8±13.7</td><td>4.7±17.7</td></tr>
<tr><td>Pain</td><td>5.2±15.0</td><td>3.9±14.1</td><td>2.7±11.0</td></tr>
<tr><td>Emotional reaction</td><td>12.1±23.3</td><td>3.9±12.0</td><td>3.0±9.8</td></tr>
<tr><td>Sleep</td><td>12.7±26.6</td><td>11.7±22.9</td><td>6.3±17.2</td></tr>
<tr><td>Physical ability</td><td>4.1±9.0</td><td>2.5±7.1</td><td>3.7±10.9</td></tr>
<tr><td>Social isolation</td><td>6.9±17.8</td><td>2.0±7.7</td><td>0.9±5.6</td></tr>
<tr><td>Total</td><td>49.7±87.4</td><td>26.8±59.8</td><td>3.5±7.6</td></tr>
<tr><td>MFI-20</td><td></td><td></td><td></td></tr>
</table>
</td></tr>
</table>

<table>
<tr>
<td></td>
<td></td>
<td>The total score is the mean of the six subscales. A high score points to a worse QoL.

Short Form-36 (SF-36): Scores are expressed on a 0–100 scale, with higher scores indicating a better QoL.</td>
<td></td>
<td>
<table>
<tr><td>General fatigue</td><td>10.0±4.9</td><td>8.3±3.8</td><td>7.9±3.7</td></tr>
<tr><td>Physical fatigue</td><td>9.1±4.2</td><td>7.1±3.4</td><td>7.5±3.5</td></tr>
<tr><td>Reduced activity</td><td>8.7±3.7</td><td>6.5±3.3</td><td>6.9±3.1</td></tr>
<tr><td>Reduced motivation</td><td>8.4±3.4</td><td>7.0±3.5</td><td>6.8±2.7</td></tr>
<tr><td>Mental fatigue</td><td>9.3±4.4</td><td>8.1±4.0</td><td>7.2±3.5</td></tr>
<tr><td>HARDS</td><td></td><td></td><td></td></tr>
<tr><td>Anxiety</td><td>5.1±4.2</td><td>4.0±3.2</td><td>3.5±2.9</td></tr>
<tr><td>Depression</td><td>3.3±3.6</td><td>2.4±2.6</td><td>2.2±2.2</td></tr>
<tr><td>Total</td><td>8.4±7.3</td><td>6.4±5.1</td><td>5.8±4.4</td></tr>
</table>
</td>
</tr>
<tr>
<td>Henzel, 2007</td>
<td>Patients with Glomus Jugulare Tumors treated with SRT in Germany</td>
<td>Short Form-36 (SF-36): Scores are expressed on a 0–100 scale, with higher scores indicating a better QoL.</td>
<td>94%</td>
<td>
<table>
<tr><th>Domains</th><th>Patients (n=16) (mean, 95%CI not reported)</th><th>General normal population (mean, 95%CI not reported)</th></tr>
<tr><td>Physical functioning</td><td>71.9</td><td>85.7</td></tr>
<tr><td>Role limitations due to physical health</td><td>56.3</td><td>83.7</td></tr>
<tr><td>Role limitations due to emotional problems</td><td>63.9</td><td>90.4</td></tr>
<tr><td>Social functioning</td><td>76.4</td><td>88.7</td></tr>
<tr><td>Mental health</td><td>72.5</td><td>73.9</td></tr>
<tr><td>Pain</td><td>66.8</td><td>79.1</td></tr>
<tr><td>Vitality</td><td>53.1</td><td>63.3</td></tr>
<tr><td>General health</td><td>58.1</td><td>68.1</td></tr>
</table>
</td>
</tr>
</table>

Kennisvragen

Tijdens de ontwikkeling van deze module is gebleken dat er binnen deze module nog te weinig bewijs is voor de onderbouwing van de aanbeveling en dus kennisvragen bestaan. De werkgroep meent dat (vervolg)onderzoek wenselijk is om in de toekomst een duidelijker antwoord te kunnen geven op vragen uit de praktijk.

Kennisvraag:

1. Wat is het longitudinale beloop van KvL en relevante symptoomdomeinen per type HNPGL onder verschillende behandel strategieën?

2a. Welke combinatie van generieke en symptoom specifieke PROMs is het meest valide, gevoelig voor verandering en haalbaar als 'kernset' voor HNPGL, en welke minimal clinically important differences (MCID) gelden voor deze vragenlijsten binnen deze populatie?

2b. Op dit moment ontbreekt een specifieke, gevalideerde ziektespecifieke vragenlijst voor de kwaliteit van leven bij patiënten met een HNPGL. Welke items moeten geïncludeerd worden in een te valideren ziektespecifieke vragenlijst?

Toelichting:

1. De huidige evidence is grotendeels cross-sectioneel en heterogeen, waardoor het effect van behandelstrategie op KvL onvoldoende duidelijk is. Prospectieve cohortstudies met baseline-meting en herhaalde metingen zijn nodig om klinisch relevante veranderingen en risicoprofielen te bepalen.

2. Er bestaat geen ziekte-specifieke KvL-vragenlijst; studies gebruiken uiteenlopende instrumenten. Een consensus-based kernset met evaluatie van meeteigenschappen en MCID maakt interpretatie en implementatie in de praktijk beter mogelijk.

Verkeerslichtanalyse en Implementeren- en Agenderen-tabel

Verkeerslichtanalyse (ten behoeve van commentaar- en autorisatiefase)

Kruis aan		
	ROOD	Sterke aanbeveling tegen, geldend voor de gehele populatie, en waar passend bewijs voor is [1]
	ORANJE	Aanbeveling waar geen passend bewijs is voor gehele populatie • Sterke aanbeveling tegen (geen passend bewijs voor gehele populatie en subpopulaties/ condities) • Conditionele aanbeveling (geen passend bewijs voor gehele populatie, maar wel passend bewijs voor een subgroep/-conditie (overweging))
X	**GROEN**	Sterke aanbeveling voor, geldend voor de gehele populatie, en waar passend bewijs voor is [1,2]

[1] Er kan ook sprake zijn van passend bewijs bij een low of very low GRADE; bijvoorbeeld omdat er overwegingen zijn die zwaarwegend zijn in het aanbevolen beleid.

[2] Deze categorie geldt ook indien er passend bewijs is waaruit blijkt dat er geen voorkeur is voor één van de onderzochte interventies/diagnostiekmethoden/verwijspaden, voorbeeld: twee chirurgische technieken zijn even effectief, hebben vergelijkbare complicatierisico's, keuze is afhankelijk van het besluit dat de chirurg samen met de patiënt maakt.

Implementatietabel

De implementatietabel brengt in kaart welke factoren de uitvoering van een aanbeveling bevorderen of belemmeren, en welke aanvullende acties nodig zijn voor succesvolle invoering.

Vraag	***Antwoord:*** *Kruis aan en licht toe/ beschrijf*		***Toelichting keuze:***
I1. Wat was het onderliggende probleem om deze uitgangsvraag uit te werken?		**Ongewenste praktijkvariatie**	
	x	**Nieuwe evidentie**	Symptomatologie correleert niet uniform met kwaliteit van leven. Daardoor is het onvoldoende om alleen uitval of klinische symptomen als proxy voor kwaliteit van leven te gebruiken
		Anders	
I2. Maak een inschatting over hoeveel patiënten het ongeveer gaat waar de aanbeveling betrekking op heeft?	**x**	**< 1000**	
		< 5000	
		5000-40.000	
		> 40.000	
I3. Is de aanbeveling onderdeel van een bredere set interventies of verwant aan andere richtlijnen of modules? Zo ja, hoe verhoudt zij zich daartoe en moet hiermee rekening worden gehouden bij de implementatie, of kan de aanbeveling als losstaand worden beschouwd?		**Ja**	
	x	**Nee**	
I4. Belemmeringen en kansen op verschillende niveaus voor landelijke toepassing van de aanbeveling:		**Belemmerende factoren**	**Bevorderende factoren/ kansen**
Richtlijn/ klinisch traject (innovatie)		Er is nog geen gevalideerde ziekte-specifieke HNPGL-KvL vragenlijst beschikbaar. De evidence is heterogeen, grotendeels observationeel en beperkt	De module geeft duidelijke meetmomenten en een praktisch voorstel voor generieke en

		longitudinaal. Er is nog geen internationaal vastgestelde PROM-kernset.	domeinspecifieke PROMs.
Zorgverleners (artsen en verpleegkundigen)		Extra tijdsinvestering voor afname, interpretatie en bespreking van vragenlijsten.	PROM-uitkomsten kunnen klinisch relevante klachten zichtbaar maken die anders onderbelicht blijven.
Patiënt/ cliënt (naasten)		Vragenlijstbelasting en mogelijke emotionele belasting bij confrontatie met klachten. Patiënten kunnen nut minder ervaren als terugkoppeling of vervolgzorg uitblijft.	Systematische KvL-meting sluit aan bij patiëntgerichte zorg en samen beslissen.
Sociale context		n.v.t.	n.v.t.
Organisatorische context		Implementatie vraagt inbedding in EPD of ander afnamesysteem.	Een vooraf ingevulde PROM kan tijd besparen in de spreekkamer.
Financiële en juridische context		Er is geen kosten-effectiviteitsbewijs specifiek voor deze module.	De additionele kosten worden naar verwachting beperkt geacht.
I5. A) Welke personen/partijen zijn van belang bij het toepassen van de aanbeveling in de praktijk? (kruis aan) **B) Wat is er nodig van deze personen/partijen om de aanbeveling in de praktijk te kunnen brengen?** *Denk aan aanpassingen in gedrag, werkwijzen, beleid, samenwerking of andere randvoorwaarden.*		**A**	**B**
	x	Patiënt/ cliënt (naaste)	Actieve deelname aan het invullen van vragenlijsten
	x	Professional	Structureel af nemen, interpreteren en bespreken van de vragenlijst
	x	Beroepsvereniging, nl	Ondersteunen van implementatie via richtlijndisseminatie
		Ziekenhuis (raad van bestuur/UMCNL (voorheen NFU)/NVZ)	

		Zorgverzekeraars/ NZa	
		Zorginstituut [duiding nodig]	
		Anders	
I6. Binnen welk tijdsbestek moet de aanbeveling zijn geïmplementeerd?	**x**	< 1 jaar	**De module adviseert reeds beschikbare instrumenten waardoor implementatie op relatief korte termijn kan starten.**
		binnen 2-3 jaar	
I7. Conclusie: is er extra actie en/of ondersteuning nodig voor implementatie van de aanbeveling? *De reguliere implementatieroutes (publicatie en disseminatie via officiele kanalen, opname in professionele standaarden, scholing en nascholing, gebruik van bestaande ICT systemen, audits en visitaties) van de richtlijnmodule alleen is onvoldoende.*		Ja	
	x	Nee	
I8. Plaatsing op de Landelijke Implementatieagenda Medisch Specialistische zorg is gewenst. *Het gaat om zorg die (grotendeels) wordt uitgevoerd binnen de ziekenhuismuren. Succesvolle implementatie vraagt om actieve betrokkenheid en samenwerking van meerdere relevante partijen binnen de zorgpraktijk.*		Ja *	
	x	Nee	

**Deze aanbeveling komt mogelijk in aanmerking voor plaatsing op de Landelijke Implementatieagenda van het programma Zorg Evaluatie & Gepast Gebruik (ZE&GG), waarin alle betrokken partijen in de medisch-specialistische zorg samenwerken aan de implementatie van bewezen beste zorg. De Federatie levert namens het veld goed onderbouwde aanbevelingen aan, die zijn getoetst op de behoefte aan een implementatie-impuls. De onderwerpen op de Implementatieagenda zijn onderdeel van landelijke zorginkoopafspraken tussen zorgverzekeraars en zorgaanbieders. Voor de beoordeling van aanbevelingen uit richtlijnen wordt gebruikgemaakt van de implementatietabel. Op basis hiervan kunnen we de andere partijen goed informeren en gezamenlijk besluiten of plaatsing op de Implementatieagenda passend is.*

Agenderen-tabel

Vraag	***Antwoord*** *Kruis aan*	 *Vul in*
A1. Is onderzoek wenselijk om de <u>uitgangsvraag of zoekvraag</u> (met meer/voldoende zekerheid) te kunnen beantwoorden?		Nee. *Tijdens de ontwikkeling van deze module is gebleken dat er volgens het cluster sprake is van passend bewijs voor de uitgangsvraag en zoekvraag.* [Geef toelichting indien gewenst] *Ga verder bij vraag A5.*
	x	Ja
A2. Wat is de kennisvraag?	Kennis-vraag	Welke items moeten worden opgenomen in een te ontwikkelen en te valideren ziekte-specifieke KvL-vragenlijst voor patiënten met HNPGL?
	P	Patiënten met (risico op) HNPGL, eventueel aangevuld met naasten en betrokken zorgprofessionals.
	I	Ontwikkeling en validatie van een HNPGL-specifieke KvL-vragenlijst.
	C	Bestaande generieke en domeinspecifieke PROMs.
	O	Inhoudsvaliditeit, constructvaliditeit, betrouwbaarheid, responsiviteit, patiëntbelasting en klinische bruikbaarheid.
A3. Waarom is dit een belangrijke kennisvraag?	Toelichting	Er is momenteel geen gevalideerde ziekte-specifieke KvL-vragenlijst voor HNPGL en studies gebruiken uiteenlopende instrumenten. Daardoor is onduidelijk welke PROMs het best geschikt zijn voor structurele monitoring en hoe veranderingen in scores klinisch geïnterpreteerd moeten worden.
A4. Welk onderzoeksdesign is passend om deze kennisvraag te beantwoorden?		RCT
		Observationeel onderzoek
		Kwaliteitsregistratie
	x	Anders, namelijk: mixed-methods vragenlijstontwikkeling en validatiestudie
	Toelichting	Start met kwalitatief onderzoek/interviews voor itemselectie, gevolgd door prospectieve validatie.
A5. Zijn er een andere kennisvragen naar voren gekomen die passen bij het <u>onderwerp van de module</u>, maar niet hetzelfde zijn als de uitgangs- of zoekvraag en waar *geen* passend bewijs voor is?		Nee
	x	Ja
A6. Wat is de kennisvraag?	Kennis-vraag	Wat is het longitudinale beloop van kwaliteit van leven en relevante

		symptoomdomeinen per type HNPGL en per behandelstrategie?
	P	Patiënten met HNPGL, gestratificeerd naar tumortype, erfelijkheid/SDHx-status, symptomatologie en behandelstatus.
	I	Behandelstrategie: wait-and-scan, chirurgie, radiotherapie/stereotactische radiotherapie of combinaties hiervan.
	C	Vergelijking tussen behandelstrategieën, of vergelijking met baseline binnen dezelfde patiënt.
	O	Longitudinale verandering in globale KvL, fysiek functioneren, sociaal functioneren, vermoeidheid, angst/depressieve klachten, slaap, gehoor, duizeligheid, stem- en slikfunctie.
A7. Waarom is dit een belangrijke kennisvraag?	Toelichting	De huidige evidence is grotendeels cross-sectioneel en heterogeen. Daardoor is onvoldoende duidelijk hoe KvL zich ontwikkelt over de tijd en welke patiënten risico lopen op relevante verslechtering. Deze kennis is nodig om meetmomenten, counseling en behandelkeuzes beter te onderbouwen.
A8. Welk onderzoeksdesign is passend om deze kennisvraag te beantwoorden?		RCT
	x	Observationeel onderzoek, matched cohort
	x	Kwaliteitsregistratie
		Anders, namelijk:
	Toelichting	Een prospectieve multicenter registratie met vaste meetmomenten rond diagnose, vóór interventie, na interventie en tijdens follow-up is het meest passend. Randomisatie is voor deze vraag niet noodzakelijk en waarschijnlijk niet haalbaar.

[Kopieer en plak deze tabel indien er meerdere kennisvragen bestaan. Verwijder 1) de cellen bij vragen A2-A4 en/of A6-A8 indien je deze niet invult, 2) de grijze tekst en [tekst] als je deze vakjes niet invult en 3) de voetnoten die hieronder staan

5 [a)] Formuleer hier de kennisvraag als een onderzoekvraag. Dit kan de zoekvraag zijn, maar kan ook afwijken. Om het juiste onderzoek te doen is het van groot belang dat de kennisvragen scherp geformuleerd worden, in de vorm van een PICO. Uitgangspunt is dat een kennisvraag met één zorgevaluatie onderzoek opgelost kan worden.
[b)] Beschrijf in 2 à 3 zinnen waarom dit een relevante kennisvraag is.

Literatuur

Canu L, Zanatta L, Sparano C, Santoro R, Mannelli G, Zamengo S, Jance B, Amore F, Ercolino T, Mannelli M, Maggi M, Rapizzi E. Pros and cons of surgical versus conservative management for head and neck paraganglioma: a real-world data analysis. Endocrine. 2025 May;88(2):607-615. doi: 10.1007/s12020-025-04167-1. Epub 2025 Jan 26. PMID: 39864047; PMCID: PMC12069424.

de Bresser CJM, Rijken JA, van Treijen MJC, van Nesselrooij BPM, de Ridder M, de Bree R, de Borst GJ, Petri BJ, van Leeuwaarde RS. Low psychosocial burden in patients with paraganglioma syndrome: results from the Head and Neck Paraganglioma Registry in a single center. Eur J Endocrinol. 2025 Mar 3;192(3):257-265. doi: 10.1093/ejendo/lvaf033. PMID: 39993160.

Ehret F, Kufeld M, Fürweger C, Haidenberger A, Schichor C, Tonn JC, Muacevic A, Hempel JM. Single-session image-guided robotic radiosurgery and quality of life for glomus jugulare tumors. Head Neck. 2020 Sep;42(9):2421-2430. doi: 10.1002/hed.26231. Epub 2020 May 12. PMID: 32394483.

Galland-Girodet S, Maire JP, De-Mones E, Benech J, Bouhoreira K, Protat B, Demeaux H, Darrouzet V, Huchet A. The role of radiation therapy in the management of head and neck paragangliomas: impact of quality of life versus treatment response. Radiother Oncol. 2014 Jun;111(3):463-7. doi: 10.1016/j.radonc.2014.06.002. Epub 2014 Jul 1. PMID: 24996453.

García-Alva R, Lozano-Corona R, Anaya-Ayala JE, Lizola R, Lopez-Rocha S, Cuen-Ojeda C, Laparra-Escareno H, Hinojosa CA. Assessment of health-related quality of life in patients prior to carotid body tumor resection. Vascular. 2019 Dec;27(6):612-616. doi: 10.1177/1708538119848522. Epub 2019 May 12. PMID: 31081492.

Havekes B, Kastelein F, van der Klaauw AA, van Duinen N, Jansen JC, Smit JW, van Kralingen KW, Vriends AH, Romijn JA, Corssmit EP. Head-and-neck paragangliomas are associated with sleep-related complaints, especially in the presence of carotid body tumors. Sleep Breath. 2012 Jun;16(2):527-34. doi: 10.1007/s11325-011-0538-5. Epub 2011 May 27. PMID: 21614574; PMCID: PMC3306847.

Havekes B, van der Klaauw AA, Hoftijzer HC, Jansen JC, van der Mey AG, Vriends AH, Smit JW, Romijn JA, Corssmit EP. Reduced quality of life in patients with head-and-neck paragangliomas. Eur J Endocrinol. 2008 Feb;158(2):247-53. doi: 10.1530/EJE-07-0464. PMID: 18230833.

Hebb ALO, Erjavec N, Morris DP, Shoman NM, Mulroy L, Walling SA. Treatment of patients with glomus jugulare tumours (GJT) and its subjective effect on quality of life (QoL) measures. Am J Otolaryngol. 2020 Nov-Dec;41(6):102559. doi: 10.1016/j.amjoto.2020.102559. Epub 2020 May 27. PMID: 32527669.

Henzel M, Hamm K, Gross MW, Surber G, Kleinert G, Failing T, Sitter H, Strassmann G, Engenhart-Cabillic R. Fractionated stereotactic radiotherapy of glomus jugulare tumors. Local control, toxicity, symptomatology, and quality of life. Strahlenther Onkol. 2007 Oct;183(10):557-62. doi: 10.1007/s00066-007-1701-6. PMID: 17896087.

Molina-Romero OI, Fonnegra-Caballero A, Diez-Palma JC, Segura-Hernández A, Rodriguez-Noreña V, Segura-Hernández G, Corredor-Torres V, Rojas-Ortiz MC, Useche-Aroca D, Fonnegra-Pardo JR. Gamma Knife radiosurgery for the management of glomus jugulare tumors: A systematic review and report of the experience of a radioneurosurgery unit in Latin America. Surg Neurol Int. 2024 Mar 8;15:78. doi: 10.25259/SNI_866_2023. PMID: 38628524; PMCID: PMC11021112.

Patel NS, Link MJ, Tombers NM, Pollock BE, Carlson ML. Quality of Life in Jugular Paraganglioma Following Radiosurgery. Otol Neurotol. 2019 Jul;40(6):820-825. doi: 10.1097/MAO.0000000000002250. PMID: 31135667.

Samlal DPS, Hristova M, Albrecht A, Schipper J, Jansen TTG, Delsing CPA, Kunst HPM. Mapping the neglected topic in head and neck paraganglioma research: a PRISMA scoping review on quality of life. Qual Life Res. 2026 Mar 13;35(4):97. doi: 10.1007/s11136-026-04218-8. PMID: 41824145; PMCID: PMC12987911.

5 van Hulsteijn LT, Louisse A, Havekes B, Kaptein AA, Jansen JC, Hes FJ, Smit JW, Corssmit EP. Quality of life is decreased in patients with paragangliomas. Eur J Endocrinol. 2013 Apr 15;168(5):689-97. doi: 10.1530/EJE-12-0968. PMID: 23392211.

Table of excluded studies

Reference	Reason for exclusion
Carotid baroreceptor dysfunction after carotid body tumour resections	wrong outcome
Carotid body tumors are not associated with an increased risk for sleep-disordered breathing	wrong outcome
Dignity of carotid body tumors. Review of the literature and clinical experiences	Article in German
Evolving concepts in the management of jugular paraganglioma: A comparison of radiotherapy and surgery in 88 cases	wrong outcome
Excellent local control of paraganglioma in the head and neck with fractionated radiotherapy	wrong outcome
Extracranial temporal bone paragangliomas: Re-defining the role of otologic surgery within the scope of function-preserving multimodal concepts	wrong outcome
Gamma Knife surgery for the management of glomus tumors: A multicenter study - Clinical article	wrong outcome
[Individualized treatment of bilateral carotid body tumor]	Article in Chinese
Intradural jugular paragangliomas: Complications and sequelae	wrong outcome
Less-aggressive surgical management and long-term outcomes of jugular foramen paragangliomas: A neurosurgical perspective	wrong outcome
Long-Term Outcomes in Head and Neck Paragangliomas Managed with Intensity-Modulated Radiotherapy	wrong outcome
Long-Term Outcomes of Jugular Paragangliomas Undergoing Gamma Knife Radiosurgery: A Single Center Experience	wrong outcome
Morbidity and Long-Term Patient-Reported Outcomes Following Advanced Carotid Body Tumor Resection	No specific data about quality of life
Paraganglioma of the head and neck - Tumor control, functional results and quality of life	Article in German
Paragangliomas of the head and neck: Local control and functional outcome following fractionated stereotactic radiotherapy	wrong outcome
Pheochromocytoma and Paraganglioma Genetic Testing: Psychological Impact	Wrong intervention
Protontherapy of head and neck paragangliomas: A monocentric study	wrong outcome
Stereotactic LINAC-radiosurgery for glomus jugulare tumors: A long-term follow-up of 27 patients	wrong outcome
Temporal Bone Paraganglioma: Hearing Outcomes and Rehabilitation	wrong outcome
Quality of life in patients with skull base tumors: Current status and future challenges	Wrong study design
Surgical treatment options for cervical paragangliomas	Article in German

Vagal Paragangliomas: From Reducing Morbidity to Improving Quality of Life	Wrong study design
Quality of life in patients with adrenal disease: A systematic review	No relevante information reported

Literature search strategy

Zoekstrategie

Embase.com

No.	Query	Results
#1	'paraganglioma'/exp OR 'glomus tumor'/exp OR paraganglio*:ti,ab,kw OR chemodectom*:ti,ab,kw OR ((('carotid body' OR 'carotid glomus' OR 'glomus caroticum' OR 'glomus jugular*' OR jugulotympanic OR 'jugular glomus' OR 'jugular body' OR 'glomus tympanicum' OR 'glomus vagale' OR 'vagus nerve*' OR 'vagal nerve*' OR glomus) NEAR/3 (cancer OR tumor* OR tumour*)):ti,ab,kw) OR glomangioma*:ti,ab,kw OR 'catecholamine-producing tumor'/exp OR pheochromocytom*:ti,ab,kw OR phaeochromocytom*:ti,ab,kw OR pheochromoblastoma*:ti,ab,kw OR phaeochromoblastoma*:ti,ab,kw OR (((cathecholamin* OR epinephrin* OR norepinephrin*) NEAR/3 (tumor* OR tumour*)):ti,ab,kw) OR ppgl:ti,ab,kw OR hnpgl:ti,ab,kw	61332
#2	'quality of life'/exp OR 'disease burden'/exp OR ((life NEAR/2 qualit*):ti,ab,kw) OR 'qol':ti,ab,kw OR 'ql':ti,ab,kw OR 'hrql':ti,ab,kw OR 'hrqol':ti,ab,kw OR ((disease NEAR/3 burden):ti,ab,kw) OR 'health status'/exp OR 'health status':ti,ab,kw OR 'patient-reported outcome'/exp OR ((('patient report*' OR patientreport* OR 'self report*' OR selfreport*) NEAR/3 outcome*):ti,ab,kw) OR 'hr pro':ti,ab,kw OR 'hrpro':ti,ab,kw OR (((patient* OR self) NEXT/2 ('reported' OR 'reporting' OR 'rated' OR 'rating' OR 'ratings')):ti,ab,kw) OR 'patient* perspective*':ti,ab,kw OR 'social psychology'/de OR (((psychosocial OR 'psycho social') NEAR/3 (aspect* OR burden OR factor* OR function* OR overload OR stabilit* OR stress OR study)):ti,ab,kw) OR ((social NEAR/3 (aspect* OR burden OR distress OR factor* OR function* OR psychology OR strain OR stress)):ti,ab,kw)	2081569
#3	#1 AND #2 NOT ('conference abstract'/it OR 'clinical trial':dtype) NOT (('editorial'/it OR 'letter'/it OR 'note'/it) NOT 'evidence based medicine'/exp) NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	753
#4	#3 AND [2005-2025]/py	645
#5	'meta analysis'/exp OR 'systematic review'/exp OR 'scoping review'/exp OR 'rapid review'/exp OR 'umbrella review'/exp OR 'cochrane database of systematic reviews'/jt OR 'network meta-analysis'/exp OR 'networkmeta analy*':ti,ab,kw OR 'networkmetaanaly*':ti,ab,kw OR metaanaly*:ti,ab,kw OR	1153041

	'meta analy*':ti,ab,kw OR metanaly*:ti,ab,kw OR prisma:ti,ab,kw OR prospero:ti,ab,kw OR metaanali*:ti,ab,kw OR 'meta anali*':ti,ab,kw OR metanali*:ti,ab,kw OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab,kw) OR (((structured OR systemic*) NEAR/3 (review* OR overview* OR synth*) NEAR/3 literature):ti,ab,kw) OR ((systemic* NEAR/1 review*):ti,ab,kw) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab,kw) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab,kw) OR (((literature NEAR/3 (review* OR overview*)):ti,ab,kw) AND (search*:ti,ab,kw OR database*:ti,ab,kw OR 'data base*':ti,ab,kw)) OR (('data extraction*':ti,ab,kw OR 'data source*':ti,ab,kw) AND ('study selection*':ti,ab,kw OR 'studies selection*':ti,ab,kw)) OR ('search strateg*':ti,ab,kw AND 'selection criteria*':ti,ab,kw) OR ('data source*':ti,ab,kw AND 'data synth*':ti,ab,kw) OR medline*:ti,ab,kw OR pubmed*:ti,ab,kw OR 'pub med*':ti,ab,kw OR embase:ti,ab,kw OR cochrane*:ti,ab,kw OR (((critical* OR rapid*) NEAR/2 (review* OR overview* OR synth*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synth*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynth*:ti,ab,kw OR 'meta synth*':ti,ab,kw OR 'review* of review*':ti,ab,kw	
#6	'major clinical study'/de OR 'clinical study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR 'prospective study'/de OR 'cohort analysis'/de OR 'case control study'/de OR 'comparative study'/exp OR 'control group'/de OR 'controlled study'/de OR 'controlled clinical trial'/de OR 'crossover procedure'/de OR 'double blind procedure'/de OR 'phase 2 clinical trial'/de OR 'phase 3 clinical trial'/de OR 'phase 4 clinical trial'/de OR 'pretest posttest design'/de OR 'pretest posttest control group design'/de OR 'quasi experimental study'/de OR 'single blind procedure'/de OR 'triple blind procedure'/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) OR (((control OR controlled) NEAR/6 trial):ti,ab,kw) OR (((control OR controlled) NEAR/6 (study OR studies)):ti,ab,kw) OR (((control OR controlled) NEAR/1 active):ti,ab,kw) OR 'open label*':ti,ab,kw OR (((double OR two OR three OR multi OR trial) NEAR/1 (arm OR arms)):ti,ab,kw) OR ((allocat* NEAR/10 (arm OR arms)):ti,ab,kw) OR placebo*:ti,ab,kw OR 'sham-control*':ti,ab,kw OR (((single OR double OR triple OR assessor) NEAR/1 (blind* OR masked)):ti,ab,kw) OR nonrandom*:ti,ab,kw OR 'non-random*':ti,ab,kw OR 'quasi-	18943227

	experiment*':ti,ab,kw OR crossover:ti,ab,kw OR 'cross over':ti,ab,kw OR 'parallel group*':ti,ab,kw OR 'factorial trial':ti,ab,kw OR ((phase NEAR/5 (study OR trial)):ti,ab,kw) OR ((case* NEAR/6 (matched OR control*)):ti,ab,kw) OR ((match* NEAR/6 (pair OR pairs OR cohort* OR control* OR group* OR healthy OR age OR sex OR gender OR patient* OR subject* OR participant*)):ti,ab,kw) OR ((propensity NEAR/6 (scor* OR match*)):ti,ab,kw) OR versus:ti OR vs:ti OR compar*:ti OR ((compar* NEAR/1 study):ti,ab,kw) OR (('observational study'/de OR 'cross-sectional study'/de OR 'multicenter study'/de OR 'correlational study'/de OR 'follow up'/de OR cohort*:ti,ab,kw OR 'follow up':ti,ab,kw OR followup:ti,ab,kw OR longitudinal*:ti,ab,kw OR prospective*:ti,ab,kw OR retrospective*:ti,ab,kw OR observational*:ti,ab,kw OR 'cross sectional*':ti,ab,kw OR cross?ectional*:ti,ab,kw OR multicent*:ti,ab,kw OR 'multi-cent*':ti,ab,kw OR consecutive*:ti,ab,kw) AND (group:ti,ab,kw OR groups:ti,ab,kw OR subgroup*:ti,ab,kw OR versus:ti,ab,kw OR vs:ti,ab,kw OR compar*:ti,ab,kw OR 'odds ratio*':ab OR 'relative odds':ab OR 'risk ratio*':ab OR 'relative risk*':ab OR 'rate ratio':ab OR aor:ab OR arr:ab OR rrr:ab OR ((('or' OR 'rr') NEAR/6 ci):ab)))	
#7	#4 AND #5	43
#8	#4 AND #6 NOT #7	266
#9	#4 NOT (#7 OR #8)	336
#10	#7 OR #8 OR #9	645

Ovid/Medline

#	Searches	Results
1	exp Paraganglioma/ or exp Glomus Tumor/ or paraganglio*.ti,ab,kf. or chemodectom*.ti,ab,kf. or (('carotid body' or 'carotid glomus' or 'glomus caroticum' or 'glomus jugular*' or jugulotympanic or 'jugular glomus' or 'jugular body' or 'glomus tympanicum' or 'glomus vagale' or 'vagus nerve*' or 'vagal nerve*' or glomus) adj3 (cancer or tumor* or tumour*)).ti,ab,kf. or glomangioma*.ti,ab,kf. or pheochromocytom*.ti,ab,kf. or phaeochromocytom*.ti,ab,kf. or pheochromoblastoma*.ti,ab,kf. or phaeochromoblastoma*.ti,ab,kf. or ((cathecholamin* or epinephrin* or norepinephrin*) adj3 (tumor* or tumour*)).ti,ab,kf. or ppgl.ti,ab,kf. or hnpgl.ti,ab,kf.	39605
2	exp "Quality of Life"/ or (life adj2 qualit*).ti,ab,kf. or 'qol'.ti,ab,kf. or 'ql'.ti,ab,kf. or 'hrql'.ti,ab,kf. or 'hrqol'.ti,ab,kf. or (disease adj3 burden).ti,ab,kf. or Health Status/ or exp Functional Status/ or 'health status'.ti,ab,kf. or Patient Reported Outcome Measures/ or (('patient report*' or patientreport* or 'self report*' or selfreport*) adj3 outcome*).ti,ab,kf. or 'hr pro'.ti,ab,kf. or 'hrpro'.ti,ab,kf. or ((patient* or self) adj2 ('reported' or 'reporting' or 'rated' or	1149829

	'rating' or 'ratings')).ti,ab,kf. or 'patient* perspective*'.ti,ab,kf. or exp Psychosocial Functioning/ or Psychology, Social/ or ((psychosocial or 'psycho social') adj3 (aspect* or burden or factor* or function* or overload or stabilit* or stress or study)).ti,ab,kf. or (social adj3 (aspect* or burden or distress or factor* or function* or psychology or strain or stress)).ti,ab,kf.	
3	(1 and 2) not ((exp animals/ or exp models, animal/) not humans/) not ((letter/ or comment/ or editorial/) not (exp Clinical Trial/ or exp Meta-Analysis/ or exp Scoping Review/ or exp Systematic Review/))	403
4	limit 3 to yr="2005 -Current"	297
5	exp Meta-Analysis/ or exp Network Meta-Analysis/ or exp Systematic Review/ or (networkmeta analy* or networkmetaanaly* or metaanaly* or meta analy* or metanaly* or prisma or prospero or metaanali* or meta anali* or metanali*).ti,ab,kf. or ((systemati* or scoping or umbrella or structured literature) adj3 (review* or overview*)).ti,ab,kf. or ((structured or systemic*) adj3 (review* or overview* or synth*) adj3 literature).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 (review* or overview*)) and (search* or database* or data base*)).ti,ab,kf. or ((data extraction* or data source*) and (study selection* or studies selection*)).ti,ab,kf. or (search strateg* and selection criteria*).ti,ab,kf. or (data source* and data synth*).ti,ab,kf. or (medline* or pubmed* or pub med* or embase or cochrane*).ti,ab,kf. or cochrane.jw. or ((critical* or rapid*) adj2 (review* or overview* or synth*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synth*)) and (search* or database* or data base*)).ab. or metasynth*.ti,ab,kf. or meta synth*.ti,ab,kf.	853588
6	Case-control Studies/ or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ or comparative study/ or control groups/ or controlled before-after studies/ or controlled clinical trial/ or double-blind method/ or historically controlled study/ or matched-pair analysis/ or single-blind method/ or (((control or controlled) adj6 (study or studies or trial)) or (compar* adj (study or studies)) or ((control or controlled) adj1 active) or "open label*" or ((double or two or three or multi or trial) adj (arm or arms)) or (allocat* adj10 (arm or arms)) or placebo* or "sham-control*" or ((single or double or triple or assessor) adj1 (blind* or masked)) or nonrandom* or "non-random*" or "quasi-experiment*" or "parallel group*" or "factorial trial" or "pretest posttest" or (phase adj5 (study or trial)) or (case* adj6 (matched or control*)) or (match* adj6 (pair or pairs or cohort* or control* or group* or healthy or age or sex or gender or patient* or	8141485

	subject* or participant*)) or (propensity adj6 (scor* or match*))).ti,ab,kf. or (confounding adj6 adjust*).ti,ab. or (versus or vs or compar*).ti. or exp cohort studies/ or epidemiologic studies/ or ((multicenter study/ or observational study/ or seroepidemiologic studies/ or (cohort* or 'follow up' or followup or longitudinal* or prospective* or retrospective* or observational* or multicent* or 'multi-cent*' or consecutive*).ti,ab,kf.) and ((group or groups or subgroup* or versus or vs or compar*).ti,ab,kf. or ('odds ratio*' or 'relative odds' or 'risk ratio*' or 'relative risk*' or aor or arr or rrr).ab. or (("OR" or "RR") adj6 CI).ab.)) or Case control.tw. or cohort.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/	
7	4 and 5	20
8	(4 and 6) not 7	117
9	4 not (7 or 8)	160
10	7 or 8 or 9	297

Bijlage 9 Verantwoording 5

Voor meer details over de gebruikte richtlijnmethodologie verwijzen wij u naar de Werkwijze. Relevante informatie voor de ontwikkeling/herziening van deze richtlijnmodule is hieronder weergegeven.

Initiatief
Initiatief: Cluster Hoofd-halstumoren

Samenstelling van de werkgroep
Voor het ontwikkelen van de richtlijnmodule is eind 2024 een multidisciplinair cluster ingesteld. Het cluster Hoofd-halstumoren bestaat uit meerdere richtlijnen (zie hier de actuele clusterindeling). De stuurgroep bewaakt het proces van modulair onderhoud binnen het cluster. De expertisegroepsleden brengen hun expertise in, indien nodig. De volgende personen uit het cluster zijn betrokken geweest bij de herziening van deze module:

Clusterstuurgroepleden

- Prof. dr. R. (Remco) de Bree, voorzitter (NVKNO)
- Dr. M. (Mischa) de Ridder (NVRO)
- Dr. L.A. (Lot) Devriese (NIV)
- Prof. dr. M.J.H. (Max) Witjes (NVMKA)
- Dr. H.P.M. (Dirk) Kunst (NVKNO)
- R.A. (Rob) Burdorf (PVHH)

Betrokken clusterexpertisegroepleden

- Prof. dr. H.J.L.M. (Henri) Timmers (NIV)
- Dr. B.P.M. (Bernadette) Nesselrooij
- W. (Willie) van Delft (NVPG)

Met ondersteuning van

- Dr. A. (Anja) van der Hout (Kennisinstituut van de Federatie Medisch Specialisten)
- Dr. E. (Eline) Pruijn-de Heus (Kennisinstituut van de Federatie Medisch Specialisten)
- Dr. J. (Jing) de Haan-Du (Kennisinstituut van de Federatie Medisch Specialisten)
- Drs. J. (Joline) Rohof (Kennisinstituut van de Federatie Medisch Specialisten)
- Dr. M.S. (Michiel) Oerbekke (Kennisinstituut van de Federatie Medisch Specialisten)
- Alies Oost (Kennisinstituut van de Federatie Medisch Specialisten)

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

Clusterstuurgroepleden

Tabel 9 Gemelde (neven)functies en belangen stuurgroep

Naam	Hoofdfunctie	Nevenwerkzaamheden	Persoonlijke financiële belangen	Persoonlijke relaties	Extern gefinancierd onderzoek	Intellectuele belangen en reputatie	Overige belangen	Datum	Restrictie
Prof. dr. R. (Remco) de Bree	KNO-arts / hoofd-halschirurg	Onbetaald: Board member	Geen	Geen	KWF. Ultrasound and microbubbles to improve tumor perfusion of head	Geen	Geen	12-12-2024	Restricties ten aanzien

(voorzitter)	Hoogleraar / afdelingshoofd UMC Utrecht	Dutch Head and Neck Society (NWHHT) Chair Research Steering Committee Dutch Head and Neck Society (NWHHT) Member Clinical Audit Board Dutch Head and Neck Audit (DHNA) Chair committtee Revision Dutch Head and Neck Tumor Guidelines Board member Patient advocacy group Patiëntenvereniging Hoofd-Hals (PVHH) Chair advisory committee research data Dutch registries (PRISMA) Chair Dutch section Collegium Oto-Rhino-Laryngologicum Amicitiae Sacrum (CORLAS) Council Member International Academy of Oral Oncology (IAOO)			and neck cancers. co-applicant ZonMw. Metastatic-directed stereotactic body radiation therapy of oligometastases in head and neck squamous cell carcinoma patients. Projectleider KWF. Personalized follow-up in HPV-related oropharyngeal cancer patients using liquid biopsies. Projectleider Maurits en Anna de Kock Stichting en Vaillantfonds. Fluorescentie geassisteerde reconstructieve chirurgie: beoordeling van vitaliteit van weefsels. Projectleider 1. KWF- FDG-PET/CT to reduce the need for sentinel lymph node biopsy in early stage oral cancer (Projectleider JA) 2. KWF - Ex vivo 7T MRI of resection specimen of oral cancer to improve margin control (Projectleider NEE) 3. KWF - Sentinel lymph node detection in early oral cancer using [68Ga]Ga-tilmanocept PET/CT lymphoscintigra (Projectleider JA) 4. Nutricia - Perioperative nutritional intervention with Fortifit Energy® in combination with excersice verstus standard of care (Projectleider JA) 5. Hanarth Fonds - Triage of Patients with High-risk Oral Squamous cell Carcinoma using Artificial Intelligence (TOSCA) (Projectleider NEE)				van besluitvorming betreffende perioperatieve voedingsinterventies. Indien relevant: Vice-voorzitter aan te stellen voor wanneer perioperatieve voedingsinterventies worden besproken.
Dhr. Dr. M. (Mischa) de Ridder	Radiotherapeut-oncoloog UMC Utrecht	Secretaris LPRHHT van de NVRO. Lid METC NED-MED	Geen	Geen	Elekta: To evaluate evidence for eventual transition from PDR treatments to HDR treatments in case of possib (Projectleider JA). Hanarth fonds: Improved response assessment after (chemo)-	Geen	Geen	3-1-2025	Geen restricties.

					radiotherapy for locally advanced head and neck squamous (Projectleider NEE).				
Mevr. Dr. L.A. (Lot) Devriese	Internist UMC Utrecht	Dit project en eerder bij FMS kwaliteits agenda. Werkgroep binnen NVMO, CieOOM, off-label oncologische medicatie (vacatiegelden naar UMC Utrecht). Bestuurslid NWHHT	Geen	Geen	Ja, als lokale PI van studies gesponsord door Farma. Met uitbetaling aan de werkgever, niet aan mij persoonlijk. 1. ISAPharm - Fase 3 onderzoek ISA101b (Projectleider NEE) 2. MERUS - Fase 3 onderzoek petosemtamab (Projectleider NEE) 3. CISLOW studie - Fase 2 IIS gesponsord door ZOnMw (Projectleider NEE)	Geen	Geen	14-11-2024	Geen restricties.
Prof. dr. M.J.H. (Max) Witjes	MKA chirurg-HH oncoloog Universitair Medisch Centrum Groningen	Geen	Geen	Geen	• Fluoguide FG001sponsor initiated trial (2024): Determination of Optimal Dose for Visualization of Inadequate Margins in Oral Squamous Cell Carcinoma Using FG001. Protocol: 2024-514508-14-00. Witjes MJH Voskuil FJ, Fluoguide team. (budget € 378.293) (Projectleider JA) • NIH grant (National Institute of Dental and Craniofacial Research 2023) : Ex vivo intraoperative surgical basal margin analysis in head and neck cancer resection: clinical validation (1R01DE033449-01). Tichauer K, J Broncovic & Witjes MJH, Voskuil FJ.(budget USD 2.5Milj) (Projectleider JA) • SNN Grant (2023) : JTF application for IMPACT-Implants . (Budget € 3.6 Milj) Kraeima J, Witjes MJH, Veldsink JW & Center for Business Development UMCG. (Projectleider NEE) • KWF Kankerbestrijding: RUG 13215 (2021) Witjes MJH, GB Halmos, WM Nagengast. Real-time targeted fluorescence endoscopy in patients for detection of unknown primary cancers of the head and neck area (REFLECT study) (Budget €476.000) (Projectleider JA) • WJ Thijn stichting (2021) : Witjes MJH lichtgevende stoffen helpen de chirurg	Geen	Geen	16-1-2025	Restricties ten aanzien van besluitvorming betreffende de bepaling van de optimale dosis voor visualisatie van onvoldoende snijmarges bij oraal plaveiselcelcarcinoom.

					de tumor beter te verwijderen. (Budget €250.000). (Projectleider JA)				
Dhr. H.P.M. (Dirk) Kunst	KNO-arts; Radboudumc-MUMC+	Voorzitter van het "Radboudumc-MUMC+ Expertisecentrum Schedelbasispathologie" Voorzitter "Academische Alliantie Schedelbasispathologie Radboudumc-MUMC+" Voorzitter "Landelijk Overleg Expertisecentra Schedelbasispathologie" (LOES) President van de "European Skull Base Society" (ESBS) Betrokkenheid patientenverenigingen: Neurofibromatose type 2 patientenvereniging Paragangliomen patientenvereniging	Geen	Geen	Euregio: Hoofd-hals paragangliomen; verschillen management Nederland Duitsland (projectleider JA). TU Eindhoven/Tilburg (aflopende ZonMw studie), over voorspellen van groei obv MRI scans bij brughoektumoren (projectleider NEE).	Geen	Geen	14-2-2025	Geen restricties.
Dhr. R.A. (Rob) Burdorf	Neem niet meer deel aan het arbeidsproces (met pensioen)	Lid wetenschappelijke advies commissie van de PVHH	Geen	Geen	Geen	Geen	Geen	12-11-2024	12-11-2024

Betrokken clusterexpertisegroepleden

Tabel 10 Gemelde (neven)functies en belangen expertisegroep

Naam	Hoofdfunctie	Nevenwerkzaam-heden	Persoonlijke financiële belangen	Persoonlijke Relaties	Extern gefinancierd onderzoek	Intellectuele belangen en reputatie	Overige belangen	Datum	Actie
Henri Timmers (NIV)	Hoogleraar Interne geneeskunde in het bijzonder endocrinologie Internist-endocrinoloog Radboudumc Nijmegen	Geen	Geen	Geen	Geen	Geen	Geen	22-06-2026	Geen restricties.
Bernadette Nesselrooij (VKGN)	Klinisch Geneticus, afdeling Genetica, UMC Utrecht	Geen	Geen	Geen	Geen	Geen	Geen	22-06-2026	Geen restricties.
Willie van Delft (NVPG)	Bestuur NVPG	Geen	Geen	Geen	Geen	Geen	Geen	22-06-2026	Geen restricties.

5 Kwalitatieve raming van mogelijke financiële gevolgen in het kader van de Wkkgz

Bij de richtlijnmodule voerden de clusterleden conform de Wet kwaliteit, klachten en geschillen zorg (Wkkgz) een kwalitatieve raming uit om te beoordelen of de aanbevelingen mogelijk leiden tot substantiële financiële gevolgen. Bij het uitvoeren van deze beoordeling is de richtlijnmodule op verschillende domeinen getoetst (zie het stroomschema bij 10 Werkwijze).

Module	Uitkomst raming	Toelichting
Module [naam]	[geen/ mogelijk] financiële gevolgen	[plaatsen desbetreffende uitkomst 1, 2, 3, 4 of 5]

Bijlage 10 Literatuursamenvatting module 5 inclusief alle bijlagen

Introduction

In individuals with a pathogenic germline variant in one of the SDHx genes (SDHA, SDHB, SDHC, SDHD or SDHAF2), surveillance is aimed at the early detection of (potentially malignant) tumors, mainly paragangliomas and pheochromocytomas and in rare cases renal cell carcinoma and gastrointestinal stromal tumors (GIST). Early detection enables treatment with lower morbidity and may improve prognosis.

At present, there is considerable variation in clinical practice regarding how, when and for whom surveillance is used. This variation includes differences in the age at which screening is initiated, the frequency and type of investigations performed, and the approaches used in children versus adults. The principle tools for surveillance are a combination of biochemical screening (plasma or 24h urinary metanephrines) to detect catecholamine producing paraganglioma and imaging (MRI and/or CT and and/or PET) targeted at biochemically negative tumors. Although a generic surveillance protocol is suggested for all SDHx genes ("one-size-fits-all") based on international consensus (Amar, 2021), there is evidence that the risk profile and tumor spectrum differ by gene. In particular, SDHB mutations appear to be associated with a higher risk of malignancy, whereas carriers of SDHA variants have a different risk profile, mainly due to low penetrance.

A systematic review of the literature was performed to answer the following question(s): What is the optimal surveillance strategy among patients with a pathogenic germline variant in one of the SDHx genes?

PICO

Patients	Patients with a pathogenic germline variant in one of the SDHx genes
Intervention	Tumor surveillance (imaging (MRI, PET), biochemical screening)
Control	N/A
Outcomes	Age-dependent penetrance of (clinically relevant) tumors, impact on prognosis including: tumor recurrence, multifocality, metastasis, morbidity/treatment burden, and overall survival
Other selection criteria	Study design: systematic review, randomized controlled trials, observational studies

<u>Relevant outcome measures</u>

The guideline panel considered **penetrance of (clinically relevant) tumors** as a **critical** outcome measure for decision making; and **impact on prognosis including: tumor recurrence, multifocality, metastasis, morbidity/treatment burden, and overall survival** as an **important** outcome measure for decision making.

The guideline panel defined the following as minimal clinically (patient) important differences:

- Routine tumor surveillance is justified when age specific penetrance of clinically relevant tumors is at least 5% (number needed to screen =20)
- The diagnosis of any SDHx related tumor resulting from surveillance is considered as potentially relevant for prognosis when there is a possible beneficial impact of the

surveillance program on morbidity, complications, recurrence rate, (metastatic) disease progression and survival.

Search and select (Methods)
A systematic literature search was performed by a medical information specialist using the following bibliographic databases: Embase.com and Ovid/Medline all. Both databases were searched from 2005 to August 11th 2025 for systematic reviews, guidelines, RCTs and observational studies. Systematic searches were completed using a combination of controlled vocabulary and natural language keywords. The overall search strategy was derived from the following primary search concepts: (1) SDHx genes; (2) surveillance. Duplicates were removed using EndNote software. After deduplication a total of 545 records were imported for title/abstract screening. Initially, 51 studies were selected based on title and abstract screening. After reading the full text, 42 studies were excluded (see the exclusion table under the tab 'Evidence tabellen'), and 9 studies were included.

Summary of literature

Description of studies

A total of 9 studies were included in the analysis of the literature. Key study characteristics and results are summarized in Table 1. Since the research question did not include a comparison group and the included studies were descriptive in nature, a formal assessment of the risk of bias was not performed.

The systematic review of Davidoff (2024) included 16 studies describing age-specific penetrance, metastatic disease, risk of second tumor, and mortality in SDHB pathogenic variant carriers. Retrospective and prospective observational studies were included if they reported any of these outcomes. Studies were limited to human research. The systematic search was performed in March 2022.

Bausch (2017) analyzed the prospective, longitudinal European-American-Asian Pheochromocytoma-Paraganglioma Registry. They analyzed prevalence of SDHA, TMEM127, MAX, and SDHAF2 germline mutation carriers from 1993 to 2016. Mutation positive registrants and their relatives were offered genetic predictive testing and clinical investigation to clinically characterize the disease associated with the genes. The objective of this study was to describe age-related penetrance and spectra of the germline mutations, as well as clinical features of the disease.

The retrospective study of Daniel (2016) was performed between 2005 and 2015. The clinical and imaging data of 47 patients were collected. The patients all had SDHx mutations (SDHB, SDHC, SDHD) and had surveillance for detection of paragangliomas by rapid-sequence non-contrast MRI. The participants included 12 index cases and 35 mutation-positive relatives.

Greenberg (2020) conducted a multicenter retrospective longitudinal observational study investigating individuals with germline SDHx pathogenic variants. The 263 included participants underwent clinical whole-body imaging and biochemical testing.

Greenberg (2021) identified individuals with SDHA, SDHB, SDHC, and SDHD pathogenic variants through an institutional database up to the 1st of October 2017. A total of 165 patients being SDHx PV carriers from 34 kindreds were included. The number of affected persons was described, with a focus on patients above 50 years of age.

The retrospective single-center cohort study of Heesters (2025) included 49 SDHA, SDHB, and SDHD variant carriers. SDHx carriers were identified from 2000 to 2022. The authors determined the annual risk of developing paraganglioma for the SDHx variants.

A cohort of 50 SDHx genetic variant carriers was followed by Hong (2019) to determine the optimal surveillance strategy. The cohort study described the outcomes of a surveillance protocol involving annual clinical review with plasma/urine metanephrines and biennial MRI from skull base to pelvis.

To define tumor detection rate in a large cohort Saie (2021) performed a retrospective study. They included 249 asymptomatic SDHx variant carriers between 2005 and 2019 to investigate the benefit of screening protocols.

Van der Tuin (2018) included n=30 index SDHA carriers from patients with an established diagnosis of PGL between February 2011 through July 2016. Relatives (n=94) were tested for cascade screening. There were n=51 non-index SDHA carriers and n=5 obligate carriers.

White (2022) performed a retrospective analysis of records of 74 non-index SDHx variant carriers. The aim of the study was to describe the clinical presentation of paraganglioma in the cohort. They also reported the penetrance in non-index family members.

Williams (2021) described 91 SDHC cases in a retrospective case series in the UK. The patients were both asymptomatic and disease-affected with confirmed SDHC variants. The assessed clinical data included information on tumor type and location, surveillance outcomes and interventions, SDHC genetic variant assessment and tumor risk calculation.

Table 2. Characteristics of included studies and summary of results

<table>
<tr><th>Study</th><th>Population</th><th>Penetrance</th><th>Other outcomes</th><th>Suggestion for Surveillance in the article</th></tr>
<tr>
<td>Davidoff, 2024 (Systematic review)</td>
<td>SDHB PV carriers whose carrier status was confirmed on genetic testing.</td>
<td>
<table>
<tr><th>Age</th><th>Studies (n)</th><th>n</th><th>Penetrance of HNPGL (%, 95%CI)</th><th>Prediction interval (%)</th></tr>
<tr><td>20</td><td>5</td><td>761</td><td>4 (3-6)</td><td>2-7</td></tr>
<tr><td>40</td><td>6</td><td>831</td><td>11 (8-15)</td><td>5-25</td></tr>
<tr><td>60</td><td>7</td><td>1202</td><td>24 (19-31)</td><td>9-50</td></tr>
<tr><td>80</td><td>4</td><td>889</td><td>35 (25-47)</td><td>5-84</td></tr>
</table>
</td>
<td>Risk of Metastatic Disease (carriers with disease)
9% (5%-16%),
prediction interval: 2%-34%
I^2=33%
based on 5 studies, n=251

Risk of a Second Tumor (carriers with disease)
24% (18%-31%),
prediction interval: 15%-37%
I^2=0%
based on 5 studies, n=156

Five-year mortality:
18% (6%-40%),
prediction interval: 1%-90%
I^2=86%
based on 6 studies, n=254

Data for probands and nonprobands/nonindex cases were combined due to insufficient data for nonindex carriers alone.</td>
<td>Penetrance for PPGLs in SDHB PV carriers increases linearly with age. Affected carriers are at risk of developing and dying of metastatic disease, or of developing second tumors. Lifelong surveillance is appropriate.</td>
</tr>
<tr>
<td>Bausch, 2017</td>
<td>SDHA, and SDHAF2 germline mutation carriers in the prospective, longitudinally followed up European-American-Asian Pheochromocytoma-</td>
<td>
<table>
<tr><th colspan="3">Penetrance at 40 age of any tumor (%)</th></tr>
<tr><th>All SDHA variants (n=37)</th><th>Index patients (n=29)</th><th>Relatives (n=8)</th></tr>
<tr><td>39 (21-53)</td><td>45 (23-60)</td><td>13 (0-33)</td></tr>
</table>
</td>
<td>Risk of Metastatic Disease Index + Relatives:
SDHA: Malignant pheochromocytoma or paraganglioma
4/34, 12% (4% -28%)

Risk of a Second Tumor
Not reported.</td>
<td>The SDHA, and SDHAF2 genes may contribute to hereditary pheochromocytoma and paraganglioma.</td>
</tr>
</table>

<table>
<tr>
<td></td>
<td>Paraganglioma Registry.</td>
<td></td>
<td>Mortality:
Not reported.</td>
<td></td>
</tr>
<tr>
<td>Daniel, 2016</td>
<td>Patients with SDHx mutations who had surveillance for detection of paragangliomas by rapid-
sequence non-contrast MRI (base of skull to pubic symphysis)</td>
<td>
<table>
<tr><th></th><th>N</th><th>age at the end of the study (Mean ±sd)</th><th>Index cases</th><th>Mutation positive relatives</th><th>N of patients who developed tumors</th><th>N of patients who developed tumors on surveilance program</th></tr>
<tr><td>SDHB</td><td>36</td><td>46.9 ±17.6</td><td>9</td><td>27</td><td>11 (31%)</td><td>4</td></tr>
<tr><td>SDHC</td><td>6</td><td>42.3±24.4</td><td>1</td><td>5</td><td>2 (33%)</td><td>2</td></tr>
<tr><td>SDHD</td><td>5</td><td>54.9±10.6</td><td>2</td><td>3</td><td>6 (67%)</td><td>3</td></tr>
</table>
</td>
<td>Risk of Metastatic Disease
SDHB: 1 metastatic
SDHC: 0
SDHD: 0

Risk of a Second Tumor
Not specified.

Mortality:
Two patients died during the study, one from complications of metastatic sPGL and one from an unrelated cause.</td>
<td>Biannual rapid-sequence non-contrast MRI is effective to monitor patients with SDHx mutations for detection of new tumours and monitoring of known tumours.</td>
</tr>
<tr>
<td>Greenberg, 2020</td>
<td>all individuals with SDHx variants with at least one screen from the start of the screening protocol in a multicenter study in the USA.</td>
<td>
<table>
<tr><th>Variant</th><th>N*</th><th>Penetrance of SDHx-related tumor (%)</th></tr>
<tr><td>SDHA</td><td>9</td><td>1</td></tr>
<tr><td>SDHB</td><td>188</td><td>29</td></tr>
<tr><td>SDHC</td><td>28</td><td>1</td></tr>
<tr><td>SDHD</td><td>35</td><td>14</td></tr>
<tr><td>SDHAF2</td><td>3</td><td>0</td></tr>
</table>
*including both patients with a history of prior PGL/PCC (69/263) and patients without a history of prior PGL/PCC (194/263). The exact number of patients without prior history of PGL/PCC per variant was not reported.
Individuals with germline SDHx pathogenic variants underwent clinical whole-body imaging and biochemical testing.
</td>
<td>Risk of Metastatic Disease
Not reported.

Risk of a Second Tumor
Not reported.

Mortality:
Not reported.</td>
<td>Tumor detection rates vary by
SDHx gene and screening has the potential to uncover actionable secondary findings. Imaging is an essential part of the screening
process as biochemical testing alone does not detect all disease.</td>
</tr>
</table>

<table>
<tr>
<td>Greenberg, 2021</td>
<td>Individuals with SDHA, SDHB, SDHC, or SDHD. Participants were either molecularly diagnosed with SDHx, were considered an obligate carrier, or had and SDHx-related tumor and a known SDHx pathogenic variant in a first-degree relative. All individuals were selected through an institutional database.</td>
<td>Total carriers: n=165 (from 34 kindreds), not affected: n=97, affected: n=68
<table>
<tr><th>Variant</th><th>N genetic status (n=165 total)</th><th>N kindreds (n=34 total)</th><th>N diagnosed with SDHx-related tumor (%) (n=68)</th><th>Mean age of diagnosis of the primary tumor</th></tr>
<tr><td>SDHA</td><td>2</td><td>2</td><td>1 (50%)</td><td>41</td></tr>
<tr><td>SDHB</td><td>112</td><td>22</td><td>40 (35.7%)</td><td>35</td></tr>
<tr><td>SDHC</td><td>22</td><td>2</td><td>4 (21.1%)</td><td>19.5</td></tr>
<tr><td>SDHD</td><td>29</td><td>8</td><td>23 (79.3%)</td><td>26.9</td></tr>
</table>

The cohort had n=50 (30.3%) persons over 50 years old with SDHx PVs, where n=26 were unaffected. The of the other n=24 affected individuals, n=9 developed SDHx-related tumors after the age of 50 (mean age of first diagnosis: 60.6 years). Here, SDHB PV was prevalent in n=8, while SDHC PV was prevalent in n=1. Those diagnosed after the age of 50 were identified due to symptoms, other cancer work-ups, or baseline SDHx screening protocols.</td>
<td>Other outcomes do not seem to be described for the entire (affected) cohort.</td>
<td>The number of tumor identified within one year after molecular screening reinforces baseline screening at all ages.

Tumors identified after age 50 might have been diagnosed before age 50, if molecular diagnosis and baseline screening had occurred earlier. Those diagnosed after 50 were identified on baseline screening or due to symptoms. Discontinuation of screening may be warranted if baseline screening is negative and there is no history of prior tumors.</td>
</tr>
<tr>
<td>Heesters, 2025</td>
<td>SDHA, SDHB, and SDHD variant carriers with a negative first screening and at least one follow-up in a single-center in the Netherlands.

Asymptomatic SDHD variant carriers through maternal transmission were excluded.</td>
<td>
<table>
<tr><th>Variant</th><th>n</th><th>Age at first screening (median)</th><th>Males (%)</th><th>Follow-up (median, ys)</th><th>Penetrance of paraganglioma (%)</th></tr>
<tr><td>SDHA</td><td>2</td><td>25 (16-34)</td><td>0</td><td>4.09 (3.00-5.17)</td><td>0 (0/2)</td></tr>
<tr><td>SDHB</td><td>24</td><td>43 (12-75)</td><td>20.8</td><td>5.92 (2.33-13.33)</td><td>0 (0/24)</td></tr>
<tr><td>SDHD</td><td>23</td><td>30 (16-64)</td><td>54.2</td><td>4.83 (1.08-17.17)</td><td>39.1 (9/23)</td></tr>
</table>

<table>
<tr><th>SDHD carriers</th><th>Annual risk of developing a HNPGL (%, 95%CI)</th></tr>
<tr><td>After 5 years</td><td>17.5 (15.9–19.1)</td></tr>
<tr><td>After 10 years</td><td>62.9 (33.5-92.3)</td></tr>
<tr><td>After 15 years</td><td>82.4 (52.8-112.0)</td></tr>
</table>
</td>
<td>Mortality
No death during the follow-up was reported.</td>
<td>The 5-year risk for HNPGL in pathological SDHx variant carriers is less than 20%. A 5-year interval for screening SDHx carriers seems sufficient to prevent the unnoticed development of HNPGL that warrant treatment.</td>
</tr>
</table>

<table>
<tr>
<td>Hong, 2019</td>
<td>SDHx mutation carriers followed at a tertiary Australian hospital using a surveillance protocol involving annual clinical review with plasma/urine metanephrines and biennial magnetic resonance imaging from skull base to pelvis.</td>
<td>
<table>
<tr><th>Non-probands</th><th>n</th><th>Age (mean)</th><th>Males (%)</th><th>Follow-up (median, ys)</th><th>Penetrance of tumors (%)</th><th>New tumor during follow-up (%)</th><th>Metastases (%)</th></tr>
<tr><td>SDHB</td><td>22</td><td>36.3</td><td>36.4</td><td>5 (1-13)</td><td>8 (8/101)</td><td>0/22</td><td>0/22</td></tr>
<tr><td>SDHC</td><td>6</td><td>53.0</td><td>16.7</td><td>3 (2-9)</td><td>0 (0/12)</td><td>0/6</td><td>0/6</td></tr>
<tr><td>SDHD</td><td>9</td><td>40.4</td><td>66.7</td><td>7 (1-13)</td><td>18 (2/11)</td><td>5/9</td><td>1/9</td></tr>
</table>
</td>
<td>Risk of Metastatic Disease
Probands:
SDHB:3/10
SDHD:0/3

Risk of a Second Tumor
Probands:
SDHB:1/10
SDHD:1/3

Mortality:
1 patient with SDHB variant developed melignant disease died.</td>
<td>MRI is useful in the surveillance of SDHx patients for tumours.

SDHD mutations are highly penetrant but are rarely malignant while SDHB mutations are of lower penetrance, but are associated with a higher risk of malignancy.</td>
</tr>
<tr>
<td>Saie, 2021</td>
<td>SDHx mutation carriers variant carriers with a negative first screening and at least one follow-up managed in 6 different referral French center.

Asymptomatic SDHD mutation carriers with a mutation inherited from the maternal branch were excluded.</td>
<td>
<table>
<tr><th>Variant</th><th>n</th><th>Age at first screening (median)</th><th>Males (%)</th><th>Follow-up (median, ys)</th><th>Penetrance of any tumor (%)</th></tr>
<tr><td>SDHB</td><td>101</td><td>38 (6-75)</td><td>49</td><td>5 (1-13)</td><td>8 (8/101)</td></tr>
<tr><td>SDHC</td><td>12</td><td>46 (11-71)</td><td>39</td><td>3 (2-9)</td><td>0 (0/12)</td></tr>
<tr><td>SDHD</td><td>11</td><td>41 (7-86)</td><td>60</td><td>7 (1-13)</td><td>18 (2/11)</td></tr>
</table>
</td>
<td>Risk of Metastatic Disease
No patient presented with a metastatic PPGL at the first screening and during follow-up.

Risk of a Second Tumor
Not reported.

Mortality:
None SDHx mutation-related death was reported.</td>
<td>Imaging screening enabled detection of tumors in asymptomatic SDHx mutation carriers, with a higher detection rate in SDHD than in SDHB and SDHC mutation carriers, arguing for a gene-by-gene approach.</td>
</tr>
</table>

<table>
<tr>
<td>Van der Tuin, 2018</td>
<td>Patients with an established PGL referred for SDHA analysis were recruited. Family members of index patients were offered genetic counseling and testing via cascade screening.</td>
<td>N=94 relatives (from 19 SDHA families) received cascade screening for SDHA: n=51 non-index carriers and n=5 obligate carriers. In all families, except one, the mutation was inherited from an unaffected parent. Three of the 56 non-index SDHA carriers were diagnosed with having one (possible) related tumor (NHPGL: 1, GIST: 1, RCC: 1).

Age-related penetrance of all n=86 SDHA carriers (including index cases) were:
<table>
<tr><td>Age</td><td>% penetrance</td></tr>
<tr><td>25</td><td>7% (95%CI: 2-12)</td></tr>
<tr><td>50</td><td>26% (95%CI: 16-36)</td></tr>
<tr><td>70</td><td>50% (95%CI: 34-66)</td></tr>
</table>
Age-related penetrance of all n=56 non-index SDHA carriers were:
<table>
<tr><td>Age</td><td>% penetrance</td></tr>
<tr><td>25</td><td>0%</td></tr>
<tr><td>50</td><td>2% (95%CI: 0-6)</td></tr>
<tr><td>70</td><td>10% (95%CI: 0-21)</td></tr>
</table></td>
<td>Other outcomes do not seem to be described for SDHA families/non-index cases.</td>
<td>For genetic counseling: Exploring genetic basis of hereditary PGL provides opportunities for early detection of PGL in patients and relatives.</td>
</tr>
<tr>
<td>White, 2022</td>
<td>Asymptomatic non-index cases identified through genetic records excluding who had prior diagnosis of PPGL entered into the surveillance screening programme in a single tertiary referral centre in the UK.</td>
<td>
<table>
<tr><td>Variant</td><td>n</td><td>Age at start of screening* (median)</td><td>Males (%)</td><td>Screening duration (median, ys)</td><td>Penetrance of PPGL at 50 ys (%)</td><td>Penetrance of PPGL at 70 ys (%)</td></tr>
<tr><td>SDHB</td><td>56</td><td>40 (8-71)</td><td>50.9</td><td>3 (1-15)</td><td>15.2</td><td>47.2</td></tr>
<tr><td>SDHD</td><td>18</td><td>25 (13-74)</td><td>61.5</td><td>3 (1-14)</td><td>71.6</td><td>78.7</td></tr>
</table>
* Surveillance screening for asymptomatic relatives consisted of annual plasma metanephrine measurement and whole-body MRI with contrast at 3–5 yearly intervals.</td>
<td>Risk of Metastatic Disease
Metastatic disease was not detected at diagnosis or during follow-up.

Risk of a Second Tumor
No other SDHx-related tumours (RCC, GIST and pituitary adenoma) were detected during surveillance screening.

Mortality:
No death during the follow-up was reported.</td>
<td>Surveillance screening with combined biochemical testing and imaging enables early detection of PPGL in asymptomatic relatives with SDHx pathogenic variants.</td>
</tr>
</table>

<table>
<tr>
<td>Williams, 2021</td>
<td>SDHC variant case collated from 18 UK Genetics and Endocrinology departments</td>
<td>
<table>
<tr><th rowspan="2">Age</th><th colspan="2">Non-probands (n=45)</th><th colspan="2">Probands (n=37)*</th></tr>
<tr><th>Penetrance of PPGL or GIST (%)</th><th>Cumulative risk of PPGL or GIST (%)</th><th>Penetrance of PPGL or GIST (%)</th><th>Cumulative risk of PPGL or GIST (%)</th></tr>
<tr><td>20</td><td>Not reported</td><td>0</td><td>Not reported</td><td>0.05 (0-0.12)</td></tr>
<tr><td>40</td><td>4.4</td><td>0.08 (0-0.18)</td><td>40.5</td><td>0.4 (0.22-0.54)</td></tr>
<tr><td>60</td><td>6.7</td><td>0.16 (0-0.31)</td><td>94.6</td><td>0.94 (0.79-0.99)</td></tr>
</table>
*Probands with PPGL or GIST. There were probands with extra-adrenal paraganglioma (EAPGL, n = 13) and phaeochromocytomas (PCC) (n = 3).
</td>
<td>Risk of Metastatic Disease (with disease)
19.6% (9/46)

Risk of a Second Tumor (with disease)
No new PPGLs were identified.

Mortality: (Non-proband and proband)
1 PPGL death was reported.</td>
<td>Disease-affected SDHC variant cases develop isolated HNPGL disease in nearly 2/3 of patients, EAPGL and PCC in 1/3, with an increased risk of GIST and RCC. One fifth developed malignant disease, requiring comprehensive lifelong tumour screening and surveillance.

Non-probands commence annual clinical review with biochemistry and a full blood count from 10 years, and WB-MRI (skull base, neck, thorax, abdomen and pelvis), as above, from 15 years.</td>
</tr>
</table>

Table 3. Summary of findings in penetrance per variant

<table>
<tr><th>Variant</th><th>Study</th><th>Penetrance (95%)</th></tr>
<tr><td rowspan="5">SDHA</td><td>Heesters, 2025</td><td>Penetrance of paraganglioma: 0</td></tr>
<tr><td>Greenberg, 2020</td><td>Penetrance of SDHx-related tumor : 1%</td></tr>
<tr><td>Bausch, 2017</td><td>
<table>
<tr><td colspan="3">Penetrance at 40 age of any tumor (%)</td></tr>
<tr><td>All SDHA variants</td><td>Index patients</td><td>Relatives</td></tr>
<tr><td>39 (21-53)</td><td>45 (23-60)</td><td>13 (0-33)</td></tr>
</table>
</td></tr>
<tr><td>Greenberg, 2021</td><td>
<table>
<tr><td>Variant</td><td>N genetic status (n=165 total)</td><td>N kindreds (n=34 total)</td><td>N diagnosed with SDHx-related tumor (%) (n=68)</td><td>Mean age of diagnosis of the primary tumor</td></tr>
<tr><td>SDHA</td><td>2</td><td>2</td><td>1 (50%)</td><td>41</td></tr>
</table>
</td></tr>
<tr><td>Van der Tuin, 2018</td><td>Age-related penetrance of all n=56 non-index SDHA carriers:
<table>
<tr><td>Age</td><td>% penetrance</td></tr>
<tr><td>25</td><td>0%</td></tr>
<tr><td>50</td><td>2% (95%CI: 0-6)</td></tr>
<tr><td>70</td><td>10% (95%CI: 0-21)</td></tr>
</table>
</td></tr>
<tr><td rowspan="8">SDHB</td><td>Davidoff, 2024</td><td>
<table>
<tr><td>Age</td><td>Penetrance of HNPGL (%)</td></tr>
<tr><td>20</td><td>4 (3-6)</td></tr>
<tr><td>40</td><td>11 (8-15)</td></tr>
<tr><td>60</td><td>24 (19-31)</td></tr>
<tr><td>80</td><td>35 (25-47)</td></tr>
</table>
</td></tr>
<tr><td>Heesters, 2025</td><td>0</td></tr>
<tr><td>White, 2022</td><td>
<table>
<tr><td>Age</td><td>Penetrance of PPGL (%)</td></tr>
<tr><td>50</td><td>15.2</td></tr>
<tr><td>70</td><td>47.2</td></tr>
</table>
</td></tr>
<tr><td>Saie, 2021</td><td>Penetrance of any tumor : 8%</td></tr>
<tr><td>Greenberg, 2020</td><td>Penetrance of SDHx-related tumor: 29%</td></tr>
<tr><td>Hong, 2019</td><td>Penetrance of any tumor : 8%</td></tr>
<tr><td>Daniel, 2016</td><td>Penetrance of any tumor: 31%</td></tr>
</table>

<table>
<tr><td></td><td>Greenberg, 2021</td><td><table><tr><td>Variant</td><td>N genetic status (n=165 total)</td><td>N kindreds (n=34 total)</td><td>N diagnosed with SDHx-related tumor (%) (n=68)</td><td>Mean age of diagnosis of the primary tumor</td></tr><tr><td>SDHB</td><td>112</td><td>22</td><td>40 (35.7%)</td><td>35</td></tr></table></td></tr>
<tr><td>SDHC</td><td>Williams, 2021</td><td><table><tr><td rowspan="2">Age</td><td colspan="2">Penetrance of PPGL or GIST (%)</td></tr><tr><td>Non-probands</td><td>Probands</td></tr><tr><td>20</td><td>Not reported</td><td>Not reported</td></tr><tr><td>40</td><td>4.4</td><td>40.5</td></tr><tr><td>60</td><td>6.7</td><td>94.6</td></tr></table></td></tr>
<tr><td></td><td>Saie, 2021</td><td>Penetrance of any tumor : 0</td></tr>
<tr><td></td><td>Greenberg, 2020</td><td>Penetrance of SDHx-related tumor : 1%</td></tr>
<tr><td></td><td>Hong, 2019</td><td>Penetrance of any tumor : 0</td></tr>
<tr><td></td><td>Daniel, 2016</td><td>Penetrance of any tumor : 33%</td></tr>
<tr><td></td><td>Greenberg, 2021</td><td><table><tr><td>Variant</td><td>N genetic status (n=165 total)</td><td>N kindreds (n=34 total)</td><td>N diagnosed with SDHx-related tumor (%) (n=68)</td><td>Mean age of diagnosis of the primary tumor</td></tr><tr><td>SDHC</td><td>22</td><td>2</td><td>4 (21.1%)</td><td>19.5</td></tr></table></td></tr>
<tr><td>SDHD</td><td>Heesters, 2025</td><td>Penetrance of paraganglioma: 39.1%<table><tr><td></td><td>Annual risk of developing a HNPGL (%, 95%CI)</td></tr><tr><td>After 5 years</td><td>17.5 (15.9–19.1)</td></tr><tr><td>After 10 years</td><td>62.9 (33.5-92.3)</td></tr><tr><td>After 15 years</td><td>82.4 (52.8-112.0)</td></tr></table></td></tr>
<tr><td></td><td>White, 2022</td><td><table><tr><td>Age</td><td>Penetrance of PPGL</td></tr><tr><td>50</td><td>71.6</td></tr><tr><td>70</td><td>78.7</td></tr></table></td></tr>
<tr><td></td><td>Saie, 2021</td><td>Penetrance of any tumor : 18%</td></tr>
<tr><td></td><td>Greenberg, 2020</td><td>Penetrance of SDHx-related tumor (%): 14%</td></tr>
<tr><td></td><td>Hong, 2019</td><td>Penetrance of any tumor : 18%</td></tr>
<tr><td></td><td>Daniel, 2016</td><td>Penetrance of any tumor (%): 67%</td></tr>
</table>

<table>
<tr><td></td><td>Greenberg, 2021</td><td><table>
<tr><td>Variant</td><td>N genetic status (n=165 total)</td><td>N kindreds (n=34 total)</td><td>N diagnosed with SDHx-related tumor (%) (n=68)</td><td>Mean age of diagnosis of the primary tumor</td></tr>
<tr><td>SDHD</td><td>29</td><td>8</td><td>23 (79.3%)</td><td>26.9</td></tr>
</table></td></tr>
<tr><td>SDHAF2</td><td>Greenberg, 2020</td><td colspan="5">Penetrance of SDHx-related tumor (%): 0</td></tr>
</table>

Kennisvragen

Tijdens de ontwikkeling van deze module is gebleken dat er binnen deze module nog te weinig bewijs is voor de onderbouwing van de aanbeveling en dus kennisvragen bestaan. De werkgroep meent dat (vervolg)onderzoek wenselijk is om in de toekomst een duidelijker antwoord te kunnen geven op vragen uit de praktijk.

Er is een Nederlands surveillance programma voor erfelijk paraganglioom dat voornamelijk wordt uitgevoerd in dedicated (multidisciplinaire) poli's/expertisecentra. Door landelijke evaluatie van deze verzamelde data kunnen onderstaande vragen beantwoord worden.

- wat is de opbrengst van het huidige surveillance programma voor SDHx in Nederland,
    - verschilt deze opbrengst bij de verschillende SDHx varianten
- is er onderbouwing voor het vervroegen van de startleeftijd voor asymptomatische dragers (zoals voorgesteld in de huidige richtlijn),
- Is er aanleiding om de methode van surveillance aan te passen, met name ook als gekeken wordt naar:
    - weegt deze opbrengst op tegen nadelige gevolgen van screening zoals angst/onrust voor uitslagen (QOL),
    - aantal nevenbevindingen bij gebruikte surveillance methode
    - kosten ?[Rd1] [HT2]

Toelichting:

De surveillance van symptomatische en asymptomatische dragers van een (L)PV in een van de genen voor erfelijk paraganglioom in Nederland wordt voor het grootste deel in gespecialiseerde centra uitgevoerd. De DNA diagnostiek wordt in de geaccrediteerde diagnostische DNA laboratoria uitgevoerd en de presymptomatische aanvragen voor DNA diagnostiek gaan via de klinisch genetische centra/klinisch genetici. In 2018 is een multicenter analyse gepubliceerd over de SDHA (van der Tuin, 2018). Er zijn aanwijzingen dat de daaruit gepubliceerde resultaten inmiddels bijgesteld moeten worden nu de follow up periode een kleine 10 jaar langer is en er nauwelijks paragangliomen zijn vastgesteld in de surveillance groep. Er is behoefte aan een landelijke infrastructuur om de resultaten van de surveillance voor de erfelijk paragangliomgenen landelijk te bundelen voor de onderbouwing van de adviezen.

Verkeerslichtanalyse en Implementeren- en Agenderen-tabel

Verkeerslichtanalyse (ten behoeve van commentaar- en autorisatiefase)
Aanbeveling 1

Kruis aan		
	ROOD	Sterke aanbeveling tegen, geldend voor de gehele populatie, en waar passend bewijs voor is [1]
	ORANJE	Aanbeveling waar geen passend bewijs is voor gehele populatie • Sterke aanbeveling tegen (geen passend bewijs voor gehele populatie en subpopulaties/ condities) • Conditionele aanbeveling (geen passend bewijs voor gehele populatie, maar wel passend bewijs voor een subgroep/-conditie (overweging))

X	**GROEN**	Sterke aanbeveling voor, geldend voor de gehele populatie, en waar passend bewijs voor is [1,2]

[1] Er kan ook sprake zijn van passend bewijs bij een low of very low GRADE; bijvoorbeeld omdat er overwegingen zijn die zwaarwegend zijn in het aanbevolen beleid.

[2] Deze categorie geldt ook indien er passend bewijs is waaruit blijkt dat er geen voorkeur is voor één van de onderzochte interventies/diagnostiekmethoden/verwijspaden, voorbeeld: twee chirurgische technieken zijn even effectief, hebben vergelijkbare complicatierisico's, keuze is afhankelijk van het besluit dat de chirurg samen met de patiënt maakt.

Aanbeveling 2

Kruis aan		
	ROOD	Sterke aanbeveling tegen, geldend voor de gehele populatie, en waar passend bewijs voor is [1]
X	**ORANJE**	Aanbeveling waar geen passend bewijs is voor gehele populatie • Sterke aanbeveling tegen (geen passend bewijs voor gehele populatie en subpopulaties/ condities) • Conditionele aanbeveling (geen passend bewijs voor gehele populatie, maar wel passend bewijs voor een subgroep/-conditie (overweging))
	GROEN	Sterke aanbeveling voor, geldend voor de gehele populatie, en waar passend bewijs voor is [1,2]

Implementeren-tabel

De implementatietabel brengt in kaart welke factoren de uitvoering van een aanbeveling bevorderen of belemmeren, en welke aanvullende acties nodig zijn voor succesvolle invoering. De adviseur en (cluster)werkgroep vullen de tabel in op basis van gerichte vragen over het onderliggende probleem, relevante randvoorwaarden en mogelijke knelpunten. Op basis hiervan wordt geconcludeerd of een extra implementatie-impuls wenselijk is.

Vraag	***Antwoord:*** *Kruis aan en licht toe/ beschrijf*		***Toelichting keuze:***
I1. Wat was het onderliggende probleem om deze uitgangsvraag uit te werken?	**x**	**Ongewenste praktijkvariatie**	Praktijkvariatie m.b.t. tumorscreening SDH dragers
		Nieuwe evidentie	
		Anders	
I2. Maak een inschatting over hoeveel patiënten het ongeveer gaat waar de aanbeveling betrekking op heeft?		**< 1000**	
	x	**< 5000**	
		5000-40.000	
		> 40.000	
I3. Is de aanbeveling onderdeel van een bredere set interventies of verwant aan andere richtlijnen of modules? Zo ja, hoe verhoudt zij zich daartoe en moet hiermee rekening worden gehouden bij de implementatie, of kan de aanbeveling als losstaand worden beschouwd?		**Ja**	
	x	**Nee**	
I4. Belemmeringen en kansen op verschillende niveaus voor landelijke toepassing van de aanbeveling:		**Belemmerende factoren**	**Bevorderende factoren/ kansen**
Richtlijn/ klinisch traject (innovatie)		**-**	**Update richtlijn Erfelijke en Familiaire Tumoren – Richtlijnen voor Diagnostiek en Preventie (https://vkgn.stoet.nl/)**
Zorgverleners (artsen en verpleegkundigen)		**-**	**Update lokale ziekenhuis protocollen**
Patiënt/ cliënt (naasten)		**-**	**Uniform beleid**
Sociale context		**-**	**-**

Organisatorische context		**Beschikbaarheid PET scan**	**Centralisatie van zorg**
Financiële en juridische context		**Zorgkosten**	**-**
I5. A) Welke personen/partijen zijn van belang bij het toepassen van de aanbeveling in de praktijk? (kruis aan) **B) Wat is er nodig van deze personen/partijen om de aanbeveling in de praktijk te kunnen brengen?** *Denk aan aanpassingen in gedrag, werkwijzen, beleid, samenwerking of andere randvoorwaarden.*		**A**	**B**
	x	Patiënt/ cliënt (naaste)	Informed consent
	x	Professional	Update landelijke (VKGN/StOET) richtlijn en lokale protocollen. Multidisciplinaire samenwerking
	x	Beroepsvereniging, nl **KNO** **NIV/endocrinologie** **VKGN** **NVK**	Informatie, samenwerking Betrokkenheid van andere zorgverleners, met name kinderendocrinologen
		Ziekenhuis (raad van bestuur/UMCNL (voorheen NFU)/NVZ)	
		Zorgverzekeraars/ NZa	
		Zorginstituut [duiding nodig]	
		Anders	
I6. Binnen welk tijdsbestek moet de aanbeveling zijn geïmplementeerd?		< 1 jaar	
	x	binnen 2-3 jaar	
I7. Conclusie: is er extra actie en/of ondersteuning nodig voor implementatie van de aanbeveling? *De reguliere implementatieroutes (publicatie en disseminatie via officiele kanalen, opname in professionele standaarden, scholing en nascholing, gebruik van bestaande ICT systemen, audits en visitaties) van de richtlijnmodule alleen is onvoldoende.*	**x**	Ja	Aanpassing VKGN/StOET richtlijn Voor dit proces zijn reguliere lijnen die na autorisatie in gang kunnen worden gezet
		Nee	
I8. Plaatsing op de Landelijke Implementatieagenda Medisch Specialistische zorg is gewenst. *Het gaat om zorg die (grotendeels) wordt uitgevoerd binnen de*	**x**	Ja *	Hoewel het om een relatief kleine groep patienen gaat, is het surveillance protocol belastend en intensief.

ziekenhuismuren. Succesvolle implementatie vraagt om actieve betrokkenheid en samenwerking van meerdere relevante partijen binnen de zorgpraktijk.			Evaluatie op landelijk niveau zal inzicht geven over doelmatigheid en efficiëntie van de surveillance programma's. Daarnaast is er een lopend KWF project waardoor de toegang tot mensen met een erfelijke aanleg/predispositie voor tumoren waardoor evaluatie projecten ook makkelijker en completer wordt
		Nee	

**Deze aanbeveling komt mogelijk in aanmerking voor plaatsing op de Landelijke Implementatieagenda van het programma Zorg Evaluatie & Gepast Gebruik (ZE&GG), waarin alle betrokken partijen in de medisch-specialistische zorg samenwerken aan de implementatie van bewezen beste zorg. De Federatie levert namens het veld goed onderbouwde aanbevelingen aan, die zijn getoetst op de behoefte aan een implementatie-impuls. De onderwerpen op de Implementatieagenda zijn onderdeel van landelijke zorginkoopafspraken tussen zorgverzekeraars en zorgaanbieders. Voor de beoordeling van aanbevelingen uit richtlijnen wordt gebruikgemaakt van de implementatietabel. Op basis hiervan kunnen we de andere partijen goed informeren en gezamenlijk besluiten of plaatsing op de Implementatieagenda passend is.*

Vraag	***Antwoord*** *Kruis aan*	*Vul in*
A1. Is onderzoek wenselijk om de <u>uitgangsvraag of zoekvraag</u> (met meer/voldoende zekerheid) te kunnen beantwoorden?		ja
		Ja
A2. Wat is de kennisvraag?	Kennis-vraag	wat is de opbrengst van het huidige surveillance programma voor SDHx in Nederland, • verschilt deze opbrengst bij de verschillende SDHx varianten
	P	patienten/gezonde personen met een (Likely) pathogene variant (LPV) in een van de paraganglioom genen SDHA, SDHB, SDHC, SDHD, SDHAF2 (SDHx)
	I	Surveillance conform de richtlijn

	C	1. Familieleden bij wie de aanleg is uitgesloten 2. Patienten met een sporadisch paraganglioom
	O	Vaststellen van een paraganglioom
A3. Waarom is dit een belangrijke kennisvraag?	Toelichting	Beantwoorden van deze vraag/vragen geeft inzicht of de surveillance voldoende is
A4. Welk onderzoeksdesign is passend om deze kennisvraag te beantwoorden?		RCT
	X	Observationeel onderzoek
		Kwaliteitsregistratie
		Anders, namelijk
	Toelichting	Er zijn lopende initiatieven en projecten om de benodigde gegevens landelijk te verzamelen waardoor de mogelijkheid voor een landelijke multidisciplinaire studie vorm kan krijgen en aansluit op deze initiatieven.
A5. Zijn er een andere kennisvragen naar voren gekomen die passen bij het <u>onderwerp van de module</u>, maar niet hetzelfde zijn als de uitgangs- of zoekvraag en waar *geen* passend bewijs voor is? *Bijvoorbeeld:* het onderwerp van de module is 'Behandeling van aandoening X', waarin behandeling A en behandeling B met elkaar worden vergeleken. De voor- en nadelen van behandeling C ten opzichte van A en/of B is dan nog een openstaande kennisvraag als hier geen passend bewijs voor is. Het past wel bij het onderwerp van deze module en de resultaten van zorgevaluatie onderzoek zouden wel in deze module geduid kunnen worden.	X	Nee
		Ja
A6. Wat is de kennisvraag?	Kennis-vraag	[tekst] [a)]
	P	[tekst]
	I	[tekst]
	C	[tekst]
	O	[tekst]
A7. Waarom is dit een belangrijke kennisvraag?	Toelichting	[tekst] [b)]
		RCT

A8. Welk onderzoeksdesign is passend om deze kennisvraag te beantwoorden?		Observationeel onderzoek
		Kwaliteitsregistratie
		Anders, namelijk:
	Toelichting	[tekst]

Literatuur

Amar L, Pacak K, Steichen O, Akker SA, Aylwin SJB, Baudin E, Buffet A, Burnichon N, Clifton-Bligh RJ, Dahia PLM, Fassnacht M, Grossman AB, Herman P, Hicks RJ, Januszewicz A, Jimenez C, Kunst HPM, Lewis D, Mannelli M, Naruse M, Robledo M, Taïeb D, Taylor DR, Timmers HJLM, Treglia G, Tufton N, Young WF, Lenders JWM, Gimenez-Roqueplo AP, Lussey-Lepoutre C. International consensus on initial screening and follow-up of asymptomatic SDHx mutation carriers. Nat Rev Endocrinol. 2021 Jul;17(7):435-444. doi: 10.1038/s41574-021-00492-3. Epub 2021 May 21. PMID: 34021277; PMCID: PMC8205850.

Bausch B, Schiavi F, Ni Y, Welander J, Patocs A, Ngeow J, Wellner U, Malinoc A, Taschin E, Barbon G, Lanza V, Söderkvist P, Stenman A, Larsson C, Svahn F, Chen JL, Marquard J, Fraenkel M, Walter MA, Peczkowska M, Prejbisz A, Jarzab B, Hasse-Lazar K, Petersenn S, Moeller LC, Meyer A, Reisch N, Trupka A, Brase C, Galiano M, Preuss SF, Kwok P, Lendvai N, Berisha G, Makay Ö, Boedeker CC, Weryha G, Racz K, Januszewicz A, Walz MK, Gimm O, Opocher G, Eng C, Neumann HPH; European-American-Asian Pheochromocytoma-Paraganglioma Registry Study Group. Clinical Characterization of the Pheochromocytoma and Paraganglioma Susceptibility Genes SDHA, TMEM127, MAX, and SDHAF2 for Gene-Informed Prevention. JAMA Oncol. 2017 Sep 1;3(9):1204-1212. doi: 10.1001/jamaoncol.2017.0223. PMID: 28384794; PMCID: PMC5824290.

Burnichon N, Rohmer V, Amar L, Herman P, Leboulleux S, Darrouzet V, Niccoli P, Gaillard D, Chabrier G, Chabolle F, Coupier I, Thieblot P, Lecomte P, Bertherat J, Wion-Barbot N, Murat A, Venisse A, Plouin PF, Jeunemaitre X, Gimenez-Roqueplo AP; PGL.NET network. The succinate dehydrogenase genetic testing in a large prospective series of patients with paragangliomas. J Clin Endocrinol Metab. 2009 Aug;94(8):2817-27. doi: 10.1210/jc.2008-2504. Epub 2009 May 19. PMID: 19454582.

Daniel E, Jones R, Bull M, Newell-Price J. Rapid-sequence MRI for long-term surveillance for paraganglioma and phaeochromocytoma in patients with succinate dehydrogenase mutations. Eur J Endocrinol. 2016 Dec;175(6):561-570. doi: 10.1530/EJE-16-0595. Epub 2016 Sep 15. PMID: 27634942.

Davidoff DF, De Abreu Lourenco R, Tsang VHM, Benn DE, Clifton-Bligh RJ. Outcomes of SDHB Pathogenic Variant Carriers. J Clin Endocrinol Metab. 2024 Aug 13;109(9):2400-2410. doi: 10.1210/clinem/dgae233. PMID: 38605204; PMCID: PMC11318991.

Greenberg SE, Holman R, Kohlmann W, Buchmann L, Naumer A. Paraganglioma and other tumour detection rates in individuals with SDHx pathogenic variants by age of diagnosis and after the age of 50. Clin Endocrinol (Oxf). 2021 Sep;95(3):447-452. doi: 10.1111/cen.14559. Epub 2021 Jul 22. PMID: 34255389.

Greenberg SE, Jacobs MF, Wachtel H, Anson A, Buchmann L, Cohen DL, Bonanni M, Bennett B, Naumer A, Schaefer AM, Kohlmann W, Nathanson KL, Else T, Fishbein L. Tumor detection rates in screening of individuals with SDHx-related hereditary paraganglioma-pheochromocytoma syndrome. Genet Med. 2020 Dec;22(12):2101-2107. doi: 10.1038/s41436-020-0921-3. Epub 2020 Aug 3. PMID: 32741965; PMCID: PMC7710583.

Hanson H, Durkie M, Lalloo F, Izatt L, McVeigh TP, Cook JA, Brewer C, Drummond J, Butler S, Cranston T, Casey R, Tan T, Morganstein D, Eccles DM, Tischkowitz M, Turnbull C, Woodward ER, Maher ER; UK Cancer Genetics Centres. UK recommendations for *SDHA* germline genetic testing and surveillance in clinical practice. J Med Genet. 2023 Feb;60(2):107-111. doi: 10.1136/jmedgenet-2021-108355. Epub 2022 Mar 8. PMID: 35260474; PMCID: PMC9887350.

Heesters AF, Tops C, Potjer T, Corssmit EPM, Bayley JP, Hensen E, Jansen J. Optimal Screening for Hereditary Head and Neck Paraganglioma in Asymptomatic SDHx

Variant Carriers in the Netherlands. J Neurol Surg B Skull Base. 2024 Mar 1;86(1):1-5. doi: 10.1055/s-0044-1781438. PMID: 39881751; PMCID: PMC11774608.

Hong A, Shanahan M, Schenberg T, Inder W, MacIsaac R, James P, Sachithanandan N. Higher risk of phaeochromocytoma/paraganglioma (Phaeo-Pgl) in SDHD than SDHB carriers: an Australian cohort study. Intern Med J. 2019 Apr;49(4):529-532. doi: 10.1111/imj.14250. PMID: 30957378.

Saie C, Buffet A, Abeillon J, Drui D, Leboulleux S, Bertherat J, Zenaty D, Storey C, Borson-Chazot F, Burnichon N, Vincent M, Favier J, Baudin E, Giraud S, Gimenez-Roqueplo AP, Amar L, Lussey-Lepoutre C. Screening of a Large Cohort of Asymptomatic SDHx Mutation Carriers in Routine Practice. J Clin Endocrinol Metab. 2021 Mar 8;106(3):e1301-e1315. doi: 10.1210/clinem/dgaa888. PMID: 33247927.

Skefos CM, Brock PL, Blouch E, Greenberg SE. SDHA secondary findings in germline testing: counseling and surveillance considerations. Endocr Oncol. 2024 May 13;4(1):e230043. doi: 10.1530/EO-23-0043. PMID: 38770192; PMCID: PMC11103753.

Tufton N, Shapiro L, Sahdev A, Kumar AV, Martin L, Drake WM, Akker SA, Storr HL. An analysis of surveillance screening for SDHB-related disease in childhood and adolescence. Endocr Connect. 2019 Mar 1;8(3):162-172. doi: 10.1530/EC-18-0522. PMID: 30694796; PMCID: PMC6391899.

van der Tuin K, Mensenkamp AR, Tops CMJ, Corssmit EPM, Dinjens WN, van de Horst-Schrivers ANA, Jansen JC, de Jong MM, Kunst HPM, Kusters B, Leter EM, Morreau H, van Nesselrooij BMP, Oldenburg RA, Spruijt L, Hes FJ, Timmers HJLM. Clinical Aspects of SDHA-Related Pheochromocytoma and Paraganglioma: A Nationwide Study. J Clin Endocrinol Metab. 2018 Feb 1;103(2):438-445. doi: 10.1210/jc.2017-01762. Erratum in: J Clin Endocrinol Metab. 2018 May 1;103(5):2077. doi: 10.1210/jc.2018-00533. PMID: 29177515.

White G, Velusamy A, Anandappa S, Masucci M, Breen LA, Joshi M, McGowan B, Hubbard JGH, Obholzer R, Christodoulou D, Jacques A, Touska P, Hassan FU, Izatt L, Carroll PV. Tumour detection and outcomes of surveillance screening in SDHB and SDHD pathogenic variant carriers. Endocr Connect. 2022 Feb 16;11(2):e210602. doi: 10.1530/EC-21-0602. PMID: 35060925; PMCID: PMC8859962.

Williams ST, Chatzikyriakou P, Carroll PV, McGowan BM, Velusamy A, White G, Obholzer R, Akker S, Tufton N, Casey RT, Maher ER, Park SM, Porteous M, Dyer R, Tan T, Wernig F, Brady AF, Kosicka-Slawinska M, Whitelaw BC, Dorkins H, Lalloo F, Brennan P, Carlow J, Martin R, Mitchell AL, Harrison R, Hawkes L, Newell-Price J, Kelsall A, Igbokwe R, Adlard J, Schirwani S, Davidson R, Morrison PJ, Chung TT, Bowles C, Izatt L. SDHC phaeochromocytoma and paraganglioma: A UK-wide case series. Clin Endocrinol (Oxf). 2022 Apr;96(4):499-512. doi: 10.1111/cen.14594. Epub 2021 Sep 24. PMID: 34558728.

Bijlagen bij module […]

Risk of Bias tables

[Insert Risk of Bias tables]

Table of excluded studies

Reference	Reason for exclusion
Devouge AC, Lasolle H, Dupin C, Vergniol J, De-Mones-Del Pujol E, Abeillon J, Giraud S, Ceruse P, Gaudillière M, Borson-Chazot F, Raverot G, Tabarin A, Lussey-Lepoutre C, Haissaguerre M. Outcomes and Therapeutic Strategies for Head-and-neck Paragangliomas Associated With Succinate Dehydrogenase Mutations. J Clin Endocrinol Metab. 2025 Nov 18;110(12):e4030-e4037. doi: 10.1210/clinem/dgaf193. PMID: 40257095.	Wrong population
Cardot-Bauters C, Vantyghem MC, Do Cao C, Desailloud R, Joubert M, Coppin L, Odou MF, Pigny P. Genetic predisposition to pheochromocytoma and paraganglioma: 21 years of experience in the field. Ann Endocrinol (Paris). 2024 Jul;85(4):276-283. doi: 10.1016/j.ando.2024.05.024. Epub 2024 May 28. PMID: 38815921.	Wrong population
Darrat M, Lau L, Leonard C, Cooke S, Shahzad MA, McHenry C, McCance DR, Hunter SJ, Mullan K, Lindsay JR, Graham U, Bailie N, Hampton S, Rajendran S, Houghton F, Conkey D, Morrison PJ, Johnston PC. Clinical management and outcome of head and neck paragangliomas (HNPGLs): A single centre retrospective study. Clin Endocrinol (Oxf). 2024 Sep;101(3):243-248. doi: 10.1111/cen.15070. Epub 2024 May 2. PMID: 38696538.	Wrong population
Guha A, Vicha A, Zelinka T, Kana M, Musil Z, Pacak K, Betka J, Chovanec M, Plzak J, Boucek J. High incidence of occult familial SDHD cases amongst Czech patients with head and neck paragangliomas. Front Endocrinol (Lausanne). 2023 Dec 8;14:1278175. doi: 10.3389/fendo.2023.1278175. PMID: 38144572; PMCID: PMC10739302.	Wrong population
Davidoff DF, Benn DE, Field M, Crook A, Robinson BG, Tucker K, De Abreu Lourenco R, Burgess JR, Clifton-Bligh RJ. Surveillance Improves Outcomes for Carriers of SDHB Pathogenic Variants: A Multicenter Study. J Clin Endocrinol Metab. 2022 Apr 19;107(5):e1907-e1916. doi: 10.1210/clinem/dgac019. PMID: 35037935; PMCID: PMC9016424.	Included in Davidoff 2024
Petenuci J, Guimaraes AG, Fagundes GFC, Benedetti AFF, Afonso ACF, Pereira MAA, Zerbini MCN, Siqueira S, Yamauchi F, Soares SC, Srougi V, Tanno FY, Chambo JL, Lopes RI, Denes FT, Hoff AO, Latronico AC, Mendonca BB, Fragoso MCBV, Almeida MQ. Genetic and clinical aspects of paediatric pheochromocytomas and paragangliomas. Clin Endocrinol (Oxf). 2021 Jul;95(1):117-124. doi: 10.1111/cen.14467. Epub 2021 Mar 28. PMID: 33745191.	Wrong population
Jochmanova I, Abcede AMT, Guerrero RJS, Malong CLP, Wesley R, Huynh T, Gonzales MK, Wolf KI, Jha A, Knue M, Prodanov T, Nilubol N, Mercado-Asis LB, Stratakis CA, Pacak K. Clinical characteristics and outcomes of SDHB-related pheochromocytoma and paraganglioma in children and adolescents. J Cancer Res Clin Oncol. 2020 Apr;146(4):1051-1063. doi: 10.1007/s00432-020-03138-5. Epub 2020 Feb 15. PMID: 32062700; PMCID: PMC7388579.	Included in Davidoff 2024
Main AM, Rossing M, Borgwardt L, Grønkær Toft B, Rasmussen ÅK, Feldt-Rasmussen U. Genotype-phenotype associations in PPGLs in 59 patients with variants in SDHX genes. Endocr Connect. 2020 Aug;9(8):793-803. doi: 10.1530/EC-20-0279. PMID: 32688340; PMCID: PMC7487185.	Wrong population
Martins RG, Cunha N, Simões H, Matos MJ, Silva J, Torres I, Rodrigues F, Leite V, Teixeira MR, Bugalho MJ. Surveillance of succinate dehydrogenase gene mutation carriers: Insights from a nationwide cohort. Clin Endocrinol (Oxf). 2020 Jun;92(6):545-553. doi: 10.1111/cen.14184. Epub 2020 Apr 16. PMID: 32181896.	Wrong outcome

Gómez AM, Soares DC, Costa AAB, Pereira DP, Achatz MI, Formiga MN. Pheochromocytoma and paraganglioma: implications of germline mutation investigation for treatment, screening, and surveillance. Arch Endocrinol Metab. 2019 Jul 29;63(4):369-375. doi: 10.20945/2359-3997000000145. PMID: 31365623; PMCID: PMC10528659.	Wrong population
Buffet A, Ben Aim L, Leboulleux S, Drui D, Vezzosi D, Libé R, Ajzenberg C, Bernardeschi D, Cariou B, Chabolle F, Chabre O, Darrouzet V, Delemer B, Desailloud R, Goichot B, Esvant A, Offredo L, Herman P, Laboureau S, Lefebvre H, Pierre P, Raingeard I, Reznik Y, Sadoul JL, Hadoux J, Tabarin A, Tauveron I, Zenaty D, Favier J, Bertherat J, Baudin E, Amar L, Gimenez-Roqueplo AP; French Group of Endocrine Tumors (GTE) and COMETE Network. Positive Impact of Genetic Test on the Management and Outcome of Patients With Paraganglioma and/or Pheochromocytoma. J Clin Endocrinol Metab. 2019 Apr 1;104(4):1109-1118. doi: 10.1210/jc.2018-02411. PMID: 30698717.	Wrong intervention
White G, Tufton N, Akker SA. First-positive surveillance screening in an asymptomatic SDHA germline mutation carrier. Endocrinol Diabetes Metab Case Rep. 2019 May 30;2019(1):19-0005. doi: 10.1530/EDM-19-0005. PMID: 31368675; PMCID: PMC6548220.	Wrong study design
Kong G, Schenberg T, Yates CJ, Trainer A, Sachithanandan N, Iravani A, Ravi Kumar A, Hofman MS, Akhurst T, Michael M, Hicks RJ. The Role of 68Ga-DOTA-Octreotate PET/CT in Follow-Up of SDH-Associated Pheochromocytoma and Paraganglioma. J Clin Endocrinol Metab. 2019 Nov 1;104(11):5091-5099. doi: 10.1210/jc.2019-00018. PMID: 30977831.	Wrong outcome
Maniam P, Zhou K, Lonergan M, Berg JN, Goudie DR, Newey PJ. Pathogenicity and Penetrance of Germline SDHA Variants in Pheochromocytoma and Paraganglioma (PPGL). J Endocr Soc. 2018 Jun 18;2(7):806-816. doi: 10.1210/js.2018-00120. PMID: 29978154; PMCID: PMC6030830.	Wrong population
Benn DE, Zhu Y, Andrews KA, Wilding M, Duncan EL, Dwight T, Tothill RW, Burgess J, Crook A, Gill AJ, Hicks RJ, Kim E, Luxford C, Marfan H, Richardson AL, Robinson B, Schlosberg A, Susman R, Tacon L, Trainer A, Tucker K, Maher ER, Field M, Clifton-Bligh RJ. Bayesian approach to determining penetrance of pathogenic SDH variants. J Med Genet. 2018 Nov;55(11):729-734. doi: 10.1136/jmedgenet-2018-105427. Epub 2018 Sep 10. PMID: 30201732; PMCID: PMC6252366.	Wrong population
Eijkelenkamp K, Osinga TE, de Jong MM, Sluiter WJ, Dullaart RP, Links TP, Kerstens MN, van der Horst-Schrivers AN. Calculating the optimal surveillance for head and neck paraganglioma in SDHB-mutation carriers. Fam Cancer. 2017 Jan;16(1):123-130. doi: 10.1007/s10689-016-9923-3. PMID: 27573198; PMCID: PMC5243881.	Included in Davidoff 2024
Jochmanova I, Wolf KI, King KS, Nambuba J, Wesley R, Martucci V, Raygada M, Adams KT, Prodanov T, Fojo AT, Lazurova I, Pacak K. SDHB-related pheochromocytoma and paraganglioma penetrance and genotype-phenotype correlations. J Cancer Res Clin Oncol. 2017 Aug;143(8):1421-1435. doi: 10.1007/s00432-017-2397-3. Epub 2017 Apr 3. PMID: 28374168; PMCID: PMC5505780.	Included in Davidoff 2024
Tufton N, Shapiro L, Srirangalingam U, Richards P, Sahdev A, Kumar AV, McAndrew L, Martin L, Berney D, Monson J, Chew SL, Waterhouse M, Druce M, Korbonits M, Metcalfe K, Drake WM, Storr HL, Akker SA. Outcomes of annual surveillance imaging in an adult and paediatric cohort of succinate dehydrogenase B mutation carriers. Clin Endocrinol (Oxf). 2017 Feb;86(2):286-296. doi: 10.1111/cen.13246. Epub 2016 Oct 24. PMID: 27678251.	Included in Davidoff 2024
Bourdeau I, Grunenwald S, Burnichon N, Khalifa E, Dumas N, Binet MC, Nolet S, Gimenez-Roqueplo AP. A SDHC Founder Mutation Causes Paragangliomas (PGLs) in the French Canadians: New Insights on the SDHC-Related PGL. J Clin Endocrinol Metab. 2016 Dec;101(12):4710-4718. doi: 10.1210/jc.2016-1665. Epub 2016 Oct 4. PMID: 27700540; PMCID: PMC5155677.	Wrong population
Kornaczewski ER, Pointon OP, Burgess JR. Utility of FDG-PET imaging in screening for succinate dehydrogenase B and D mutation-related lesions. Clin Endocrinol	Wrong outcome

(Oxf). 2016 Aug;85(2):172-9. doi: 10.1111/cen.13020. Epub 2016 Feb 16. PMID: 26776272.	
Gravel G, Niccoli P, Rohmer V, Moulin G, Borson-Chazot F, Rousset P, Pasco-Papon A, Marcus C, Dubrulle F, Gouya H, Bidault F, Dupas B, Gabrillargues J, Caumont-Prim A, Hernigou A, Gimenez-Roqueplo AP, Halimi P. The value of a rapid contrast-enhanced angio-MRI protocol in the detection of head and neck paragangliomas in SDHx mutations carriers: a retrospective study on behalf of the PGL.EVA investigators. Eur Radiol. 2016 Jun;26(6):1696-704. doi: 10.1007/s00330-015-4024-5. Epub 2015 Oct 1. PMID: 26427697.	Wrong outcome
Lepoutre-Lussey C, Caramella C, Bidault F, Déandreis D, Berdelou A, Al Ghuzlan A, Hartl D, Borget I, Gimenez-Roqueplo AP, Dumont F, Deschamps F, Nascimento C, Lumbroso J, Guillaud Bataille M, Schlumberger M, Baudin E, Leboulleux S. Screening in asymptomatic SDHx mutation carriers: added value of ^{18}F-FDG PET/CT at initial diagnosis and 1-year follow-up. Eur J Nucl Med Mol Imaging. 2015 May;42(6):868-76. doi: 10.1007/s00259-015-3003-z. Epub 2015 Feb 13. PMID: 25676472.	Wrong outcome
Bausch B, Wellner U, Bausch D, Schiavi F, Barontini M, Sanso G, Walz MK, Peczkowska M, Weryha G, Dall'igna P, Cecchetto G, Bisogno G, Moeller LC, Bockenhauer D, Patocs A, Rácz K, Zabolotnyi D, Yaremchuk S, Dzivite-Krisane I, Castinetti F, Taieb D, Malinoc A, von Dobschuetz E, Roessler J, Schmid KW, Opocher G, Eng C, Neumann HP. Long-term prognosis of patients with pediatric pheochromocytoma. Endocr Relat Cancer. 2013 Dec 16;21(1):17-25. doi: 10.1530/ERC-13-0415. PMID: 24169644.	Wrong population
Else T, Marvin ML, Everett JN, Gruber SB, Arts HA, Stoffel EM, Auchus RJ, Raymond VM. The clinical phenotype of SDHC-associated hereditary paraganglioma syndrome (PGL3). J Clin Endocrinol Metab. 2014 Aug;99(8):E1482-6. doi: 10.1210/jc.2013-3853. Epub 2014 Apr 23. PMID: 24758179; PMCID: PMC4121019.	Wrong population
Lepoutre-Lussey C, Deandreis D, Chougnet C, Lumbroso J, Schlumberger M, Baudin E, Leboulleux S, Caramella C, Bidault F, Al Ghuzlan A, Borget I. Value of 18FDG-PET/CT for screening of paraganglioma in pre-symptomatic SDHx mutation carriers.	Wrong outcome
Gimenez-Roqueplo AP, Caumont-Prim A, Houzard C, Hignette C, Hernigou A, Halimi P, Niccoli P, Leboulleux S, Amar L, Borson-Chazot F, Cardot-Bauters C, Delemer B, Chabolle F, Coupier I, Libé R, Peitzsch M, Peyrard S, Tenenbaum F, Plouin PF, Chatellier G, Rohmer V. Imaging work-up for screening of paraganglioma and pheochromocytoma in SDHx mutation carriers: a multicenter prospective study from the PGL.EVA Investigators. J Clin Endocrinol Metab. 2013 Jan;98(1):E162-73. doi: 10.1210/jc.2012-2975. Epub 2012 Nov 15. PMID: 23162105.	Wrong outcome
Miederer M, Fottner C, Rossmann H, Helisch A, Papaspyrou K, Bartsch O, Mann WJ, Musholt TJ, Weber MM, Lackner KJ, Schreckenberger M. High incidence of extraadrenal paraganglioma in families with SDHx syndromes detected by functional imaging with [18F]fluorodihydroxyphenylalanine PET. Eur J Nucl Med Mol Imaging. 2013 Jun;40(6):889-96. doi: 10.1007/s00259-013-2346-6. Epub 2013 Feb 2. PMID: 23377099.	Wrong outcome
Schiavi F, Demattè S, Cecchini ME, Taschin E, Bobisse S, Del Piano A, Donner D, Barbareschi M, Manera V, Zovato S, Erlic Z, Savvoukidis T, Barollo S, Grego F, Trabalzini F, Amistà P, Grandi C, Branz F, Marroni F, Neumann HP, Opocher G. The endemic paraganglioma syndrome type 1: origin, spread, and clinical expression. J Clin Endocrinol Metab. 2012 Apr;97(4):E637-41. doi: 10.1210/jc.2011-2597. Epub 2012 Mar 28. PMID: 22456618.	Wrong population
King KS, Prodanov T, Kantorovich V, Fojo T, Hewitt JK, Zacharin M, Wesley R, Lodish M, Raygada M, Gimenez-Roqueplo AP, McCormack S, Eisenhofer G, Milosevic D, Kebebew E, Stratakis CA, Pacak K. Metastatic pheochromocytoma/paraganglioma related to primary tumor development in childhood or adolescence: significant link to SDHB mutations. J Clin Oncol. 2011	Wrong population

Nov 1;29(31):4137-42. doi: 10.1200/JCO.2011.34.6353. Epub 2011 Oct 3. PMID: 21969497; PMCID: PMC3208535.	
Prodanov T, Havekes B, Nathanson KL, Adams KT, Pacak K. Malignant paraganglioma associated with succinate dehydrogenase subunit B in an 8-year-old child: the age of first screening? Pediatr Nephrol. 2009 Jun;24(6):1239-42. doi: 10.1007/s00467-008-1111-8. Epub 2009 Feb 3. PMID: 19189136; PMCID: PMC4714580.	Wrong study design
Havekes B, van der Klaauw AA, Weiss MM, Jansen JC, van der Mey AG, Vriends AH, Bonsing BA, Romijn JA, Corssmit EP. Pheochromocytomas and extra-adrenal paragangliomas detected by screening in patients with SDHD-associated head-and-neck paragangliomas. Endocr Relat Cancer. 2009 Jun;16(2):527-36. doi: 10.1677/ERC-09-0024. Epub 2009 Mar 16. PMID: 19289533.	Wrong population
Solis DC, Burnichon N, Timmers HJ, Raygada MJ, Kozupa A, Merino MJ, Makey D, Adams KT, Venisse A, Gimenez-Roqueplo AP, Pacak K. Penetrance and clinical consequences of a gross SDHB deletion in a large family. Clin Genet. 2009 Apr;75(4):354-63. doi: 10.1111/j.1399-0004.2009.01157.x. PMID: 19389109; PMCID: PMC4718153.	Wrong study design
Timmers HJ, Kozupa A, Eisenhofer G, Raygada M, Adams KT, Solis D, Lenders JW, Pacak K. Clinical presentations, biochemical phenotypes, and genotype-phenotype correlations in patients with succinate dehydrogenase subunit B-associated pheochromocytomas and paragangliomas. J Clin Endocrinol Metab. 2007 Mar;92(3):779-86. doi: 10.1210/jc.2006-2315. Epub 2007 Jan 2. PMID: 17200167.	Wrong population
Mora J, Cascón A, Robledo M, Catala A. Pediatric paraganglioma: an early manifestation of an adult disease secondary to germline mutations. Pediatr Blood Cancer. 2006 Nov;47(6):785-9. doi: 10.1002/pbc.20680. PMID: 16304664.	Wrong population
van Houtum WH, Corssmit EP, Douwes Dekker PB, Jansen JC, van der Mey AG, Bröcker-Vriends AH, Taschner PE, Losekoot M, Frölich M, Stokkel MP, Cornelisse CJ, Romijn JA. Increased prevalence of catecholamine excess and phaeochromocytomas in a well-defined Dutch population with SDHD-linked head and neck paragangliomas. Eur J Endocrinol. 2005 Jan;152(1):87-94. doi: 10.1530/eje.1.01833. PMID: 15762191.	Wrong population
Dannenberg H, van Nederveen FH, Abbou M, Verhofstad AA, Komminoth P, de Krijger RR, Dinjens WN. Clinical characteristics of pheochromocytoma patients with germline mutations in SDHD. J Clin Oncol. 2005 Mar 20;23(9):1894-901. doi: 10.1200/JCO.2005.07.198. PMID: 15774781.	Wrong population
Schiavi F, Boedeker CC, Bausch B, Peçzkowska M, Gomez CF, Strassburg T, Pawlu C, Buchta M, Salzmann M, Hoffmann MM, Berlis A, Brink I, Cybulla M, Muresan M, Walter MA, Forrer F, Välimäki M, Kawecki A, Szutkowski Z, Schipper J, Walz MK, Pigny P, Bauters C, Willet-Brozick JE, Baysal BE, Januszewicz A, Eng C, Opocher G, Neumann HP; European-American Paraganglioma Study Group. Predictors and prevalence of paraganglioma syndrome associated with mutations of the SDHC gene. JAMA. 2005 Oct 26;294(16):2057-63. doi: 10.1001/jama.294.16.2057. Erratum in: JAMA. 2006 Feb 8;295(6):628. PMID: 16249420.	Wrong population

Literature search strategy
Zoekverantwoording

5 ***Zoekopbrengst***

	EMBASE	**OVID/MEDLINE**	**Ontdubbeld**
SR	28	13	32
Guideline	49	17	55
RCT	51	27	63

Observationele studies	372	136	395
Totaal	500	193	**545***

in Rayyan

Zoekstrategie

5 **Embase.com**

No.	Query	Results
#1	'sdhx gene'/exp OR 'succinate dehydrogenase'/exp OR ((sdh* NEAR/6 (gene* OR mutation* OR germline OR variant* OR carrier*)):ti,ab,kw) OR 'succinate dehydrogenase':ti,ab,kw	24487
#2	'monitoring'/exp OR 'screening'/exp OR monitor*:ti,ab,kw OR surveillan*:ti,ab,kw OR screening:ti,ab,kw	4157981
#3	#1 AND #2 NOT ('conference abstract'/it OR 'clinical trial':dtype) NOT (('editorial'/it OR 'letter'/it OR 'note'/it) NOT 'evidence based medicine'/exp) NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp) AND [2005-2025]/py	1053
#4	'meta analysis'/exp OR 'systematic review'/exp OR 'scoping review'/exp OR 'rapid review'/exp OR 'umbrella review'/exp OR 'cochrane database of systematic reviews'/jt OR 'network meta-analysis'/exp OR 'networkmeta analy*':ti,ab,kw OR 'networkmetaanaly*':ti,ab,kw OR metaanaly*:ti,ab,kw OR 'meta analy*':ti,ab,kw OR metanaly*:ti,ab,kw OR prisma:ti,ab,kw OR prospero:ti,ab,kw OR metaanali*:ti,ab,kw OR 'meta anali*':ti,ab,kw OR metanali*:ti,ab,kw OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab,kw) OR (((structured OR systemic*) NEAR/3 (review* OR overview* OR synth*) NEAR/3 literature):ti,ab,kw) OR ((systemic* NEAR/1 review*):ti,ab,kw) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab,kw) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab,kw) OR (((literature NEAR/3 (review* OR overview*)):ti,ab,kw) AND (search*:ti,ab,kw OR database*:ti,ab,kw OR 'data base*':ti,ab,kw)) OR (('data extraction*':ti,ab,kw OR 'data source*':ti,ab,kw) AND ('study selection*':ti,ab,kw OR 'studies selection*':ti,ab,kw)) OR ('search strateg*':ti,ab,kw AND 'selection criteria*':ti,ab,kw) OR ('data source*':ti,ab,kw AND 'data synth*':ti,ab,kw) OR medline*:ti,ab,kw OR pubmed*:ti,ab,kw OR 'pub med*':ti,ab,kw OR embase:ti,ab,kw OR cochrane*:ti,ab,kw OR (((critical* OR rapid*) NEAR/2 (review* OR overview* OR synth*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synth*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynth*:ti,ab,kw OR 'meta synth*':ti,ab,kw OR 'review* of review*':ti,ab,kw	1147881
#5	'practice guideline'/exp OR 'standard'/de OR guideline*:ti,kw OR cpg:ti,kw OR consensus*:ti,kw OR recommend*:ti,kw OR standard*:ti,kw	1482778
#6	'clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover	4875560

	procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti	
#7	'major clinical study'/de OR 'clinical study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR 'prospective study'/de OR 'cohort analysis'/de OR 'case control study'/de OR 'comparative study'/exp OR 'control group'/de OR 'controlled study'/de OR 'controlled clinical trial'/de OR 'crossover procedure'/de OR 'double blind procedure'/de OR 'phase 2 clinical trial'/de OR 'phase 3 clinical trial'/de OR 'phase 4 clinical trial'/de OR 'pretest posttest design'/de OR 'pretest posttest control group design'/de OR 'quasi experimental study'/de OR 'single blind procedure'/de OR 'triple blind procedure'/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) OR (((control OR controlled) NEAR/6 trial):ti,ab,kw) OR (((control OR controlled) NEAR/6 (study OR studies)):ti,ab,kw) OR (((control OR controlled) NEAR/1 active):ti,ab,kw) OR 'open label*':ti,ab,kw OR (((double OR two OR three OR multi OR trial) NEAR/1 (arm OR arms)):ti,ab,kw) OR ((allocat* NEAR/10 (arm OR arms)):ti,ab,kw) OR placebo*:ti,ab,kw OR 'sham-control*':ti,ab,kw OR (((single OR double OR triple OR assessor) NEAR/1 (blind* OR masked)):ti,ab,kw) OR nonrandom*:ti,ab,kw OR 'non-random*':ti,ab,kw OR 'quasi-experiment*':ti,ab,kw OR crossover:ti,ab,kw OR 'cross over':ti,ab,kw OR 'parallel group*':ti,ab,kw OR 'factorial trial':ti,ab,kw OR ((phase NEAR/5 (study OR trial)):ti,ab,kw) OR ((case* NEAR/6 (matched OR control*)):ti,ab,kw) OR ((match* NEAR/6 (pair OR pairs OR cohort* OR control* OR group* OR healthy OR age OR sex OR gender OR patient* OR subject* OR participant*)):ti,ab,kw) OR ((propensity NEAR/6 (scor* OR match*)):ti,ab,kw) OR versus:ti OR vs:ti OR compar*:ti OR ((compar* NEAR/1 study):ti,ab,kw) OR (('observational study'/de OR 'cross-sectional study'/de OR 'multicenter study'/de OR 'correlational study'/de OR 'follow up'/de OR cohort*:ti,ab,kw OR 'follow up':ti,ab,kw OR followup:ti,ab,kw OR longitudinal*:ti,ab,kw OR prospective*:ti,ab,kw OR retrospective*:ti,ab,kw OR observational*:ti,ab,kw OR 'cross sectional*':ti,ab,kw OR cross?ectional*:ti,ab,kw OR multicent*:ti,ab,kw OR 'multi-cent*':ti,ab,kw OR consecutive*:ti,ab,kw) AND (group:ti,ab,kw OR groups:ti,ab,kw OR subgroup*:ti,ab,kw OR versus:ti,ab,kw OR vs:ti,ab,kw OR compar*:ti,ab,kw OR 'odds ratio*':ab OR 'relative odds':ab OR 'risk ratio*':ab OR 'relative risk*':ab OR 'rate ratio':ab OR aor:ab OR arr:ab OR rrr:ab OR ((('or' OR 'rr') NEAR/6 ci):ab)))	18885556
#8	#3 AND #4	28
#9	#3 AND #5 NOT #8	49
#10	#3 AND #6 NOT #8 NOT #9	51
#11	#3 AND #7 NOT #8 NOT #9 NOT #10	372
#12	#8 OR #9 OR #10 OR #11	500

Ovid/Medline

#	Searches	Results
1	exp Succinate Dehydrogenase/ or (sdh* adj6 (gene* or mutation* or germline or variant* or carrier*)).ti,ab,kf. or 'succinate dehydrogenase'.ti,ab,kf.	19182
2	(monitor* or surveillan* or screening).ti,ab,kf.	2120201
3	(1 and 2) not ((exp animals/ or exp models, animal/) not humans/) not ((letter/ or comment/ or editorial/) not (exp Clinical Trial/ or exp Meta-Analysis/ or exp Scoping Review/ or exp Systematic Review/))	665
4	limit 3 to yr="2005 -Current"	604
5	exp Meta-Analysis/ or exp Network Meta-Analysis/ or exp Systematic Review/ or (networkmeta analy* or networkmetaanaly* or metaanaly* or meta analy* or metanaly* or prisma or prospero or metaanali* or meta anali* or metanali*).ti,ab,kf. or ((systemati* or scoping or umbrella or structured literature) adj3 (review* or overview*)).ti,ab,kf. or ((structured or systemic*) adj3 (review* or overview* or synth*) adj3 literature).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 (review* or overview*)) and (search* or database* or data base*)).ti,ab,kf. or ((data extraction* or data source*) and (study selection* or studies selection*)).ti,ab,kf. or (search strateg* and selection criteria*).ti,ab,kf. or (data source* and data synth*).ti,ab,kf. or (medline* or pubmed* or pub med* or embase or cochrane*).ti,ab,kf. or cochrane.jw. or ((critical* or rapid*) adj2 (review* or overview* or synth*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synth*)) and (search* or database* or data base*)).ab. or metasynth*.ti,ab,kf. or meta synth*.ti,ab,kf.	851137
6	Guideline/ or Practice Guideline/ or guidelines as topic/ or practice guidelines as topic/ or guideline*.ti,kf. or cpg.ti,kf. or consensus*.ti,kf. or recommend*.ti,kf. or standard*.ti,kf. or guideline*.ab. /freq=2	554496
7	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.	2928210
8	Case-control Studies/ or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ or comparative study/ or control groups/ or controlled before-after studies/ or controlled clinical trial/ or double-blind method/ or historically controlled study/ or matched-pair analysis/ or single-blind method/ or (((control or controlled) adj6 (study or studies or trial)) or (compar* adj (study or studies)) or ((control or controlled) adj1 active) or "open label*" or ((double or two or three or multi or trial) adj (arm or arms)) or (allocat* adj10 (arm or arms)) or placebo* or "sham-control*" or	8130790

	((single or double or triple or assessor) adj1 (blind* or masked)) or nonrandom* or "non-random*" or "quasi-experiment*" or "parallel group*" or "factorial trial" or "pretest posttest" or (phase adj5 (study or trial)) or (case* adj6 (matched or control*)) or (match* adj6 (pair or pairs or cohort* or control* or group* or healthy or age or sex or gender or patient* or subject* or participant*)) or (propensity adj6 (scor* or match*))).ti,ab,kf. or (confounding adj6 adjust*).ti,ab. or (versus or vs or compar*).ti. or exp cohort studies/ or epidemiologic studies/ or ((multicenter study/ or observational study/ or seroepidemiologic studies/ or (cohort* or 'follow up' or followup or longitudinal* or prospective* or retrospective* or observational* or multicent* or 'multi-cent*' or consecutive*).ti,ab,kf.) and ((group or groups or subgroup* or versus or vs or compar*).ti,ab,kf. or ('odds ratio*' or 'relative odds' or 'risk ratio*' or 'relative risk*' or aor or arr or rrr).ab. or (("OR" or "RR") adj6 CI).ab.)) or Case control.tw. or cohort.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/	
9	4 and 5	13
10	(4 and 6) not 9	17
11	(4 and 7) not (9 or 10)	27
12	(4 and 8) not (9 or 10 or 11)	136
13	9 or 10 or 11 or 12	193