Effectiveness Of Reduced Versus Standard Dose Radiation Therapy On Survival And Radiation Associated Toxicity In Human Papillomavirus (HPV) Associated Oropharyngeal Squamous Cell Carcinoma (OPSCC)

A thesis submitted in partial fulfilment of the requirements for the degree of Master of Clinical Science

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Abstract

Purpose

Oropharyngeal squamous cell carcinoma is a common form of head and neck cancer. A commonly occurring associated factor with this cancer is the Human Papillomavirus, which identifies an important and prevalent subgroup of patients that experience this cancer. Management for this group of people generally involves primary chemoradiotherapy or surgery with adjuvant chemoradiotherapy. Radiation therapy can however result in both acute and late-onset complications that may lead to treatment interruptions and reduced quality of life.

Methodology

A systematic review and meta-analysis was conducted to summarise the available literature comparing treatment of Human Papillomavirus associated Oropharyngeal Squamous Cell Carcinoma with either curative intent standard dose or de-escalated radiation therapy.

A pre-defined search strategy was used across multiple databases to identify suitable articles. Two independent reviewers performed title and abstract screening against inclusion and exclusion criteria with subsequent full text review. Following screening of 1050 records, 16 studies were included and 5 individual reports had data suitable for meta-analysis. Primary outcomes included; overall survival, progression free survival, disease free survival, disease specific survival and radiation associated toxicity. Secondary outcomes included; hospital re-admissions and patient reported quality of life measures.

Results

Meta-analysis revealed no significant differences in two- or three-year overall survival or progression free survival between those treated with curative intent reduced versus standard dose radiation therapy. The certainty in the evidence ranged from low to very low. In general, reduced dose radiation therapy was associated with better objective and subjective swallowing outcomes, reduced gastrostomy tube requirement and improved quality of life.

Conclusion

Findings from this systematic review have not provided any strong evidence to support a change in management to reduced dose radiation therapy for Human Papillomavirus associated Oropharyngeal Squamous Cell Carcinoma.

Declaration

I, Timothy Lee, certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint award of this degree.

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Timothy Lee
18/06/2023

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Abbreviations used

AJCC American Joint Committee on Cancer
CT - Computed Tomography
CTCAE - Common Terminology Criteria for Adverse Events
DFS - Disease Free Survival
DSS - Disease Specific Survival
EAT-10 - Eating Assessment Tool-10
ECOG - Eastern Cooperative Oncology Group
ENE – Extranodal Extension
EORTC QLQ-H&N35 - European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Head and Neck Module
FACT-H&N - Functional Assessment of Cancer Therapy – Head & Neck
FDA - Food and Drug Administration
FDG - Fluorodeoxyglucose
FOIS - Functional Oral Intake Scale
GRADE - Grading of Recommendations Assessment, Development and Evaluation
Gy - Gray
HPV - Human Papilloma Virus
IHC - Immunohistochemistry
IMPT - Intensity Modulated Proton Therapy
IMRT - Intensity Modulated Radiation therapy
ISH - In Situ Hybridisation
LVI – Lymphovascular Invasion
MBS - Modified Barium Swallow
MDADI - M. D. Anderson Dysphagia Inventory
MLC - Multileaf Collimator
MRI - Magnetic Resonance Imaging
NCCN - National Comprehensive Cancer Network
NCDB - National Cancer Database
OPSCC - Oropharyngeal Squamous Cell Carcinoma
ORN - Osteoradionecrosis
OS - Overall Survival
PAS - Penetration Aspiration Scale
PCR - Polymerise Chain Reaction
PET - Positron Emission Tomography

PF - Cisplatin and Fluorouracil

PFS - Progression Free Survival

PNI – Perineural Invasion

PRISMA - Preferred Reporting Items for Systematic reviews and Meta-Analyses

PSS-H&N - Performance Status Scale – Head & Neck

PT - Proton Therapy

RCT – Randomised Controlled Trials

RECIST - Response Evaluation Criteria in Solid Tumors

RoB 2 - Risk of Bias 2

ROBINS-I - Risk of Bias in Non-randomized Studies - of Interventions

cRCT – cluster Randomised Controlled Trials

SPS - Swallowing Performance Score

TLM - Transoral Laser Microsurgery

TMJ - Temporomandibular Joint

TORS - Trans-Oral Robotic Surgery

TPF - Cisplatin, Fluorouracil and Docetaxel

US - United States

UW-QOL - University of Washington Quality of Life Questionnaire

VMAT - Volumetric Modulated Arc Therapy

XeQoLS - Xerostomia Quality of Life Scale

2DRT - Two Dimensional Radiation therapy

3DRT - Three Dimensional Radiation therapy

5-FU - Fluorouracil

Chapter 1: Introduction

With over 930,000 cases recorded worldwide in 2020, head and neck carcinoma represents the sixth most common cancer type worldwide.[1] Oropharyngeal squamous cell carcinoma (OPSCC) is a subset of this cancer type, and contributes to approximately 15% of head and neck cancers.[1] OPSCC typically affects two clinically distinct populations. Those with Human Papillomavirus (HPV+) associated and those without Human Papillomavirus (HPV-) associated OPSCC. HPV+ OPSCC is associated with a favourable prognosis and higher survival rate compared to HPV- OPSCC.[2]

1.1: Anatomy of the oropharynx and neck region and relevance to head and neck squamous cell carcinoma

The oropharynx is a subsite of the pharynx, which is a fibromuscular tube about 12cm in length, extending from the skull base into the oesophagus with anterior openings that allow communication from the nose and oral cavity into the larynx. The pharynx is subdivided at each of these opening levels into the nasopharynx, oropharynx and laryngopharynx (or hypopharynx), see Figure 1.[3]

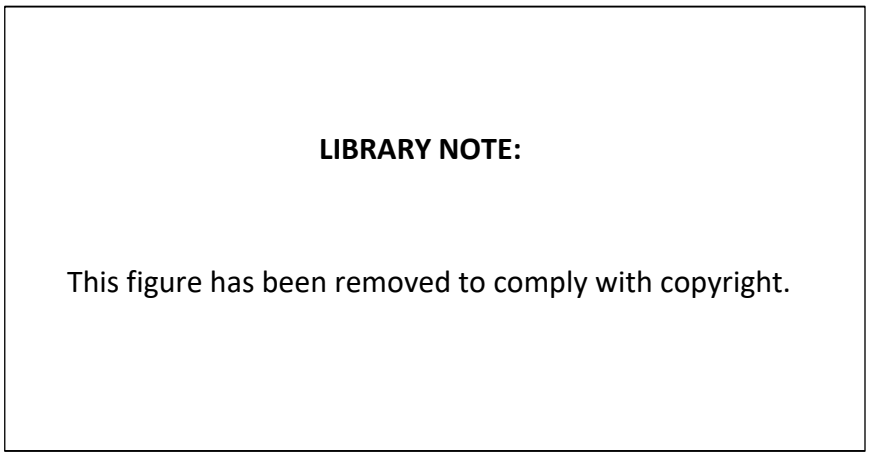

Figure 1: Anatomical structure of the pharynx and relations
From: "Normal endoscopic anatomy of the pharynx and larynx" Merati et al. 2003.[3]

The nasopharynx forms the upper part of the pharynx and is continuous inferiorly with the oropharynx, with the soft palate junction representing the boundary between the two. The palatine tonsils sit between the tonsillar pillars forming the lateral boundaries of the oropharynx. The palatine tonsils are mucosa-associated lymphoid tissue.[4] Antero-inferiorly within the oropharynx lie the tongue base, vallecula and epiglottis. The anatomical structures within the oropharynx play an important role in swallowing. Dysfunction of which may result in dysphagia characterised by velopharyngeal insufficiency, poor laryngeal elevation and aspiration.[5] Anteriorly and inferiorly the oropharynx is continuous with the oral cavity and hypopharynx respectively.[6] The most common sites for squamous cell carcinoma of the oropharynx includes the palatine tonsil and tonsillar fossa.[6] The other main anatomical consideration when assessing a patient with head and neck cancer is the regional lymphatic drainage to the neck.

Henri Rouviere initially described the regional lymphatic drainage of the head and neck in 1932.[7] Early descriptions used palpable superficial landmarks to separate the neck regions into anterior and posterior triangles.[8] The anterior triangle is bounded medially by the midline of the neck, superiorly by the body of the mandible and laterally by the anterior border of the sternocleidomastoid. The posterior triangle is related anteriorly to the sternocleidomastoid muscle, posteriorly with the trapezius muscle and inferiorly with the middle third of the clavicle.[8]

In order to improve characterisation and description of cervical lymph nodes, Som et al recommended an updated system.[9] This would act as an adjunct to the American Joint Committee on Cancer (AJCC) staging system for head and neck cancer.[10, 11] Lymph nodes were divided into seven surgical levels with their respective anatomical relations outlined in Table 1 and Figure 2.[9, 12]

Table 1: Cervical lymph node levels and anatomical boundaries

Lymph node level	Anatomical borders
Level Ia	Mandible Hyoid Anterior border of digastric muscle bilaterally
Level Ib	Anterior belly of digastric muscle Stylohyoid muscle Mandible

Level IIa	Skull base Inferior border of the hyoid Stylohyoid muscle Spinal accessory nerve
Level IIb	Skull base Inferior border of hyoid Spinal accessory nerve Sternocleidomastoid muscle
Level III	Inferior body of hyoid Inferior border of cricoid cartilage Lateral border of sternohyoid muscle Lateral border of Sternocleidomastoid muscle
Level IV	Inferior border of cricoid cartilage Clavicle Lateral border of sternohyoid muscle Lateral border of the Sternocleidomastoid muscle
Level Va	Apex of junction of the Sternocleidomastoid and Trapezius muscles Lower border of cricoid cartilage Posterior border of Sternocleidomastoid muscle Anterior border of trapezius muscle
Level Vb	Lower border of cricoid cartilage Clavicle Posterior border of the Sternocleidomastoid Anterior border of trapezius
Level VI	Hyoid bone Suprasternal notch Common carotid arteries laterally
Level VII	Manubrium Left and right common carotid arteries Innominate vein

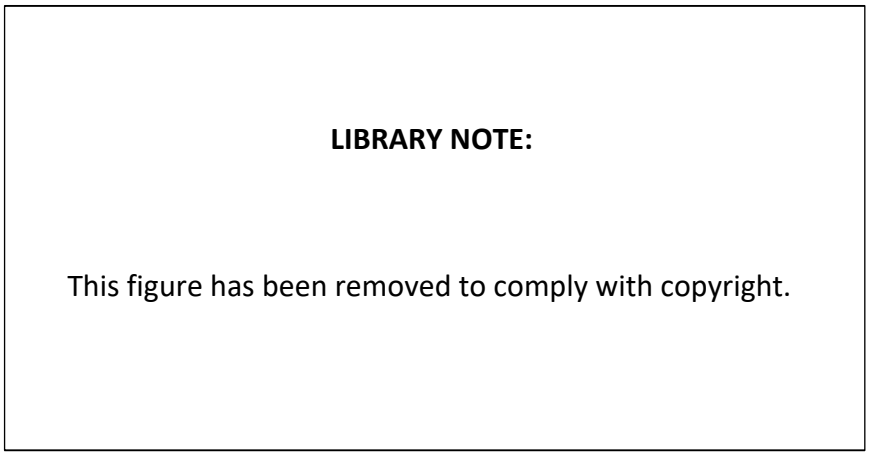

Figure 2: Seven surgical levels of the neck
From: "An imaging-based classification for the cervical nodes designed as an adjunct to recent clinically based nodal classifications". Som et al. 1999.[9]

Understanding the anatomical relations of the neck levels is important for several reasons. Regional spread of cancer to lymph nodes in the neck is an important factor when staging a patient's cancer, discussing treatment options and prognosis. Identification of a neoplasm within a certain lymph node may also aid in identification of where it originated from given the common routes of lymphatic drainage in the head and neck.[8] In regards to oropharyngeal cancer, the common regional lymphatic drainage pathway is primarily to the level II and level III cervical lymph nodes. Other common associated primary and regional lymphatic regions are outlined in Table 2.[8]

Table 2: Common patterns of regional lymph node metastases from primary head and neck cancers

Cervical lymph node level	Common associated primary tumour origin
Level I	Oral cavity, lip, sinonasal, floor of mouth, anterior tonsillar pillar, eyelid, nose, sublingual and submandibular glands
Level II	Pharynx, oral cavity, floor of mouth, tongue, supraglottis, parotid, eye
Level III	Hypopharynx, larynx, thyroid gland
Level IV	Larynx, thyroid gland, cervical oesophagus, breast/lung/gastric metastasis
Level V	Nasopharynx, occipital scalp/neck
Level VI	Larynx, thyroid

1.2: Pathophysiology of oropharyngeal squamous cell carcinoma

Human papillomavirus (HPV) is a non-enveloped circular double-stranded DNA virus from the papillomaviridae family.[13-15] HPV is a group of more than 200 viruses that can be further classified into high-risk and low-risk subtypes.[16] The World Health Organisation classified 14 high risk HPV subtypes, these include HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68.[16] The most commonly encountered strain of HPV, seen in around 86.7% of OPSCC is HPV-16, followed by HPV-18.[17] This virus is transmitted either vertically during birth or horizontally via direct physical contact and can affect cutaneous and mucosal surfaces.[15, 18] Within the United States (US), HPV is the most common sexually transmitted infection with around six million new infections per year.[19] Risk factors for HPV infection include, orogenital sexual practice, early age at first intercourse and increased sexual partners.[20] The incidence of HPV infection follows a bimodal distribution with peaks around the ages of 30-34 and 60-64 years old.[18, 21] Infection with HPV is best known for its oncogenic role in the development of cervical cancer however it also plays a role in cancer of the head and neck, vagina, vulva, anus and penis.[13, 14] With regards to OPSCC, the incidence of HPV related disease has increased by 225% between 1988 and 2004.[13] The HPV genome encodes for multiple viral proteins including but not limited to 3 oncoproteins (E5, E6 and E7) and two capsid proteins (L1 and L2). Once transmitted, high-risk HPV subtypes lead to inhibition of apoptosis and promotion of uncontrolled cell proliferation through the E6 and E7 proteins. E6 has downstream effects that result in degradation of p53, a tumour

suppressor gene. E7 targets the retinoblastoma protein that leads to overexpression of p16 and increased cell proliferation.[14, 21] In comparison, 75% of patients with HPV- OPSCC will have a p53 mutation and a loss of p16 expression.[14]

Generally, infection with HPV will be asymptomatic and cleared by the immune system. However, infection may persist for months to years in some people leading to development of cancer.[19] Introduction of multiple vaccinations over the past few decades has helped to limit the spread of HPV. The currently available vaccinations include the bivalent Cervavix (HPV16 and HPV18), quadrivalent Gardasil (HPV6, HPV11, HPV 16, HPV 18) and nonavalent Gardasil (HPV6, HPV11, HPV16, HPV18, HPV31, HPV33, HPV45, HPV52, HPV58).[18] The benefit of the vaccination is that it not only covers multiple common strains of HPV but produces at least a 10-1,000 times greater immune response compared to natural infection with HPV.[18] Despite the recent introduction of these vaccines, it is expected that the rates of HPV+ OPSCC will continue to rise over the next 20-30 years.[16]

1.3: Clinical presentation

In comparison to patients with HPV- OPSCC, patients with HPV+ OPSCC are generally younger (median 57 versus 64 years old) and less likely to heavily use alcohol or tobacco.[14] HPV+ OPSCC will generally also present with a smaller, poorly differentiated primary tumour but more advanced regional lymph node metastases compared to HPV- OPSCC.[21] Other common presenting symptoms for OPSCC include; sore throat, dysphagia, globus, otalgia, haemoptysis and weight loss.[22]

1.4: Diagnostic evaluation

Investigation of suspected OPSCC involves imaging with a Computed Tomography (CT) scan. A CT scan is a cross sectional imaging modality used to locate and characterise the primary lesion, regional spread to the cervical lymph nodes or distant spread to the chest/upper abdomen. Biopsies of concerning cervical lymphadenopathy are generally performed under ultrasound or CT guidance. In the absence of cervical nodal disease, direct examination of the breathing and swallowing passages under general anaesthesia (panendoscopy) is performed to identify and stage the primary lesion.[23]

Positron Emission Tomography (PET) scans are used as an adjunct to the above investigations and utilise a radiolabelled biological compound, ^{18}F-

Fluorodeoxyglucose(FDG).[24] When administered intravenously and metabolised by tumour cells or cells with a high metabolic rate a by-product is produced that accumulates in these areas. The FDG-PET scan improves the sensitivity in identifying the unknown primary cancer, or regional and distant metastatic disease.[23]

There are multiple methods of testing for HPV infection in patients with OPSCC including immunohistochemistry (IHC), high risk HPV subtype in situ hybridisation (ISH) and HPV polymerise chain reaction (PCR). The test recommended by the College of American Pathologists is p16 IHC. A cut off of 70% nuclear and cytoplasmic expression has been advised for clinical use.[25] The elevated expression of p16 as discussed earlier provides a suitable surrogate marker of HPV associated OPSCC with a sensitivity of 94% and specificity 83% for HPV infection in OPSCC.[26, 27] p16 can however be elevated in other disease states including, inflammation, regeneration and p53 mutations.[26] For this reason, the College of American Pathologists have also recommended further HPV testing at the pathologists discretion if there are concerns regarding non HPV-related disease.[25]

1.5: Staging of OPSCC

Information from the above clinical and radiological assessments are separated into three distinct categories that aid in staging of disease. These categories include 1) the size and extent of the primary tumour (T-category), 2) presence and extent or absence of regional lymph node metastases (N-category) and 3) presence or absence of distant metastases (M-category).[28] These categories combine to provide overall stages that reflect a similar survival for patients within each stage (hazard consistency) with a difference in survival between separate stages (hazard discrimination).[11] The current classification system for OPSCC is the Eighth edition of the AJCC Staging Manual.[29] A new staging system was required due to the inability of the seventh edition to accurately stage and prognosticate patients with HPV+ OPSCC who despite presenting with a higher N-category generally had a better prognosis compared to HPV- OPSCC patients. For this reason, the eighth edition of the AJCC staging guidelines incorporated HPV status as determined by p16 IHC as an independent prognostic factor. Separate staging systems were developed for HPV+ and HPV- OPSCC to reflect the different outcome measures.[29] An example of this discrepancy is a patient presenting with a 2cm primary palatine tonsil SCC expressing p16 on IHC with two ipsilateral cervical lymph nodes less than 6cm in size. In the seventh edition, this patient would have been classified as stage

IV OPSCC, reflecting a poor prognosis. However, the survival of this patient was significantly better than a patient with similar features but HPV- OPSCC. Re-staging using the eighth edition (see Appendix 1) would classify this patient as stage I HPV+ OPSCC, reflecting a better and more accurate prognosis compared to the stage IV HPV- OPSCC.[11] Cancer staging has important clinical implications including guiding treatment recommendations, disease counselling and prognostication, eligibility for clinical trials and generation of meaningful data for future research.[28]

1.6: Treatment of oropharyngeal squamous cell carcinoma

Treatment for OPSCC involves surgery, and/or radiation therapy, and chemotherapy. The principle of curative intent treatment is to utilize single modality instead of multi-modality treatment where possible to minimize treatment related morbidity.[23] Historically OPSCC is treated with radical chemoradiotherapy alone or surgery followed by adjuvant radiation therapy or chemoradiotherapy.[23] Similar survival rates have also been identified when comparing patients with HPV+ OPSCC treated with surgery alone to surgery with post-operative radiation therapy.[30]

1.6.1: Surgical approaches

Surgical management of OPSCC has evolved significantly over the last century. Large open resections splitting the mandible were often necessary and associated with significant morbidity.[31] With patients being diagnosed with OPSCC at younger ages, a focus has been made on minimising both treatment related morbidity and impact on quality of life. The advent of minimally invasive options including Transoral Laser Microsurgery (TLM) and Trans-Oral Robotic Surgery (TORS) has supported the role surgery plays in the treatment of OPSCC.

TLM was first developed in the 1970s utilising a carbon dioxide laser.[32, 33] This form of treatment has historically provided patients with good oncological outcomes. This was demonstrated in a prospective study of 204 patients treated with TLM for tonsil or tongue base cancer with a 3-year overall survival of 86%.[34] TLM is however limited by the linear nature of the laser and inability to cut around curved surfaces as well as being a technically challenging procedure.[32]

There have been multiple TORS devices since its development in the 1990's. The first product was AESOP® (Computer Motion) that evolved to become ZEUS® (Computer Motion).[35] The other main device is the da Vinci® system (Intuitive Surgical).[35] The ZEUS® and da Vinci® robots were in competition until the acquisition of Computer Motion by Intuitive Surgical in 2003. Following this, the ZEUS® system was phased out with a focus made on the da Vinci® system.[35] The current da Vinci® TORS system comprises three components. These are a patient-side robotic cart, surgeons console and a high-definition three-dimensional vision system. The robotic cart has arms on which various surgical instruments alongside an endoscopic camera can be mounted. In addition to three-dimensional visualisation, TORS provides tremor filtration, wristed augmentation and an ability to operate remote from the patient.[35] The US Food and Drug Administration (FDA) approved TORS for resection of benign and malignant lesions of the head and neck in 2009.[36] When comparing TORS with neck dissection to Primary (Chemo)Radiotherapy for OPSCC, recent evidence has not demonstrated any significant difference in overall survival between the treatment arms.[37]

1.6.2: Chemotherapy

A meta-analysis by Pignon et al. showed an absolute survival benefit at 5 years of 6.5% for concurrent chemoradiotherapy and 2.4% for induction chemotherapy when compared to radiation therapy alone.[38] Primary chemoradiotherapy typically utilises one of two options. The first line option commonly utilised is cisplatin. The anticancer properties of cisplatin and platinum-based compounds were first discovered in 1965.[39] Cisplatin was subsequently approved by the United States Food and Drug Administration for testicular and ovarian cancer.[39] Cisplatin is administered intravenously every three weeks for a total of three cycles alongside concurrent radiation therapy.[40] Side effects include nausea and vomiting, taste alterations, neutropenia/thrombocytopenia, oral mucositis, diarrhoea, anorexia, fatigue, peripheral neuropathy, nephrotoxicity and ototoxicity. Treatment related side effects can result in an inability to tolerate standard treatment over three cycles. If required, treatment can be delivered weekly at a lower dose over the course of six weeks.[40] The other main chemotherapeutic options are cetuximab or a combination of carboplatin and Fluorouracil (5-FU).[40]

1.6.3: Radiation therapy

Treatment of cancer with radiation therapy has evolved significantly over time. Two-dimensional radiation therapy (2DRT) was the initial form of treatment. Tumours were targeted with photons through simple shaped windows with the aim of delivering sufficient irradiation of the target field. The problem with this technique was the collateral exposure of large volumes of normal tissue to radiation and associated toxicity.[41] Three-dimensional conformal radiation therapy (3DCRT) was introduced in the 1980's. Pre-treatment Computed Tomography imaging and guidance allowed for improved visualisation of the tumour and surrounding structures. Multileaf collimators (MLC) were used to customise and focus radiation fields depending on the shape and size of the specific target field.[41] The next improvement was in the 1990's with the introduction of Intensity Modulated Radiation Therapy (IMRT). IMRT is the recommended treatment modality used in today's practice.[23] IMRT has the benefit of utilizing dynamic multileaf collimators that enable different shaped radiation fields to be produced from various angles. Along with this, the intensity within each radiation field can be modified depending on the specific target area and dose required.[41] The final benefit of IMRT over 3DCRT is the pre-treatment use of inverse treatment planning. This method of treatment planning begins by selecting the required dose for the target volume as well as the surrounding tissue. Computer software is utilized to select the ideal number, shape, size and intensity of beams required to deliver this dose from specific treatment directions whilst sparing as much normal tissue as possible. An updated version of IMRT is Volumetric Modulated Arc Therapy (VMAT). VMAT uses all the features of IMRT however it can continuously adjust both the MLC shape and beam intensity whilst rotating around the patient. This not only provides more accurate treatment delivery but also reduces treatment time.[41]

External beam radiation therapy can also be delivered using either protons or electrons; this however is not part of routine practice. The use of proton therapy (PT) produces a different and characteristic delivery of radiation to target tissues. Treatment with PT utilises the Bragg peak, a localised and intense delivery of radiation that increases treatment at the intended site with the benefit of significantly reduced treatment delivery to surrounding structures.[41] Initial research into this area has suggested PT is associated with reduced levels of radiation therapy associated toxicity. Unlike Proton and Photon therapy, Electron therapy is unable to penetrate deep into tissues. Hence, electron therapy is utilised predominantly in superficial or cutaneous tumours.[42]

Radiation therapy is delivered in repeated treatments, also termed fractions, over multiple weeks resulting in structural tissue damage and inflammation.[42] Standard treatment for OPSCC is daily fractions of 1.8-2Gray (Gy), five days per week for seven weeks (total 63-70Gy).[43] A complicating factor in the delivery of radiation therapy is the three-dimensional layout of the primary tumour and/or lymph nodes in relation to surrounding structures. Structures in close proximity to radiation fields are referred to as 'organs at risk'. For OPSCC these include the brachial plexus, brainstem, cervical oesophagus and pharyngeal constrictors, cochlea, larynx, eyes, mandible/temporomandibular joint(TMJ), spinal cord and thyroid.[43]

1.7: Radiation therapy associated adverse effects

Radiation therapy can result in acute as well as late complications. Short-term complications occur whilst patients are undergoing therapy or shortly after completion and generally resolve within months of onset. The mechanism behind short-term toxicity is secondary to radiation induced p53 mediated apoptosis.[42] Short-term complications occur in hematopoietic tissues, hair follicles, intestinal epithelium and dermis. As such dermatitis, mucositis, dysphagia, odynophagia and alopecia are identified in this period.[42] Long-term complications of radiation therapy are characterized by fibrogenesis secondary to persistent and amplified wound healing and matrix deposition. They include swallowing dysfunction, skin changes, xerostomia, dental caries, trismus, lymphedema, osteoradionecrosis, carotid stenosis, stroke and secondary malignancy.[42] Acute and late toxicity may result in treatment interruptions and reduced quality of life respectively.

1.7.1: Skin reactions

Skin reactions are a common side effect of radiation therapy affecting up to 95% of patients.[44] Skin changes typically develop within weeks of treatment onset and can continue weeks after completion of therapy.[44] Skin changes can range from mild erythema to desquamation, bleeding, ulceration and necrosis or ultimately death.[44] Treatment and patient related factors increasing the risk of severe skin reactions include:

- Higher total and daily radiation therapy dose and treatment time
- Size of treatment field
- Concurrent chemotherapy

- Previous irradiation of the same treatment field

Preventative strategies to help reduce the risk of skin reactions include minimising trauma to the area and application of topical moisturisers. Management is generally focused around maintaining a clean and moist environment with non-adherent dressings and analgesia.[44]

1.7.2: Oral mucositis, dysphagia and odynophagia

All patients undergoing radiation therapy for head and neck cancer will develop a degree of mucositis.[45] Mucositis generally develops within weeks of treatment onset, peaks at treatment completion and may persist for months after completion of treatment.[45] Risk factors correlating with severity of mucositis and dysphagia include:

- Higher total and daily radiation therapy dose and treatment time
- Size of treatment field
- Concurrent chemotherapy
- Smoking
- Alcohol consumption
- Malnutrition

In severe cases where mucositis and dysphagia is impacting on oral intake patients may require the placement of a nasogastric or percutaneous feeding tube.[45] Management strategies include, oral hygiene, avoiding traumatic/painful stimuli, oral glutamine or honey and topical analgesia.[45] In regard to late dysphagia, mechanisms are generally attributed to soft tissue fibrosis and restricted compliance and contractility of the underlying muscles.[45] Correlations have been seen between the dosage of radiation therapy delivered and the toxicity patients' experience. For example, when treatment dosage to the middle and superior constrictors exceeds 55Gy, there is a proportionate increase in long term swallowing dysfunction.[46]

1.7.3: Xerostomia

Xerostomia results from radiation to the major and minor salivary glands and the nerves they are innervated by.[47] Symptoms develop within the first week of treatment and continue to progress over a period of six to eight months. Recovery may take place within 5 years however can be permanent.[47] Risk factors include:

- Exposure of salivary glands to treatment field
- Concurrent chemotherapy

In regards to minimising risk, xerostomia may be avoided if the mean dose to the parotid glands is less than 26Gy or if possible by sparing the contralateral parotid gland.[48] Often patients with xerostomia will develop a dry mouth and lips, thick saliva, halitosis, altered taste and speech with an increased susceptibility to dental decay and infections.[47] If symptoms are severe enough patients may be unable to tolerate oral intake and require temporary placement of a feeding tube. Management options include artificial saliva and sprays or salivary stimulants that aid in temporarily moistening the oral cavity.[47]

1.7.4: Alopecia

Significant alopecia is less commonly seen because of radiation but more so with chemotherapy.[49] Radiation associated alopecia is typically distributed within the radiation field and correlates with total treatment dose and frequency of treatment. Onset of alopecia is generally within weeks of treatment, with re-growth, if present, generally patchy and permanent.[49]

1.7.5: Osteoradionecrosis (ORN) of the Jaw

Radiation therapy of the head and neck can result in changes to the vascularity and areas of hypoxia. In the setting of xerostomia, poor oral hygiene, dental disease and smoking, these patients are at risk of oral complications.[50] For this reason, a thorough pre-treatment dental assessment and management of any pre-existing or at-risk areas is imperative in preventing post-treatment complications. Oral complications can include pain, exposed bone, dental caries and ORN. ORN of the jaw develops in 5-7% of patients undergoing radiation therapy for head and neck cancer.[50] This condition may occur spontaneously or develop subsequent to orodental trauma. Time to onset development of ORN is reported to be between 22-47months following radiation therapy.[50] Risk factors for the development of ORN include:

- Location of primary tumour irradiated (tongue/floor of mouth/tonsil/retromolar trigone)
- Total dose and field irradiated
- Dental extractions post radiation therapy
- Alcohol and tobacco use
- Poor oral hygiene

Management principles for ORN, when it occurs, are to maintain good oral hygiene, analgesia, consideration of hyperbaric oxygen and medical therapy as well as consideration of surgical management.[50] Medical therapy includes options that can help to increase blood flow to affected areas (Pentoxifylline), inhibit the breakdown of bone (Clodronate) and/or Vitamin E (Tocopherol).[50] Surgical management involves the removal of non-viable tissue (sequestrectomy).[50]

1.7.6: Lymphoedema

Benign lymphoedema typically develops secondary to surgical resection or radiation therapy-induced damage to draining lymphatics. Accumulation of protein-rich fluid develops within the interstitial tissues as a result of this causing swelling and increasing the risk of cellulitis.[51] Radiation therapy induced lymphoedema occurs within the first 18 months after treatment. Management strategies include weight control, compression therapy, physical therapy and laser therapy.[51]

1.7.7: Trismus

Trismus develops as a result of radiation therapy induced fibrotic changes within the muscles of mastication including the masseters and pterygoid muscles, their innervating nerves as well as the temporomandibular joints.[52] Trismus has been identified in patients with doses as low as 15Gy exposed to the pterygoid muscles. Trismus often results in the inability to maintain good oral hygiene, inability to meet nutritional requirements, orodental infections and airway concerns. Management of trismus generally involves various manual stretching maneuvres using various devices. Some of these devices include tongue depressors, dynamic bite openers, the TheraBite, rubber plugs and the Dynasplint Trismus System.[52]

1.7.8: Carotid stenosis and cerebrovascular accidents

The incidence of carotid artery stenosis (defined as >50% occlusion of the carotid artery) in patients treated with radiation therapy for head and neck cancer at one, two and three years are 4%, 12% and 21% respectively.[53] Various mechanisms have been proposed to explain the increased incidence of carotid stenosis seen in patients undergoing radiation therapy for head and neck cancer. These include a cascade of pro-inflammatory reactions leading to atherosclerotic plaques as well as occlusion of the blood vessels (vasa vasorum) supplying these major blood vessels.[53] Exposure to

radiation therapy has also been shown to double the relative risk of cerebrovascular accidents.[53] There is no clear consensus regarding screening of carotid stenosis in this patient population.

1.7.9: Second malignancy

Within paediatric cancer survivors the most common cause of treatment related death is second malignancy.[42] The combination of increased life expectancy in general as well as diagnosis and treatment of HPV+ OPSCC in younger individuals', second malignancy may become an important consideration in the long-term follow-up of these patients. Risk factors for the development of second malignancy include dose of radiation therapy, site of exposure and the time after exposure.[54]

1.8: Grading and reporting of treatment related adverse effects

Treatment related toxicity is graded using a variety of different objective clinical assessment tools and/or subjective patient reported outcome measures. Some of the commonly utilized tools for assessing treatment related toxicity are summarised below.

1.8.1: Modified barium swallow (MBS)

The modified barium swallow is a real-time radiological study used to visualise the transit of a radiopaque substance (barium) through the mouth and into the oesophagus. The procedure is typically performed by a radiologist in conjunction with a speech pathologist.[55] Various consistencies of liquid and food are mixed with the radiopaque substance to provide information regarding swallowing function and risk of airway penetration and/or aspiration. Information from this study can be used to create a score for the Penetration and Aspiration Scale (PAS) as well as the Swallowing Performance Score (SPS).

The PAS is an eight-point scale that utilises a MBS to assess a patient's swallow function and safety. This scale considers three key elements of ingested substances:

- Depth of airway invasion
- Patient's response to airway invasion
- Residue following swallow[56]

SPS: The SPS provides a score from one to seven that summarises the oral and pharyngeal phases of swallowing. Higher scores reflect poorer swallow function.[55]

1.8.2: Common Terminology Criteria for Adverse Events (CTCAE) version 5.0

Developed by the National Cancer Institute, the CTCAE is utilized as a grading scale for the reporting of adverse events.[57] Adverse events are organised into System Organ Classes with specific requirements required for each grade for individual adverse events. Adverse events are graded on a scale from one to five. In general, the grades are characterised by:

- Grade one: Asymptomatic or mild symptoms not requiring intervention
- Grade two: Moderate symptoms which limit age-appropriate instrumental activities of daily living requiring local or non-invasive interventions
- Grade three: Severe effects that do not pose an immediate threat to life but may result in hospitalisation or prolonged hospital stay. Effects typically have impacts on patients ability to perform self-care activities of daily living
- Grade four: Consequences with threat to life where urgent intervention is indicated
- Grade five: Adverse event resulting in death[57]

1.8.3: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Head and Neck Module (EORTC QLQ-H&N35)

Widely utilised across the world and available in 53 languages, the EORTC QLQ-H&N35 is one of the standard instruments used to assess quality of life in patients with Head and Neck Cancer.[58] This tool assesses quality of life across multiple domains including; pain in the mouth, swallowing issues, speech and social activities as well as specific concerns related to pain, dentition, mouth opening, dry mouth, saliva and weight gain/loss.[58]

1.8.4: Functional Oral Intake Scale (FOIS)

The FOIS is a seven-point scale used to rate patient's functional oral intake. This scale was initially created to assess food and liquid intake in stroke patients but has become more widely used as a measure of dysphagia.[59] The scale describes oral intake varying from level one: nothing by mouth, to level seven: total oral diet with no restrictions.[59]

1.8.5: Xerostomia Quality of Life Scale (XeQoLS)

The XeQoLS is a 15-item quality of life assessment tool. This tool focuses on the effects xerostomia has on four quality of life domains including physical function, psychological function, social function, and pain concerns.[60]

1.8.6: Performance Status Scale – Head & Neck (PSS-H&N)

The PSS-HN scale scores patients' quality of life based on three domains. This tool was developed to assess speech and swallowing concerns in patients undergoing treatment for head and neck cancer. The domains being assessed include; normalcy of diet, public eating and understandability of speech.[61]

1.8.7: Functional Assessment of Cancer Therapy – Head & Neck (FACT-H&N)

The FACT-H&N consists of 27 core and 12 head and neck cancer specific questions. The core questions assess physical, social, emotional, and functional domains. All responses are rated on a five-point Likert scale from 0-4 with a higher score reflecting better quality of life.[62]

1.8.8: University of Washington Quality of Life Questionnaire (UW-QOL)

Developed at the University of Washington the UW-QOL assesses both disease specific symptoms as well as general quality of life measures. Disease specific questions relate to pain, appearance, activity, eating, speech, saliva, shoulder function and psychosocial aspects.[62]

1.8.9: Eating Assessment Tool-10 (EAT-10)

The EAT-10 tool is used to assess patient's self-perceived swallowing impairment. The tool consists of ten questions assessed on a five-point Likert scale with a higher score indicating a more severe problem. Questions focus on swallowing issues which may have resulted in; weight loss, social issues, eating, medication administration and stress.[63]

1.8.10: M. D. Anderson Dysphagia Inventory (MDADI)

The MDADI is a 20-item questionnaire that is used to assess patient's views on their swallowing ability. The questionnaire is divided into one global question regarding the

effect their swallow has on their day-to-day activities. The remainder of the questionnaire focuses on emotional, functional, and physical effects of their swallow. Each question is scored on a five-point Likert scale from strongly agree to strongly disagree.[64]

1.9: Post-treatment surveillance

The National Comprehensive Cancer Network (NCCN) guidelines[23] recommend regular clinical follow-up including history and physical examination for head and neck cancer as follows:

- Every one to three months for the first year
- Every two to six months for the second year
- Every four to eight months for years three to five
- Yearly after five years

Follow-up imaging is generally guided by the clinical assessment given most recurrences are identified by patient reported symptoms.[23] CT or Magnetic Resonance Imaging (MRI) scans can be performed within three to four months following surgery in cases where distorted anatomy may cause challenges with clinical assessment and provide a baseline for future comparison. FDG PET/CT is also recommended at three to six months post definitive (chemo)radiotherapy to assess treatment response and presence/absence of residual tumour.[23] FDG PET/CT prior to 12 weeks post treatment is associated with a higher rate of false positive scans and should be avoided.[23]

1.10 Endpoint measures used in cancer research

Endpoint measures in the management of cancer in general help to guide clinicians and patients towards the most appropriate treatment options. Overall survival has been the gold standard primary endpoint used in research to compare the efficacy of various treatments.[65] The most utilised survival endpoints identified in our search of the literature are described below.

- Overall survival (OS): defined as time from treatment commencement to date of death from any cause.
- Progression free survival (PFS): defined as time from treatment commencement to the date of recurrence of disease and classified into 3 subgroups; local, regional, and distant.
- Disease free survival (DFS): defined as time from treatment commencement to the date of death from the disease or recurrence of

the disease.

- Disease specific survival (DSS): defined as time from treatment commencement to the date of death from disease or direct effects of treatment of the disease.

1.11 Context of this systematic review

The objective of this systematic review and meta-analysis was to assess the survival outcomes of patients with HPV+ OPSCC treated with reduced dose (de-escalated) compared to standard dose radiation therapy. The current recommended standard treatment dose for primary and adjuvant radiation therapy for HPV+OPSCC is at least 66Gy and 60Gy respectively.[23] Treatment with doses lower than this recommendation will herein be referred to as reduced dose (de-escalated) radiation therapy. The hypothesis of this work is that delivering a reduced dose of radiation therapy to these patients can achieve similar oncological outcomes, whilst reducing the number of treatment-associated adverse events. A preliminary search of the JBI Evidence Synthesis, the Cochrane library, Medline, Embase and CINAHL found four recent systematic reviews of de-escalated radiation therapy in OPSCC.[20, 46, 66, 67] These reviews were conducted in 2014, 2018, 2020 and 2021 and are summarised in Table 3. The other forms of de-escalated therapy in HPV+ OPSCC including omission of Chemotherapy or replacement of Cisplatin with Cetuximab are outside the scope of this systematic review.

Table 3: Existing reviews identified in the literature

Author	Year published	Search conducted	Grey literature	Protocol	Bias assessment	RCT only	Meta-analysis	Studies included
Masterson[46]	2014	March 2014	Yes	No	Not for de-escalated treatment	Yes	Not for de-escalated treatment	Ang 2010 RTOG-1016 Ang 2011 De-ESCALaTE NCT01855451 NCT01084083 NCT01133678 NCT01706939 NCT01687413 NCT01898494 PATHOS Rischin 2010 Posner 2011 Gillison 2012
Howard[20]	2018	April 2018	Yes	Yes, published	No	Yes	No	No studies met inclusion criteria
Patel[66]	2020	September 2019 – no formal search strategy presented	No	No	No	No	No	Chera 2018 Chera 2019 Marur 2017 Chen 2017 Seiwert 2019 Misiukiewicz 2019 Gillison 2019 Mehanna 2019 Lee 2016 Ma 2019

Iorio[67]	2021	June 2020	No	No	No	No	No	Mehanna 2019 Seiwert 2019 Chen 2017 Hedge 2018 Misiukiewicz 2019 Chera 2019 Lee 2016 Swisher-McClure 2020 Gillison 2019 Marur 2017 Chera 2015 Nichols 2019 Ma 2019 Yom 2019 Ferris 2020 NCT01855451 NCT03799445 NCT03416153 QoLATI ORATOR2 PATHOS DART-HPV ADEPT

These previous systematic reviews were limited in scope, methodologically flawed, and/or are now out of date. The Cochrane systematic review from 2018 was the most rigorously conducted previous systematic review yet found no high-quality evidence comparing standard dose radiation therapy with de-escalated radiation therapy,[20] and there was no formal evidence synthesis presented for the studies that were identified as being "in-progress" at that time of the search. Additionally, there was no evidence that this review was in the process of being updated by the original author team. The systematic review from 2014 identified 14 studies for inclusion. Of these, nine were currently in progress without data for meta-analysis. The remaining five studies underwent a bias assessment and meta-analysis but did not provide data that compares de-escalated to standard radiation therapy. The systematic review published in 2020 provided no formal search strategy,[66] and was subsequently considered as not being credible according to the criteria established by the GRADE (Grading of Recommendations Assessment, Development and Evaluation) working group.[68] Additionally, both this review, and the review conducted in 2021 did not present a meta-analysis, GRADE Summary of Findings table or Evidence Profile, and did not establish the certainty of the synthesized evidence.[66, 67]

This review aims to build on these existing reviews utilising a formalised process following established JBI methodology.[69] An up to date search across a wider selection of databases will be conducted. Data from included studies will be extracted and pairwise meta-analyses performed. Appropriate critical appraisal tools will be used to assess the risk of bias of the included studies and a GRADE certainty of evidence rating will be assigned for each outcome synthesised. The findings of this review may assist in guiding not only the safety of de-escalated radiation therapy for the treatment of HPV+ OPSCC but also provide insight into the improved survival and quality of life for these patients. These findings may assist in the implementation of new guidelines on the appropriate management for this group of patients and will identify areas for future research.

1.12 Overview and importance of evidence synthesis and the systematic review of literature

With an ever-increasing amount of primary research being conducted, consolidating this information into succinct clinical recommendations is crucial for decision-makers.[70] In the consideration of evidence-based practice and clinical decision-making information is

sought not only to provide evidence as to the effectiveness of an intervention under investigation, but is also sought to consider the context in which the decision is being made, preferences of the patient and the professional judgement of the attending physician.[71] Sackett (1996) described evidence based medicine as "the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients". Whilst acknowledging the need for the best available evidence, Sackett (1996) also highlighted the roles that clinical expertise as well as the informed consent of the patient, play in the delivery of healthcare. Pearson (2005) supported these comments whilst stressing the importance of also considering the feasibility, appropriateness and meaningfulness of the intervention.[73] Treatment for OPSCC has changed significantly over the last century as has been described earlier with various forms of surgical and non-surgical management options now available. This, alongside the advances in our understanding of the pathogenesis of OPSCC and the role of HPV, treatment response and updated clinical staging systems has resulted in a divisive landscape regarding the optimal treatment strategy for the management and care for HPV+ OPSCC. For this reason, synthesising the available evidence in a systematic review of the literature becomes important for guiding updated clinical management and further research. This is reflected in the JBI evidence-based healthcare model. This model describes five generally sequential major steps required to achieve an evidence-based approach to clinical decision-making (Figure 3).[74] These include; global health, evidence generation, evidence synthesis, evidence transfer and evidence implementation, with the systematic review forming a major component of the evidence synthesis hierarchy. Traditional literature reviews are often characterised by poor methodology that lack reproducibility and transparency, this leads to an increased risk of bias and systematic error. In contrast, a systematic review aims to minimise any potential bias by following clearly defined, peer-reviewed and scientifically accepted methodological steps.[75] Appropriately conducted systematic reviews (of interventions) can also facilitate the construction of synthesised data estimates through meta-analysis. A meta-analysis is the quantitative synthesis of data from two or more homogenous studies. A meta-analysis provides an estimate of the average effect of an intervention accompanied by the associated confidence interval, assessment of heterogeneity of results between studies and the impact of these differences.[75] Performing a rigorous systematic review of interventions and meta-analysis of randomised controlled trials allows for the synthesis of evidence that will estimate the true effect of an intervention to a greater extent than any single study alone.[76] A well conducted systematic review

and accompanying meta-analysis is critically required for the management of HPV+ OPSCC moving forward.

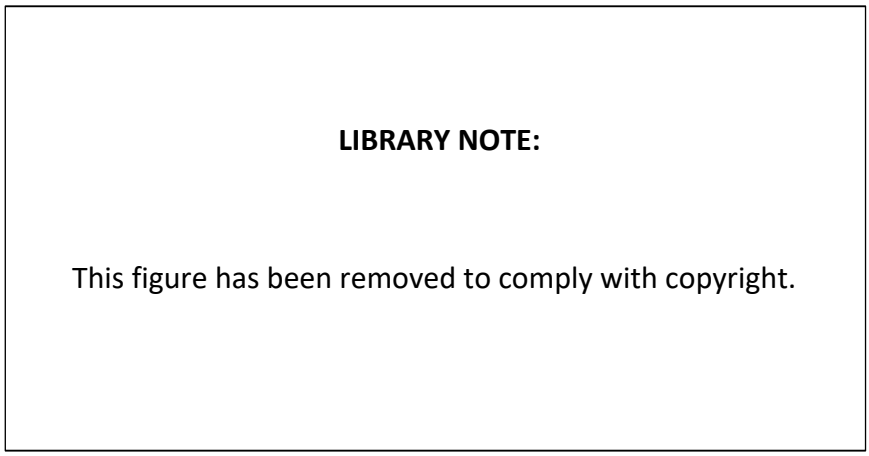

Figure 3: JBI model of Evidence-Based Healthcare
From "Redeveloping the JBI Model of Evidence-Based Healthcare" Jordan et al. 2018.[74]

1.12.1: Systematic review methodology

For a systematic review to successfully provide an unbiased synthesis of existing knowledge regarding a specific topic, it must be reported and conducted with rigour and transparency. To ensure that systematic reviews are reported consistently and to the highest possible standard, all systematic reviews must adhere to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 statement.[77] This statement is a 27-item checklist used to guide the reporting of the systematic review and to ensure that key methodological necessities of the review process are not missed.[77] The purpose of the PRISMA 2020 statement is to promote transparent and accurate reporting in systematic reviews.[77] The review methodology itself consists of a series of steps and methodological requirements sensitive to the type of review being

conducted. While all systematic reviews are expected to adhere to the PRISMA 2020 statement, the specific methodology followed may be different depending on the nature of the question being asked, and therefore, the nature of the systematic review itself. Regardless of the type of systematic review being conducted, all high-quality systematic reviews should begin with the development of an *a priori* systematic review protocol. Undertaking and publishing an *a priori* protocol is an important step in the review process as it provides a transparent overview of the aims and methods to be followed for the proposed systematic review. This in turn decreases the potential for reporting bias with any deviations from the protocol ideally being addressed in the systematic review itself.[78] Systematic reviews that are associated with a registered systematic review protocol (through PROSPERO) are associated with a higher review quality.[79]

Subsequent key methodological steps of the systematic review also include the generation of a specific research question. The research question presented in a systematic review follows a structured framework, according to the type of systematic review being conducted. For example, systematic reviews of interventions typically follow the PICO framework. This identifies the Population, Intervention, Comparison and relevant Outcomes. A defined set of inclusion and exclusion criteria are created and linked to each component of the PICO question, this then guides which studies are selected for review based on a search of multiple databases. Ideally two or more independent reviewers should be involved in the process of screening studies, following their retrieval from searching the literature. Screening occurs at the Title and Abstract stage as well as the Full text review stage. Two reviewers then perform critical appraisal in parallel. Critical appraisal tools are used to assess the risk of bias and methodological quality for each included study. Relevant data is extracted from included studies and synthesised either through meta-analysis of quantitative results or narrative synthesis (for intervention-based reviews). The results of the systematic review are finally displayed in a GRADE summary of findings table or evidence profile.

1.13 Assumptions and limitations

Despite the inherent ability for systematic reviews to consolidate and assess the certainty of the available evidence, their findings are reliant on the quality of the individual studies included. For HPV+ OPSCC, most of the research into improved survival in these patients and de-escalation of treatment over the last decade is based on observational studies, which are associated with inherent increased risks of bias. More

recently however, experimental studies (RCTs, cRCTs, stepped-wedge trials) and quasi-experimental studies addressing this clinical equipoise have contributed to this gap in knowledge.

Chapter 2: Methods

2.1 Statement of review question

What is the effectiveness of reduced dose versus standard dose radiation therapy on survival and radiation associated toxicity in patients with newly diagnosed Human Papillomavirus associated Oropharyngeal Squamous Cell Carcinoma.

2.2: Criteria for considering studies for this review

2.2.1: Types of participants

This review has considered studies that have included adult patients (aged 18 years or older) who have been treated with curative intent for Human Papillomavirus associated Oropharyngeal Squamous Cell Carcinoma of any clinical stage using either the seventh or eighth edition AJCC staging manual.

Exclusion criteria are:

- pre-clinical or animal based studies;
- studies with patients with non-SCC lesions of the oropharynx;
- studies with patients with primary lesions in other head and neck sites (eg. hypopharynx, nasopharynx, oral cavity, or larynx);
- studies with patients being treated with palliative intent; and
- studies patients with metastatic disease at the time of diagnosis

2.2.2: Types of interventions

This review has considered studies that have investigated an intervention of either de-escalated (dose-reduced) primary (<66Gy) or adjuvant (<60Gy) radiation therapy.

2.2.3: Types of comparators

This review has considered studies that have compared the intervention to a comparator of either standard-dose primary (≥66Gy) or adjuvant (≥60Gy) radiation therapy.

2.2.4: Outcomes

The review has considered studies that include data on the following primary and secondary outcome measures as defined in section 1.10.

Primary outcomes:

- Overall survival
- Progression-free survival
- Disease-free survival
- Disease-specific survival
- Radiation-associated toxicity

Secondary outcomes:

- Hospital re-admissions secondary to disease or treatment related effects
- Patient-reported quality of life after treatment initiation

2.2.5 Types of studies

As specified in the published protocol for this systematic review[80] the review team initially limited including studies into this review to only those that employed an experimental or quasi-experimental design. However, given the limited number of these studies that were identified, we have also included observational analytical studies. Studies published in any language and in any year have been considered for inclusion in this review.

2.3 Review Methods

2.3.1: Search strategy

The search strategy aimed to locate both published and unpublished studies. A three-step search strategy was conducted. Firstly, an initial search of MEDLINE was undertaken to identify articles on the topic. The text words contained in the titles and abstracts of relevant articles, and the index terms used to describe the articles, were used to develop a full search strategy as outlined below for PubMed:

Search ((Pharynx[mh] OR Palatine tonsil[mh] OR Squamous cell carcinoma of head and neck[mh] OR Throat*[tiab] OR Tonsil*[tiab]) AND (Neoplasms[mh] OR Cancer[tiab])) OR (Oropharyngeal neoplasms[mh] OR Oropharyngeal neoplasm*[tw] OR Oropharyngeal cancer[tw] OR Oropharyngeal carcinoma[tw] OR Oropharyngeal SCC[tw] OR Oropharyngeal Squamous cell carcinoma[tw] OR Oropharyngeal tumo*[tw] OR oropharynx cancer*[tw] OR Oropharynx neoplasm*[tw] OR Oropharynx carcinoma[tw] OR Oropharynx tumo*[tw] OR Oropharynx squamous cell carcinoma*[tw] OR

Oropharynx SCC[tw] OR Tonsillar Neoplasm*[tw]) AND (Deescalat*[tiab] OR De escalat*[tiab] OR De-escalat*[tiab] OR De-intensif*[tiab] OR De intensif*[tiab] OR Deintensif*[tiab] OR Dose reduc*[tiab]) AND (Radiotherapy[mh] OR Chemoradiotherapy[mh] OR Chemoradi*[tiab] OR Chemo-radi*[tiab] OR Radiochemotherapy[tiab] OR Radio-chemotherapy[tiab] OR Radiation therapy[tiab] OR Radiotherapy Dosage[mh] OR Radiation Dosage[mh])

Secondly, the search strategy, including all identified keywords and index terms, was adapted for each included database (see Appendix 2). Finally, the reference lists of all studies selected for critical appraisal were screened for additional studies. The databases searched included: MEDLINE (PubMed and Ovid), CINAHL (EBSCO), Embase (Elsevier), Web of Science, and Scopus. Gray literature will be searched through the Cochrane Register of Controlled Trials (CENTRAL), Scirus, MedNar, ClinicalTrials.gov, World Health Organization International Clinical Trials Registry Platform, and ProQuest.

2.3.2: Study selection

Following the search, all identified citations were collated and uploaded into EndNote v.X8 (Clarivate Analytics, PA, USA) where duplicates were removed. Citations were subsequently uploaded to Covidence to facilitate study screening. Two independent reviewers (TJL, GK) assessed studies at the title and abstract level on their relevance to the systematic review against the eligibility criteria listed in section 2.2. Where available, full texts of relevant studies were retrieved. Two independent reviewers (TJL, THB) reviewed the available full texts against inclusion criteria. Pilot testing was conducted prior to undertaking both title and abstract and full text screening. The screening process was conducted twice as described in section 2.2.5. Reasons for excluding studies at the full text review stage were grouped and documented in Appendix 3 and Appendix 4.

2.3.3: Assessment of risk of bias

Two independent reviewers (TJL, THB) performed an initial pilot test of the critical appraisal instruments used to assess the risk of bias of eligible studies. The Cochrane Risk of Bias 2 (RoB 2) tool was used for RCTs.[81] The Risk of Bias in Non-randomized Studies – of Interventions (ROBINS-I) tool was used for pseudo-randomized controlled trials, quasi-experimental trials, and observational studies.[82] The two reviewers

subsequently performed critical appraisal at the result level for risk of bias assessment. Discrepancies between assessments were resolved through discussion between the two reviewers (TJL, THB). All authors of eligible studies were contacted to assess if additional data was available (see Appendix 5). The results of the critical appraisal were not used for the purposes of further study exclusion.

2.3.4: Data extraction

A data extraction sheet was developed on Microsoft Excel (Redmond, Washington, USA) and has been provided as Appendix 6 and Appendix 7. Two independent reviewers performed data extraction (TJL, THB). The data extracted for each study included study methods, study populations, intervention and comparator treatments and outcomes of interest. Quantitative survival outcome data was extracted and reported as percentages with confidence intervals where available. Where Kaplan-Meier curves were used to present survival outcomes, we utilized the PlotDigitizer online software to extract survival data for relevant time points.[83]

2.3.5: Data synthesis

Studies were grouped as outlined below so that populations treated with specific co-interventions were assessed only when the comparator group had received the same co-intervention.

1. Induction chemotherapy with subsequent reduced dose (chemo)radiotherapy versus standard dose (chemo)radiotherapy
2. Primary surgery with adjuvant reduced dose (chemo)radiotherapy versus adjuvant standard dose (chemo)radiotherapy
3. Primary reduced dose (chemo)radiotherapy versus standard dose (chemo)radiotherapy

All meta-analyses were conducted using RevMan v5.4 (Copenhagen: The Nordic Cochrane Centre, Cochrane). Effect sizes were expressed as either hazard ratios (for time-to-event outcomes), relative risks (for dichotomous outcomes), or weighted (or standardized) final post-intervention mean differences (for continuous outcomes) with their 95% confidence intervals. Heterogeneity was assessed using both the standard χ^2 (Cochran's Q test) and the I^2 statistic. The fixed effects model was used given the limited number of studies identified and in accordance with guidance from Tufanaru (2015).

When sufficient comparative data was not available for meta-analysis, data was narratively synthesized and graphically presented using figures and tables. Funnel plots were not generated as there were less than ten studies included in the final meta-analyses performed.

Chapter 3. Results

This chapter will present the summary of findings tables and discuss in detail the results of the systematic review and critical appraisal.

3.1 Summary of findings

Table 4: Summary of findings - Induction chemotherapy with subsequent reduced dose (chemo)radiotherapy versus standard dose (chemo)radiotherapy

Patient or population: Patients undergoing treatment with induction chemotherapy with subsequent (chemo)radiotherapy for HPV+OPSCC
Intervention: Reduced dose radiation therapy (<66Gy)
Comparison: Standard dose radiation therapy (≥66Gy)
Authors: Misiukiewicz[85]

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IC + Reduced Dose + CRTx	IC + Standard Dose + CRTx	Relative (95% CI)	Absolute (95% CI)	
2-3 year Overall survival											
1	randomised trials	not serious	not serious	not serious	very serious[a,b]	none	10/12 (83.3%)	7/8 (87.5%)	**HR 1.26** (0.11 to 14.43)	**52 more per 1,000** (from 671 fewer to 125 more)	⨁⨁◯◯ Low
2-3 year Progression free survival											
1	randomised trials	not serious	not serious	not serious	very serious[a,c]	none	10/12 (83.3%)	7/8 (87.5%)	**HR 1.46** (0.13 to 16.40)	**77 more per 1,000** (from 638 fewer to 125 more)	⨁⨁◯◯ Low

CI: confidence interval; **HR:** hazard Ratio

Explanations

a. Optimal information size (1109): small sample size
b. Confidence interval: 95% CI are very wide (from 671 fewer to 125 more) and cross a potentially important decision making threshold (line of no effect).
c. Confidence interval: 95% CI are very wide (from 638 fewer to 125 more) and cross a potentially important decision making threshold (line of no effect).

Table 5: Summary of findings - Primary surgery with adjuvant reduced dose (chemo)radiotherapy versus adjuvant standard dose (chemo)radiotherapy

Patient or population: patients undergoing treatment with primary surgery with adjuvant (chemo)radiotherapy for HPV+OPSCC
Intervention: Reduced dose radiation therapy (<60Gy)
Comparison: Standard dose radiation therapy (≥60Gy)
Authors: Moore[86], Riaz[87]

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgery + Reduced Dose	Surgery + Standard Dose	Relative (95% CI)	Absolute (95% CI)	
3-year overall survival											
2	observational studies	very serious[a,b]	not serious	not serious	serious[c,d]	none	88/94 (93.6%)	109/119 (91.6%)	**RR 1.04** (0.96 to 1.12)	**37 more per 1,000** (from 37 fewer to 110 more)	⨁◯◯◯ Very low
2-year overall survival											
1	randomised trials	very serious[a]	not serious	not serious	serious[c,e]	none	13/15 (86.7%)	4/4 (100.0%)	**RR 0.94** (0.65 to 1.34)	**60 fewer per 1,000** (from 350 fewer to 340 more)	⨁◯◯◯ Very low
3-year progression free survival											
2	observational studies	very serious[a,b]	not serious	not serious	serious[c,f]	none	81/94 (86.2%)	106/119 (89.1%)	**RR 0.97** (0.87 to 1.08)	**27 fewer per 1,000** (from 116 fewer to 71 more)	⨁◯◯◯ Very low
2-year progression free survival											
2	observational studies	very serious[a,b]	not serious	not serious	serious[c,g]	none	84/94 (89.4%)	107/119 (89.9%)	**RR 0.99** (0.40 to 2.42)	**1 fewer per 1,000** (from 118 fewer to 57 more)	⨁◯◯◯ Very low

CI: confidence interval; **OR:** odds ratio; **RR:** risk ratio

Explanations

a. Riaz: Treatment group allocation based on imaging features. Study followed a per protocol analysis. Reporting bias in that trial registration did not mention locoregional control, progression free survival, overall survival, treatment related toxicity and patient reported outcome measures as primary or secondary outcomes of the trial. All of these outcomes have however been reported in the manuscript.
b. Moore: Retrospective cohort study with potential for confounding. Due to inappropriate control of confounding factors there us a moderate risk of bias for this study across outcomes.
c. Optimal information size: small sample size
d. Confidence interval: 95% CI are very wide (from 37 fewer to 110 more) and cross a potentially important decision making threshold (line of no effect).
e. Confidence interval: 95% CI are very wide (from 350 fewer to 340 more) and cross a potentially important decision making threshold (line of no effect).
f. Confidence interval: 95% CI are very wide (from 116 fewer to 71 more) and cross a potentially important decision making threshold (line of no effect).
g. Confidence interval: 95% CI are very wide (from 118 fewer to 57 more) and cross a potentially important decision making threshold (line of no effect).

Table 6: Summary of findings - Primary reduced dose (chemo)radiotherapy versus standard dose (chemo)radiotherapy

Patient or population: patients undergoing treatment with primary (chemo)radiotherapy for HPV+OPSCC
Intervention: Reduced dose radiation therapy (<66Gy)
Comparison: Standard dose radiation therapy (≥66Gy)
Authors: Smith[88], Tam[89]

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RTx + Reduced Dose	RTx + Standard Dose	Relative (95% CI)	Absolute (95% CI)	
2-3 year Overall survival											
2	observational studies	serious[a,b]	not serious	not serious	serious[c]	none	118/135 (87.4%)	1822/2067 (88.1%)	**RR 1.02** (0.96 to 1.09)	**18 more per 1,000** (from 35 fewer to 79 more)	⨁⨁◯◯ Low

CI: confidence interval; **RR:** risk ratio

Explanations

a. Smith: No randomisation is suspected. Authors suggest this is a case series however this is a parallel-group trial, with participants assigned to groups based on researcher selection. 40 patients included, only 29 had data, 11 were excluded for; insufficient follow-up, lack of evaluable swallowing data (early death, refusal to participate or local failure)
b. Tam: retrospective cohort study with potential for confounding
c. Confidence interval: 95% CI are very wide (from 35 fewer to 79 more) and cross a potentially important decision making threshold (line of no effect).

3.2 Description of search strategy and study selection

The database searching identified 2308 individual records, 1258 duplicates were removed. 1014 records were excluded based on review of titles and abstracts. Full text review was completed for 36 studies, of which 29 were excluded with reasons recorded (Appendix 3). Given the limited number of experimental and quasi-experimental studies identified the title and abstract screen was re-conducted to include observational analytical studies. Another 23 studies underwent assessment at full-text level, of which 14 were excluded, see Appendix 4. The total number of studies included was 16. Critical appraisal was conducted for the 16 included studies. No further studies were excluded based on the critical appraisal findings. The study selection process has been presented in Figure 4 - PRISMA diagram.

3.3 Prisma diagram

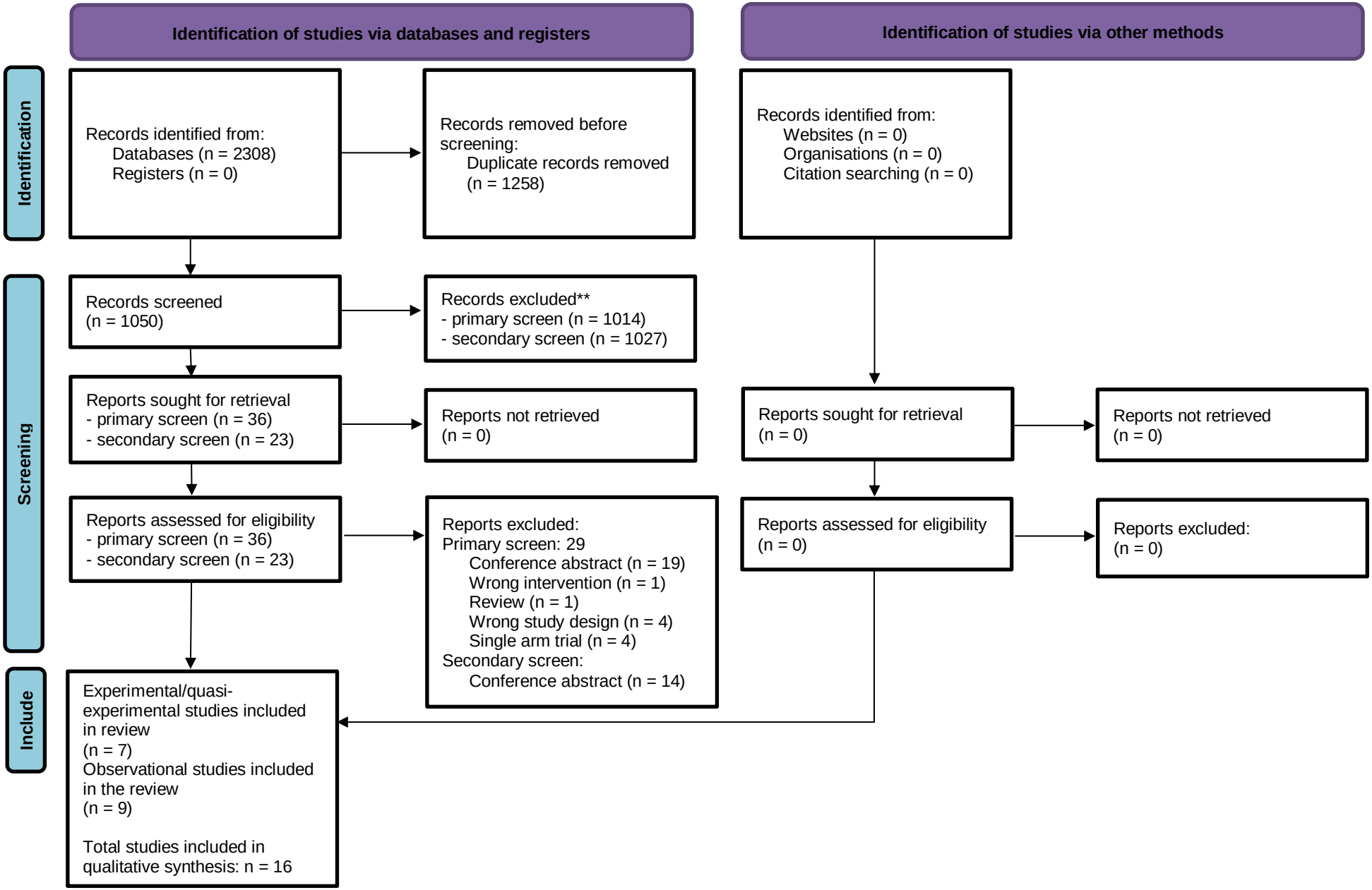

Figure 4: PRISMA 2020 flow diagram

3.4 Characteristics of included studies

3.4.1 Geographical location

There were 16 publications from 13 separate studies were included in the review. All the included studies were conducted across the United States. Five of the thirteen studies were conducted out of the Eastern States. Four were from New York[85, 87, 88, 90] and one from North Carolina.[91] Four studies used data from the National Cancer Database (NCDB).[89, 92-94] The NCDB is a program run by the American College of Surgeons Commission on Cancer and the American Cancer Society. This database catches around 70% of all newly diagnosed cancers across America.[95] The final four studies were conducted out of California[96], Chicago[97] and Rochester[86, 98].

3.4.2 Study participants

Across these studies, 5802 patients were included of which 85% were male. Patients' age at diagnosis ranged from 22 to 90 years old with median ranging from 56.5 to 62 years old across studies.[85, 89, 99] For most studies, patients were enrolled between 2003 and 2019. The exception was a study of primary chemoradiotherapy by Smith (2004) commencing in 1995.

The included studies had heterogeneous inclusion criteria when considering cancer staging. Fifteen studies used the 7th edition cancer staging manual.[55, 85-91, 93, 94, 96-100] Of these studies, seven included only patients with stage III-IV OPSCC while eight included patients with stage I-IV OPSCC. Only one of the fifteen studies also commented on re-staging with the 8th edition criteria.[90] Miles (2021) included 53 patients with 7th edition stage I-IVa OPSCC, all of which when re-staged with the 8th edition were classified as stage I. Cramer (2018) conducted the only study that reported on patients cancer stage using only the 8th edition criteria. No studies included patients with metastatic disease at the time of diagnosis.

Baseline performance status was assessed using the Eastern Cooperative Oncology Group (ECOG) score, also known as Zubrod score. Nine studies required an ECOG score of 0-1 for inclusion.[55, 85, 90, 91, 96-100] The remaining seven studies did not report on performance status.

Many studies did not report on either smoking or alcohol consumption as part of their exclusion criteria or when reporting their results. One study excluded active smokers and three studies excluded smokers with a greater than 10-pack year history.[85, 86, 91, 98] One additional study excluded patients with a greater than 20 pack year history or if they had smoked one cigarette or more daily for at least five years.[90] Only two studies screened patients based on alcohol consumption, excluding patients with an active alcohol addiction.[85, 90]

3.4.3 Testing for HPV status

Twelve of the sixteen studies recorded the method of identifying HPV status.[55, 85-87, 90, 91, 94, 96-100] In all twelve studies p16 IHC was used. Only three studies however outlined that >70% staining on IHC was required to consider the test p16 positive.[86, 87, 98] It was not clear if the remaining studies used a similar of different cut off. Five of these studies also considered alternative testing for HPV status. Judy (2018) included patients who were HPV or p16 positive however did not comment on how HPV positivity was determined.[91] Miles (2021) used p16 IHC as an initial test that they subsequently confirmed with HPV PCR.[90] The cohort of patients recruited by Seiwert (2019) also initially underwent p16 IHC and subsequent confirmation with a nucleic acid-based assay for E6/E7 (HPV PCR).[55, 97] White (2020) accepted HPV16 or HPV18 ISH and/or p16IHC as a marker of HPV positivity.[94]

3.4.4 Treatment types

Three main de-escalation treatment strategies have been reviewed as highlighted and discussed below.

1. Induction chemotherapy with subsequent reduced dose (chemo)radiotherapy versus standard dose (chemo)radiotherapy
2. Primary surgery with adjuvant reduced dose (chemo)radiotherapy versus adjuvant standard dose (chemo)radiotherapy
3. Primary reduced dose (chemo)radiotherapy versus standard dose (chemo)radiotherapy

3.4.5 Methodological quality of included studies

Two critical appraisal tools were used to assess the risk of bias of the included studies. The RoB2 tool was used for the eight included experimental/quasi-experimental studies. The ROBINS-I tool was used for the six included observational studies. All studies underwent critical appraisal by two independent reviewers (TJL, THB) with any discrepancies resolved with discussion. Risk of bias assessments have been presented in Table 7 and 8 as well as Figure 5 and Figure 6. A detailed summary of the risk of bias for each outcome of the included studies is available in Appendix 8 and Appendix 9.

The overall risk of bias for the included experimental and quasi-experimental study outcomes was either 'some concerns' (83.3%) or 'high risk' (16.7%). The main sources of bias in the included studies arose from the randomization processes conducted (high risk in 100%)[85, 87, 88, 90, 96-99] and deviations from intended interventions (some concerns in 41.7%).[87, 96, 99] Less frequently noted was a high risk of bias in the measurement of the individual outcomes.[90, 98, 99]

In regards to the randomisation process, this was not clarified in detail for two of the studies.[85, 88] The other six studies followed a quasi-experimental study design with patients assigned to either standard or reduced dose radiation therapy based on their initial treatment response (i.e. this was not true randomisation). Three studies followed a per protocol analysis which raised some concerns regarding bias due to missing participants in these studies.[87, 96, 99] All other studies used an intention to treat analysis.[85, 88, 90, 97, 98] There were no significant concerns in regards to missing outcome data and this was assessed as low risk of bias. The majority of outcomes were survival outcomes that were deemed unlikely to have been influenced by knowledge of the intervention and were therefore considered a low risk of bias. The only outcomes at high risk of bias occurred where patient reported outcomes were assessed and knowledge of the treatment assigned may have introduced bias.[90, 98, 99] Risk of bias in regards to selection of the reported results was low across all studies.

The overall risk of bias for the included observational analytical studies was low in 50%, moderate in 33% and high in 17%. The main source of bias was from moderate/serious confounding in 34% of studies. Moore (2021) did not specify any covariates in their study resulting in a risk of serious confounding bias. Their study did present a comparison of the baseline characteristics between groups compared with Wilcoxon

rank/chi square/fishers exact test however these do not identify confounder status.[86] Similarly, the analysis performed by Judy (2018) did not address confounders. The remaining studies adequately identified and controlled for confounding factors.[89, 92-94] The selection of participants and classification of interventions for the included studies were generally extracted from the National Cancer Database based on treatment type and inclusion criteria and were low risk of bias. In regard to deviations from intended interventions, no specific details regarding deviations were presented for the included studies. Despite this, it was deemed the risk of bias was low for all studies given the nature of the interventions and outcomes assessed.[86, 89, 91-94] The risk of bias due to missing data was generally low given the objective nature of the survival outcomes and missing data being unlikely.[86, 89, 92-94] The exception to this was by Judy (2018) where baseline measurements were not presented for 13 patients treated in the standard dose cohort. This resulted in a moderate risk of bias.[91] Similarly, a moderate risk of bias was identified in the outcome measurement associated with the patient reported outcome measures presented by Judy (2018). For all other outcomes the risk of bias in outcome measurement was low.[86, 89, 92-94] Results were generally transparently reported across most studies using multiple types of analyses.[86, 89, 91, 93, 94] The primary consideration presented by Cramer (2018) however was to compare low versus high risk patients with the assessment of reduced versus standard dose radiation therapy conducted via a sensitivity analysis.

Table 7: Bias summary for studies critically appraised with the ROBINS-I tool

Bias summary								
Risk Assessment	Confounding	Participant selection	Classification of intervention	Deviations from intended interventions	Missing data	Outcome measurement	Result reporting	Overall
Low	67%	100%	83%	100%	83%	83%	83%	50%
Moderate	17%	0%	17%	0%	17%	17%	17%	33%
Serious	17%	0%	0%	0%	0%	0%	0%	17%

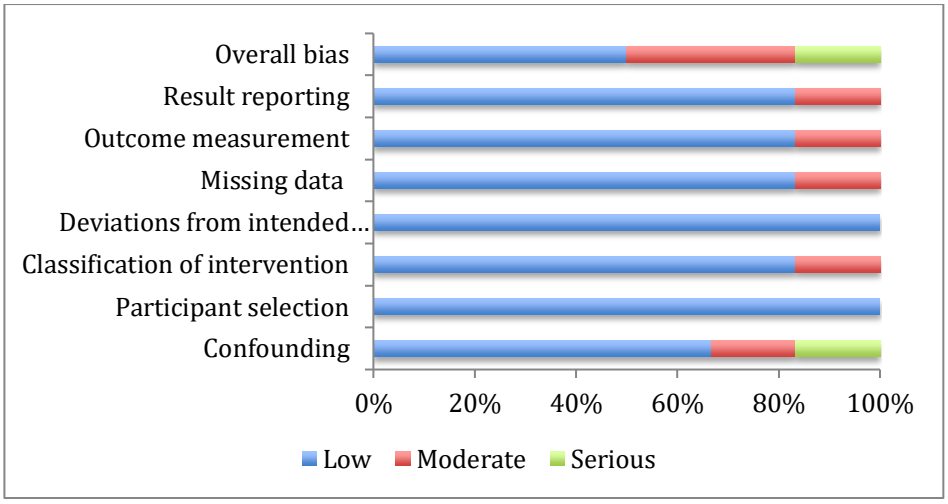

Figure 5: Bias summary for studies critically appraised with the ROBINS-I tool

Table 8: Bias summary for studies critically appraised with the ROB-2 tool

Bias summary						
Risk Assessment	**Randomization process**	**Deviations from intended interventions**	**Mising outcome data**	**Measurement of the outcome**	**Selection of the reported result**	**Overall Bias**
Low risk	0%	58.3%	94.4%	83.3%	94.4%	0%
Some concerns	0%	41.7%	0%	5.6%	2.8%	83.3%
High risk	100%	0%	5.6%	11.1%	2.8%	16.7%

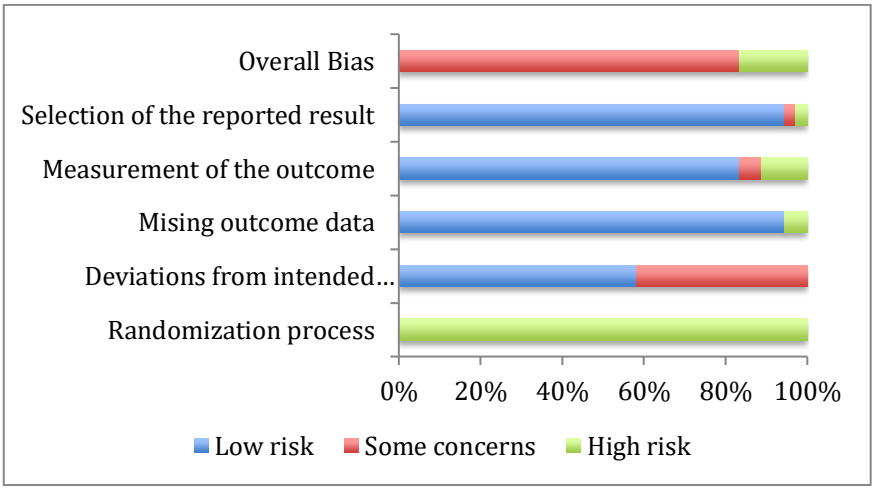

Figure 6: Bias summary for studies critically appraised with the ROB-2 tool

3.5 Induction chemotherapy with subsequent reduced dose (chemo)radiotherapy versus standard dose (chemo)radiotherapy

Six studies have been included in this review that assessed this comparison.[55, 85, 96, 97, 99, 100] Chen (2017) published the first study (NCT01716195). This was a multicentre phase II trial of 44 patients with stage III-IV OPSCC (AJCC 7th edition staging). Patients were treated with induction chemotherapy inclusive of two cycles of paclitaxel and carboplatin given 21 days apart. Response to induction chemotherapy was reported as complete or partial based on the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. The sum of maximal diameters of target lesions was assessed pre- and post-IC with complete and partial response classified as 100% and more than 30% reduction respectively. Patients then proceeded to treatment with response-based chemoradiotherapy comprising Paclitaxel and IMRT. Patients with a complete or partial response were treated with 54Gy in 27 fractions to the primary tumor. Patients with less than partial response were treated with 60Gy in 30 fractions to the primary tumor. Data was available for 2-year overall survival, 2-year progression free survival and treatment related toxicity. Patients were followed-up for a median of 30months (IQR 26-37months).[96] Hegde (2018) and Shaverdian (2019) performed separate analyses of this cohort focusing on patient reported outcome measures.[99, 100] These studies have been merged with the study by Chen 2017. The focus of the study by Hegde (2018) was to assess functional outcomes for the patients initially recruited in Chen (2017). This study used the University of Washington Quality of Life scale and the Functional Assessment of Cancer Therapy Head and neck scale as outcome measures. These patients were followed up for a median of 26-months (6-39-months).[99] Shaverdian (2019) also contributed to the analysis of data provided by this cohort. This study used the Chicago Priorities Scale and Decision Regret Scale to assess patient reported outcomes. Patients were followed-up for a median of 24 months (16-30-months).[100]

Misiukiewicz (2019) performed a single centre, phase III clinical trial of induction chemotherapy with subsequent chemoradiotherapy (NCT 01706939). This study compared 20 patients treated with either standard versus reduced dose radiation therapy. All patients had either stage III or IV HPV+ OPSCC (AJCC 7th edition staging) and a good baseline performance status (ECOG 0-1). HPV status was assessed using p16 IHC with a cut off of >75% nuclear staining of tumour cells required. Patients were treated with induction chemotherapy comprising three cycles of docetaxel, cisplatin and 5-fluorouracil. Patients with at least partial response based on RECIST 1.1 criteria were

randomized to standard (70Gy) or reduced dose (56Gy) radiation therapy. Patients were treated with daily IMRT at their assigned dosage with concurrent chemotherapy (carboplatin). Outcome measures of interest included overall survival and progression free survival. Hospital re-admissions were also reported on. Patients were followed-up for a median of 56-months (42-70).[85]

Seiwert (2019) conducted the final included trial under this comparison. This was a single centre phase II trial of induction chemotherapy with subsequent chemoradiotherapy (NCT 02258659).[97] This trial assessed 62 patients with HPV+ OPSCC staged as; T1-4, N2-3 or T3-4, any N-disease (AJCC 7th edition). All patients were ECOG 0-1. Prior to treatment patients classified as either low- or high-risk. Low risk patients were defined as T1-3, N0-2B unless bulky N2B conglomerate and ≤10 pack year smoking history. High risk patients had T4, N2C-3/bulky N2B disease or >10 pack year smoking history. All patients received induction chemotherapy with carboplatin and nab-paclitaxel. Patients were assessed post induction chemotherapy using the RECIST v1.1 criteria and separated into the following groups:

- low risk patients with ≥50% response: 50Gy radiation therapy alone
- low risk with <50% but ≥30% response and high risk with ≥50% response: chemoradiotherapy consisting of 45Gy radiation therapy and TFHX (paclitaxel, 5-fluorouracil, hydroxyurea)
- low risk with <30% response, high risk with <50% response or progression of disease: chemoradiotherapy consisting of 75Gy radiation therapy and TFHX

Radiation therapy was delivered using either VMAT or IMRT. Response to treatment was assessed four to eight weeks after completion by biopsy of the treated primary site or neck dissection. Outcomes of interest included overall survival, progression free survival and treatment-associated toxicity. Patients were followed-up for a median of 29-months (9-44).[97]

Foster (2020) contributed to the analysis of the patients included in the study by Seiwert (2019), and subsequently these studies have been merged. The focus of this study was to assess functional outcomes among this cohort.[55] Degree of penetration and/or aspiration during swallowing was assessed on Modified Barium Swallow. Swallow function was also assessed by a speech pathologist using the Swallowing Performance Status score. Diet and speech were further assessed with the Performance Status Scale for Head and Neck Cancer Patients. Patients were followed up for a median of 29.5 months.[55]

3.5.1 Primary outcomes

3.5.1.1 Overall survival

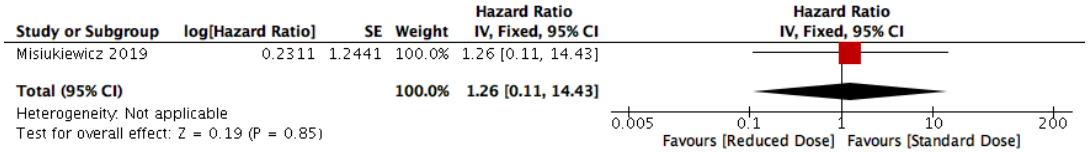

Figure 7: Forest plot of comparison, induction chemotherapy with subsequent reduced dose (chemo)radiotherapy versus standard dose (chemo)radiotherapy, 2-3 year overall survival

Quantitative data for overall survival was only available from one study comparing induction chemotherapy with standard versus reduced dose radiation therapy, Figure 7.[85] Overall survival was lower in the reduced dose (83.3%) compared to the standard dose (87.5%) radiation therapy group (HR 1.26, 95% CI 0.11 to 14.43), see Table 4. The findings were limited by the imprecision being driven by a small sample size (n=20) and optimal information size (n=1109) not having been met. Assessment of heterogeneity was not applicable given only one study was included for meta-analysis.[85]

3.5.1.2 Progression free survival

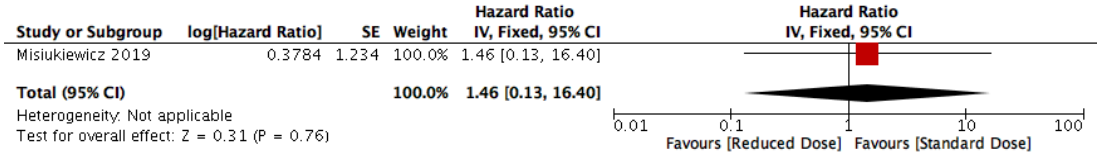

Figure 8: Forest plot of comparison, induction chemotherapy with subsequent reduced dose (chemo)radiotherapy versus standard dose (chemo)radiotherapy, 2-3 year progression free survival

Quantitative data for progression free survival was only available from one study comparing induction chemotherapy with standard versus reduced dose radiation therapy, Figure 8.[85] Progression free survival was lower in the reduced dose (83.3%) compared to the standard dose (87.5%) radiation therapy group (HR 1.46, 95% CI 0.13 to 16.40), see Table 4. The findings were limited by the imprecision secondary to small sample size (n=20) and optimal information size (n=1109) not having been met. Assessment of heterogeneity was not applicable given only one study was included for meta-analysis.[85]

3.5.1.3 Disease-free survival

No data was available for disease-free survival for this treatment group.

3.5.1.4 Disease-specific survival

No data was available for disease-specific survival for this treatment group.

3.5.1.5 Treatment related toxicity and adverse events

Two studies presented their assessment of treatment related adverse events.[96, 97] The reporting of results varied between these two studies in regards to types and grading of adverse events. For this reason a meta-analysis could not be conducted. In general the CTCAE was used to report on type and severity of adverse events. The use of induction chemotherapy prior to definitive chemoradiotherapy was associated most often with fatigue (87%), nausea (71%), anorexia (66%), blood dyscrasias (neutropenia in 60%, thrombocytopenia in 52%) and dysguesia (42%).[97] The majority of these adverse events were mild (grade 1-2) with no significant impact on treatment. The exception to this was grade 3 neutropenia in 36% of study participants.[97] The participants in this study subsequently underwent treatment with standard versus reduced dose (chemo)radiotherapy. Treatment groups included 50Gy radiation therapy alone (RT50), 45Gy radiation therapy with concurrent TFHX (CRT45) or 75Gy with concurrent TFHX (CRT75).[97] Acute grade three or higher muscositis (30% RT50, 63% CRT45, 91% CRT75 $p=0.004$) and dermatitis (0% RT50, 20% CRT45, 55% CRT75 $p<0.0001$) were the most common adverse events reported and were significantly lower in the reduced compared to standard dose group.[97]

Similar findings were reported by Chen (2017) with dysphagia, mucositis, pain and xerostomia being the most common adverse effects associated with chemoradiotherapy.

3.5.1.6 Objective swallow assessment (Modified Barium Swallow)

One study reported on the results of study participants undergoing a modified barium swallow assessment.[55] Foster (2020) reported that a larger number of patients treated with reduced dose radiation therapy (45 or 50Gy) compared to standard dose radiation therapy (75Gy) had a SPS score corresponding to swallowing function within normal

limits, 46% vs 22% respectively. In addition to this, a lower proportion of patients treated with reduced dose radiation therapy required therapeutic swallowing precautions or a modified diet compared to the standard dose arm, 21% vs 66% respectively.[55] The rate of post-treatment aspiration on MBS was also lower in those treated with reduced dose compared to standard dose radiation therapy (5% vs 33%; OR 0.11; 95%CI 0.01-0.79; p=0.04).[55]

3.5.1.7 Gastrostomy tube insertions

Four studies reported on the use of gastrostomy tubes.[55, 85, 96, 97] The reporting of gastrostomy tube use was heterogeneous in regards to indications, duration as well as comparisons between treatment groups. For this reason a meta-analysis could not be conducted and the results will be narratively synthesised. Where reported, the most common indications for gastrostomy tube insertion were either for treatment related dysphagia or prophylactically prior to treatment commencement.[96] The highest rate of gastrostomy tube insertions was in the cohort recruited in the OPTIMA trial.[97] None of the patients in this study underwent a prophylactic gastrostomy prior to the commencement of (chemo)radiotherapy.[97] Foster (2020) reported on the functional outcomes among this cohort whereby 9 of 11 patients (82%) who underwent standard dose radiation therapy (75Gy) required a gastrostomy tube.[55] The patients who underwent reduced dose radiation therapy (45Gy or 50Gy) had a significantly lower rate of requiring a gastrostomy tube (9 of 50, 18%, p<0.0001).[55, 97] This difference was noted to persist when assessed at 3-months following (chemo)radiotherapy. At this time 10% of those treated with reduced dose radiation therapy and 64% of those treated with standard dose radiation therapy still required their gastrostomy tube (p=0.0005). When assessed at 6- and 12-months post treatment this difference however was no longer significant.[55] Foster (2020) also compared the median duration the enrolled patients required their gastrostomy tube for. The median duration was significantly less in those treated with reduced dose compared to standard dose radiation therapy (3.2 vs 6.3months, p=0.0001).[55] Chen (2017) reported an overall rate of 14% (6/44) for patients requiring a gastrostomy tube. Of these three were inserted prior to and three subsequent to treatment commencement. The results in this study did not compare patients based on dose of radiation therapy.[96] Only one study reported a higher rate of gastrostomy tubes in those treated with reduced dose radiation therapy. Misiukiewicz (2019) reported 33% (4/12) of those who underwent reduced dose radiation therapy

required a gastrostomy tube compared to 25% (2/8) of those treated with standard dose radiation therapy.

3.5.2 Secondary outcomes

Multiple different instruments were used to assess and report on quality of life outcomes for this comparison. For this reason a meta-analysis could not be conducted for these outcomes and a narrative synthesis will follow.

3.5.2.1 Hospital readmissions

Only two studies reported on hospital readmissions during treatment.[85, 96] Chen (2017) reported two readmissions among their 44 patient cohort. Reasons for readmissions included one patient for aspiration pneumonia and one for anxiety/panic attacks. It was not specified if these patients were treated with reduced or standard dose radiation therapy.[96] Among the 20 patients recruited by Misiukiewicz (2019) there were five readmissions in four patients. Three readmissions in two patients in the standard dose radiation therapy arm were for syncope, dehydration and mucositis. The two patients who were readmitted in the reduced dose radiation therapy arm were for reasons of opioid overdose and mucositis/pain management.[85]

3.5.2.2 Patient reported outcome measures

Multiple patient reported outcome measures were used to assess quality of life. Outcome measures used to assess were general quality of life, swallow specific measures or xerostomia.

3.5.2.2.1 General quality of life

Hegde (2018) used the FACT-H&N questionnaire for their cohort and identified a progressive deterioration in quality of life over time. The median baseline FACT-H&N score for this cohort was 34. At 1- and 2-years post treatment this median had reduced to 32 and 29 respectively.[99] Hegde (2018) also used the UW-QOL to assess QOL amongst this same cohort. UW-QOL results were separated into three domains including swallow, physical and social. In all three domains, quality of life was seen to decline when measured at 4-weeks post-treatment compared to baseline. This decline

subsequently improved when re-assessed at 1- and 2-year follow-up, see Table 9. Results were not stratified by radiation therapy treatment dose.[99]

Table 9: UW-QoL domains as reported by Hedge 2018

Domain	Baseline	4-weeks post treatment	1-year post treatment	2-years post treatment
Swallowing	94.3	69.0	87.0	83.0
Physical	93.9	62.7	79.5	80.3
Social	78.0	69.9	89.4	88.6

Foster (2020) was the other study to assess general quality of life. This study used the PSS-H&N questionnaire to assess quality of life across three domains including diet, speech, and public eating. Fewer patients treated with reduced dose radiation therapy were found to have restrictions in these domains, see table 8.[55] The time point in relation to treatment was not reported.

Table 10: Proportion of patients requiring restrictions on daily activities as reported by Foster 2020

Domain	Reduced dose radiation therapy	Standard dose radiation therapy	p-value
Diet	16 (43%)	8 (89%)	0.33
Speech	0 (0%)	1 (11%)	N/A
Public eating	8 (22%)	5 (71%)	0.18

Restrictions on daily activities were defined as a score of <100 for each domain as measured using the PSS-H&N questionnaire.

3.5.2.2.2 Swallowing and oral intake

No data was available for swallowing specific patient reported outcomes for this treatment group.

3.5.2.2.3 Treatment priorities

Shaverdian (2019) utilized two further patient reported outcome measures to compare standard versus reduced dose radiation therapy. These included the Chicago Priorities

Scale and the Decision Regret Scale. For the majority (92%) across both treatment arms the number one treatment priority was 'being cured of my cancer'. The two patients who didn't have this as their main priority selected 'living as long as possible' and 'having no pain'.[100] The Chicago Priorities Scale was modified ('being cured of my cancer' and 'living as long as possible' removed) to assess the reasons why patients chose to undertake de-escalated therapy. The number one priority for 63% of these patients was 'being able to swallow all foods and drinks'. Other commonly selected priorities for selecting de-escalated treatment included; 'having no pain', 'having a comfortably moist mouth', 'returning to my regular activities as soon as possible' and 'keeping my normal sense of taste and smell'.[100]

When this cohort was asked about their treatment and results the majority (83%) responded that they were 'totally satisfied'. The remainder were 'somewhat satisfied' with none expressing any ambiguity or dissatisfaction. Supporting this finding was that 92% of patients also strongly disagreed with the statement, 'I regret the choice I made'. 75% strongly agreed to the statement 'I would go for the same choice if I had to do it again'.[100]

3.6 Primary surgery with adjuvant reduced dose (chemo)radiotherapy versus adjuvant standard dose (chemo)radiotherapy

Five studies have been included in this review that assessed this treatment option.[86, 87, 90, 92, 98] Cramer (2018) published the first study. This study was a retrospective review of 1677 patients treated with primary surgery with or without adjuvant radiation therapy or chemoradiotherapy between 2010 and 2013.[92] All patients with stage I HPV+ OPSCC (re-staged using AJCC 8th edition) were identified through the National Cancer Database. Patients were stratified into low- and intermediate-risk groups based on pathological features. For those receiving radiation therapy, the mean dose delivered to low- and intermediate-risk groups was 58.9Gy and 59.7Gy respectively. Surgical approaches included robotic (38.4%), endoscopic (9.7%), open (35.8%) and unknown (16%). The primary outcome of interest was overall survival. Patients were followed-up for a median of 43.9 months (0.6-80.8).[92]

Ma (2019) performed a single centre phase II trial between 2013 and 2016 of 79 patients undergoing treatment for HPV+ OPSCC.[98] All patients had stage III-IV OPSCC (AJCC 7th edition) and were ECOG 0-1. Patients initially underwent primary surgery with

the majority (n=75, 95%) being trans-oral operations. The other surgical approaches (n=4, 5%) included; hybrid transoral with transhyoid pharyngotomy and lip split mandibulotomy with radial free flap reconstruction. Outcomes of interest included locoregional control, progression free survival and overall survival. Median follow-up was 35.7 months (25.2 to 61.8).[98] Moore (2021) contributed to the results published by Ma (2019) by retrospectively comparing this existing cohort with a cohort of patients treated with standard dose adjuvant chemoradiotherapy.[86] The comparative standard dose adjuvant radiation therapy group consisted of 115 patients with HPV+ OPSCC with a ≤10 pack year smoking history. All patients within this group underwent primary Trans-Oral Robotic Surgery and neck dissection followed by adjuvant standard dose radiation therapy (60Gy IMRT) or chemoradiotherapy (60Gy IMRT with cisplatin). Outcomes of interest for this study included overall survival, progression free survival and disease free survival. Patients were followed-up for a median of 4.1-years (0.1-12.3-years).[86]

Miles (2021) performed a single centre non-randomised phase II trial of primary surgery and adjuvant dose reduced chemoradiotherapy.[90] This study assessed 53 patients treated for stage I-IVa (T1N0-2b, T2N0-2b) without extra-nodal extension (AJCC 7th edition) HPV+ OPSCC in 2014. When re-staged with the AJCC 8th edition all patients were stage I. HPV status was confirmed by >70% staining for p16 on IHC and confirmatory testing with HPV rtPCR. Patients had a good baseline performance status of ECOG 0-1. Active smokers (≥ 1 cigarette per day for five years or a >20 pack year smoking history) and those with an active alcohol addiction were excluded. Patients underwent primary Trans-Oral Robotic Surgery with selective neck dissection. Subsequent chemoradiotherapy was guided by stage of disease and pathological risk factors. Patients with early stage (T1-2, N1-2b without extranodal extension(ENE)/lymphovascular invasion(LVI)/perineural invasion(PNI)) were surveyed without adjuvant therapy. Patients with LVI/PNI and <1mm ENE were assigned to chemoradiotherapy comprising cisplatin and 50Gy IMRT. Patients with high-risk disease (>1mm ENE, supraclavicular/contralateral nodes or positive surgical margins) were treated with chemoradiotherapy comprising cisplatin and 56Gy IMRT. The median follow-up time was 43.9-months (9.6-75.8).[90]

Riaz (2021) conducted the final included study. This was a prospective single centre study conducted between 2015 and 2016.[87] This study assessed patients with T1-2, N1-2b (stage III-IVa AJCC 7th edition) HPV+ OPSCC who were treated with primary surgery

and adjuvant chemoradiotherapy. HPV status was determined with >70% staining on p16 IHC. Primary surgical options were guided by the treating surgeon but not further specified. Post-operatively patients underwent adjuvant standard versus dose-reduced chemoradiotherapy. Treatment with cisplatin was preferred however substitution with a combination of carboplatin and 5-Fluorouracil was also used. Dose of radiation therapy was guided by post-operative ^{18}F-FMISO-PET scan. This scan assessed the hypoxia status of lymphatic disease in these patients. Patients without pre-treatment hypoxia or with post-operative resolution of hypoxia on their ^{18}F-MISO-PET received 30Gy adjuvant IMRT. Those with persisting hypoxia received 70Gy IMRT. Patients were assessed for overall survival, progression free survival, locoregional control and treatment related toxicity. Median follow-up time was 34months (18-41).[87]

3.6.1 Primary outcomes

3.6.1.1 3-year Overall survival

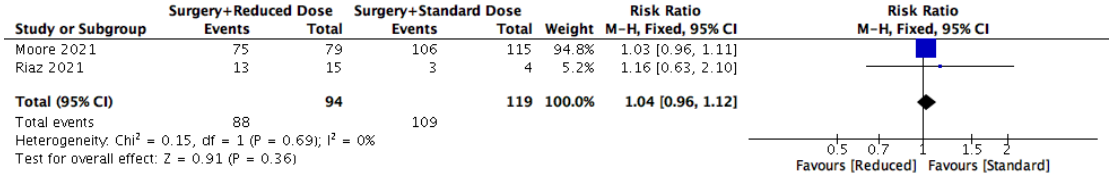

Figure 9: Forest plot of comparison, primary surgery with adjuvant reduced dose (chemo)radiotherapy versus adjuvant standard dose (chemo)radiotherapy, 3 year overall survival

Quantitative data for 3-year overall survival was available for two studies comparing primary surgery with standard versus reduced dose adjuvant (chemo)radiotherapy, Figure 9.[86, 87] Overall survival was higher in the reduced dose (93.6%) compared to the standard dose (91.6%) radiation therapy group (RR 1.04, 95% CI 0.96 to 1.12), see Table 5. The findings were limited by imprecision and small sample size (n=213). There was no heterogeneity noted between the studies, likely in part associated with the wide confidence intervals. This was supported by the heterogeneity testing reporting χ^2 = 0.15 (p=0.69), I^2 = 0%.

3.6.1.2 2-year Overall survival

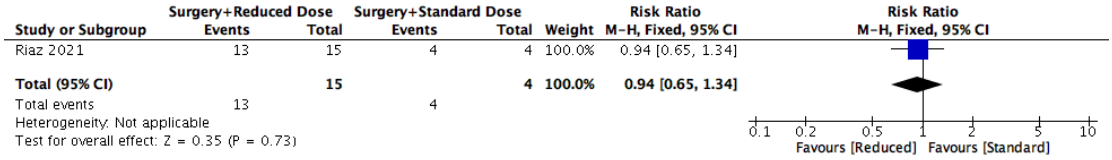

Figure 10: Forest plot of comparison, primary surgery with adjuvant reduced dose (chemo)radiotherapy versus adjuvant standard dose (chemo)radiotherapy, 2 year overall survival

Quantitative data for 2-year overall survival was available for one study comparing primary surgery with standard versus reduced dose adjuvant (chemo)radiotherapy, Figure 10.[87] Overall survival was lower in the reduced dose (86.7%) compared to the standard dose (100%) radiation therapy group (RR 0.94, 95% CI 0.65 to 1.34), see Table 5. The findings were limited by imprecision and small sample size (n=19). Assessment of heterogeneity was not applicable given only one study was included for meta-analysis.[87]

3.6.1.3 3-year Progression free survival

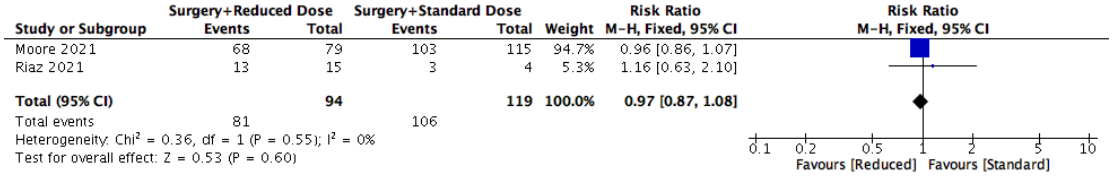

Figure 11: Forest plot of comparison, primary surgery with adjuvant reduced dose (chemo)radiotherapy versus adjuvant standard dose (chemo)radiotherapy, 3 year progression free survival

Quantitative data for 3-year progression free survival was available for two studies comparing primary surgery with standard versus reduced dose adjuvant (chemo)radiotherapy, Figure 11.[86, 87] Progression free survival was lower in the reduced dose (86.2%) compared to the standard dose (89.1%) radiation therapy group (RR 0.97, 95% CI 0.87 to 1.08), see Table 5. The findings were limited by imprecision and small sample size (n=213). There was no heterogeneity noted between the studies, likely in part associated with the wide confidence intervals. This was supported by the heterogeneity testing reporting $\chi^2 = 0.36$ (p=0.55), $I^2 = 0\%$.

3.6.1.4 2-year Progression free survival

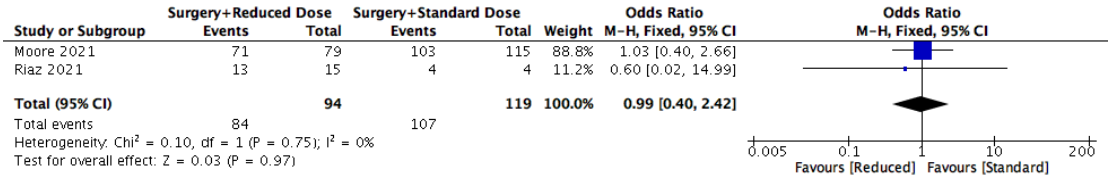

Figure 12: Forest plot of comparison, primary surgery with adjuvant reduced dose (chemo)radiotherapy versus adjuvant standard dose (chemo)radiotherapy, 2 year progression free survival

Quantitative data for 2-year progression-free survival was available for two studies comparing primary surgery with standard versus reduced dose adjuvant (chemo)radiotherapy, Figure 12.[86, 87] Progression free survival was lower in the reduced dose (89.4%) compared to the standard dose (89.9%) radiation therapy group (RR 0.99, 95% CI 0.40 to 2.42), see Table 5. The findings were limited by imprecision and small sample size (n=213). There was no heterogeneity noted between the studies, likely in part associated with the wide confidence intervals. This was supported by the heterogeneity testing reporting $\chi^2 = 0.10$ (p=0.75), $I^2 = 0\%$.

3.6.1.5 Disease-free survival

One study reported on disease-free survival. Miles (2021) reported a disease-free survival of 100% among the study cohort. No further data was available.

3.6.1.6 Disease-specific survival

One study reported on disease-specific survival. Miles (2021) reported a disease-specific survival of 98.1% in the study cohort. No further data was available.

3.6.1.7 Treatment related toxicity and adverse events

Two studies have presented their assessment of treatment related adverse events.[90, 98] The reporting of results varied between these two studies in regards to types and grading of adverse events. For this reason a meta-analysis could not be conducted. In general the CTCAE was used to report on type and severity of adverse events. The most common adverse events noted included dysphagia, severe pain, anxiety, xerostomia, mucositis and dysguesia.[90, 98] Miles (2021) reported adverse events in patients

undergoing primary surgery comparing varying amounts of adjuvant radiation therapy. Patients treated with surgery alone compared to surgery with adjuvant reduced-dose chemoradiotherapy had lower rates of dysphagia (37% vs. 100%)) and pain (30% vs. 100%). The rate of grade three mucositis in the adjuvant chemoradiotherapy arm was 50%. The rate of grade three mucositis in the surgery alone arm was not reported.

3.6.1.8 Objective swallow assessment (Modified Barium Swallow)

Ma (2019) assessed swallowing at baseline prior to undergoing radiation therapy and at 12months following treatment. Swallowing impairment was measured using the modified barium swallow impairment profile. Swallowing improved at 12months post treatment compared to pre-radiation therapy scores (5.8 vs 4.5, p=0.01). Data was only available for patients treated with reduced dose adjuvant radiation therapy.

3.6.1.9 Gastrostomy tube insertions

One study reported on the use of gastrostomy tubes.[98] In the study by Ma (2019) only 1 of 79 patients (1%) treated with reduced dose radiation therapy required a gastrostomy tube.[98] This was removed within one month following treatment. Data was only available for patients treated with reduced dose adjuvant radiation therapy.

3.6.2 Secondary outcomes

Multiple different instruments were used to assess and report on quality of life outcomes for this comparison. For this reason a meta-analysis could not be conducted for these outcomes and a narrative synthesis will follow.

3.6.2.1 Hospital readmissions

No hospital readmission data was reported for this treatment group.

3.6.2.2 Patient reported outcome measures

Multiple patient reported outcome measures were used to assess quality of life. Outcome measures used to assess were general quality of life, swallow specific measures or xerostomia.

3.6.2.2.1 General quality of life

Ma (2019) reported an improvement in 1-year post treatment compared to pre-treatment scores for both EORTC QLQ-H&N 35 (106.6 vs. 111.4, $p<0.001$) and FACT-H&N (116.9 vs. 127.2, $p<0.001$). Quality of life scores were not reported for the time between treatment and the 1-year follow-up point. Data was only available for patients treated with reduced dose adjuvant radiation therapy.

3.6.2.2.2 Swallowing and oral intake

The reporting of dysphagia and swallowing related quality of life was heterogeneous with no two studies using the same PROM tools. Ma (2019) reported on patients' functional oral intake using the FOIS tool. This study reported an improvement in functional oral intake at 12-months post-treatment compared to pre-treatment function (6.3 vs. 6.0, $p=0.01$).[98] Miles (2021) was the other study to assess patient reported swallowing outcomes. This study used the MDADI tool to longitudinally assess swallow function in those treated with surgery alone, surgery with adjuvant radiation therapy or surgery with adjuvant chemoradiotherapy. Patients treated with surgery alone were not noted to have any significant change in MDADI score compared to their pre-treatment baseline (MDADI = 89). For those who underwent adjuvant radiation therapy alone there was a significant reduction in their mean score at 3months (MDADI = 76, $p=0.027$). This decline returned to baseline by 6-months (MDADI = 85). The patients who underwent adjuvant chemoradiotherapy had a similar decline noted at 3months post-treatment (MDADI = 63, $p=0.0001$). This again improved with time with scores of 71 ($p=0.011$) after 6months, 78 ($p=0.11$) at 12-months and 88 after 2years.[90]

3.6.2.2.3 Xerostomia

Only one study used a patient reported outcome measure to assess quality of life in relation to xerostomia.[98] Ma (2019) used the XeQoLS tool to assess this outcome.

Included patients initially reported significantly worse effects of xerostomia at 1-month post treatment (0.3 vs. 0.6; P<0.001). This did however improve back to baseline when re-assessed at 12-months (0.3; p=0.67).[98] Data was only available for patients treated with reduced dose adjuvant radiation therapy.

3.7 Primary reduced dose (chemo)radiotherapy versus standard dose (chemo)radiotherapy

Five studies that assessed this treatment option have been included in this review.[88, 89, 91, 93, 94] Three studies have used information from the National Cancer Database.[89, 93, 94] It is unclear how many of the included patients for each of these studies have been duplicated given the similar inclusion criteria and dates of enrolment. For this reason only the results from the study by Tam (2020) with the largest sample size has been included in the subsequent meta-analysis.

Gabani (2019) conducted a retrospective multicentre review of 759 patients treated for HPV+ OPSCC identified through the National Cancer Database. All patients had stage I-IV (AJCC 7th edition) non-metastatic disease at time of diagnosis with no reported baseline performance status. All patients were treated with primary chemoradiotherapy. Patients were divided into two groups based on treatment with either 50Gy but less than 60Gy or 66Gy radiation therapy. The proportion of patients receiving concurrent chemotherapy or the types and dosage of chemotherapy used were not reported. The primary outcome for this study was overall survival. Patients were followed up for a median of 30.5months (2.4-81.4).[93]

Tam (2020) performed another multicentre retrospective review of patients treated for HPV+OPSCC identified through the National Cancer Database. 2173 patients underwent primary chemoradiotherapy for T1-3, N0-2c, M0 (AJCC 7th edition stage I-IV) HPV + OPSCC between 2010 and 2014. 90% (1947 of 2173) of patients underwent concurrent chemotherapy. The type and dose of concurrent chemotherapy however was not stated. Patients were grouped based on the total dosage of radiation received. The reduced dose radiation therapy group received ≥50Gy but <66Gy with the standard dose group receiving >66Gy up to a maximum of 80Gy. Patients were followed-up to assess for overall survival. Median follow-up time was 33.8-months (6-83).[89]

White (2020) conducted the final included NCDB study. This study was a multicentre retrospective review of 617 patients treated with primary chemoradiotherapy for stage III-IV (AJCC 7th edition) HPV+ OPSCC between 2010 and 2014.[94] Patients were identified through the National Cancer Database. HPV status was determined with HPV16 or HPV18 ISH and/or p16 IHC. Patients were divided into those who received dose reduced (≥54Gy but <66Gy) and those who received standard dose radiation therapy (≥66Gy up to 75Gy). The primary outcome for this study was overall survival. Patients were followed-up for a median of 31-months (2.4-81.4).[94]

Judy (2018) performed a single centre retrospective review (NCT01530997, NCT02281955) of 78 patients treated with primary chemoradiotherapy for T0-3, N0-2c HPV+OPSCC, ECOG 0-1.[91] Assessment of HPV status was broad considering any patients who were p16+ by IHC or any HPV testing. The dose reduced chemotherapy cohort were treated with cisplatin and 60Gy IMRT. The standard dose treatment group received either cisplatin, cetuximab, carboplatin alone or a combination of carboplatin and paclitaxel in conjuction with 70Gy IMRT. Outcomes of interest included patient reported outcome measures of treatment related toxicity as well as objective swallowing outcome measures as measured with a modified barium swallow test. Outcomes were assessed at baseline and up to 2-years post-treatment, average follow-up times were not recorded.[91]

Smith (2004) conducted a single centre prospective case series of 29 patients treated for oropharyngeal/hypopharyngeal cancer between 1995 and 2004. We were not able to obtain subset data from the corresponding authors in relation to primary origin or HPV status. Patients had stage III-IV disease (AJCC 7th edition) at time of recruitment and underwent treatment with primary chemoradiotherapy. Radiation therapy was administered as a standard dose of 74.4Gy or reduced dose of 60Gy. Patients underwent concurrent chemotherapy with hydroxyurea. Patients were assessed for overall survival and treatment related toxicity. Patients were followed-up for between 14-72months.[88]

3.7.1 Primary outcomes

3.7.1.1 2-3 year Overall survival

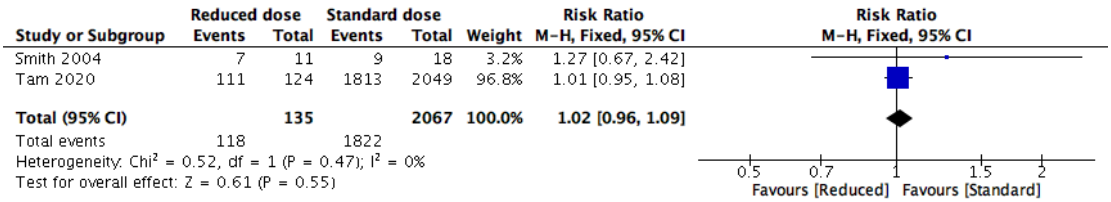

Figure 13: Forest plot of comparison, primary reduced dose (chemo)radiotherapy versus standard dose (chemo)radiotherapy, 2-3 year overall survival

Quantitative data for 2- and 3-year overall survival was available for two studies comparing primary standard versus reduced dose chemoradiotherapy, Figure 13.[88, 89] Overall survival was lower in the reduced dose (87.4%) compared to the standard dose (88.1%) radiation therapy group (RR 1.02, 95% CI 0.96 to 1.09), see Table 6. The findings were limited by imprecision with the confidence interval crossing no effect. There was no heterogeneity noted between the studies, likely in part associated with the wide confidence intervals. This was supported by the heterogeneity testing reporting $\chi^2 = 0.52$ (p=0.47), $I^2 = 0\%$.

3.7.1.2 Progression free survival

No data was available for progression free survival for this treatment group.

3.7.1.3 Disease-free survival

No data was available for disease-free survival for this treatment group.

3.7.1.4 Disease-specific survival

No data was available for disease-specific survival for this treatment group.

3.7.1.5 Treatment related toxicity and adverse events

No data was available for treatment related toxicity and adverse events for this treatment group.

3.7.1.6 Objective swallow assessment (Modified Barium Swallow)

Two studies have reported on the results of study participants undergoing a modified barium swallow assessment.[88, 91] No comparable data was available to conduct a meta-analysis between these two studies. Judy (2018) assessed the PAS with three consistencies. Rates of laryngeal penetration were higher with both thin and puree consistencies (50% vs 45%, p=0.33; 18% vs 13%, p=0.32) in those treated with standard compared to reduced dose radiation therapy.[91] Smith (2004) assessed aspiration between those treated with standard compared to reduced dose radiation therapy at 4- and 12-months post treatment. A significantly lower rate of aspiration was noted for liquids, purees and solids at both time points, see Table 11.[88] There was no worsening of aspiration over time.[88]

Table 11: Rates of aspiration at 4- and 12-months post treatment for standard and reduced dose radiation therapy as reported by Smith (2004)

Food consistency	4month			12month		
	60gy	74Gy	p-value	60Gy	74Gy	p-value
Liquid	11%(1/9)	81%(13/16)	P<0.001	11%(1/9)	60%(6/10)	P<0.04
Puree	11%(1/9)	69%(11/16)	P=0.004	11%(1/9)	60%(6/10)	P=0.03
Solid	25%(2/8)	69%(11/16)	P=0.03	0%(0/8)	60%(6/10)	P=0.007

3.7.1.7 Gastrostomy tube insertions

Two studies reported on the use of gastrostomy tubes.[88, 91] The reporting of this outcome was heterogeneous in regards to indications, duration as well as comparisons between treatment groups. For this reason a meta-analysis could not be conducted. Where reported, the most common indications for gastrostomy tube insertion were either for treatment related dysphagia or prophylactically prior to treatment commencement.[88] Judy (2018) and Smith (2004) reported similar findings amongst their treatment groups. Judy (2018) reported a lower rate of gastrostomy tube insertions and mean time to removal in those treated with reduced dose radiation therapy (55%, mean duration 14weeks) compared to standard dose radiation therapy (63%, mean duration 16 weeks).[91] The patients treated with reduced compared to standard dose radiation therapy in the study by Smith (2004) also had a lower prevalence of gastrostomy tubes (18% vs. 78%, p=0.002). Most patients in this study did have prophylactic gastrostomy tubes inserted prior to treatment commencement.[88]

3.7.2 Secondary outcomes

Only a single instrument was used to report on quality of life outcomes for this comparison. For this reason a meta-analysis could not be conducted for these outcomes and a narrative synthesis will follow.

3.7.2.1 Hospital readmissions

No hospital readmission data was reported by the studies that provided data towards this comparison.

3.7.2.2 Patient reported outcome measures

The outcome measure used to assess quality of life was a swallow specific questionnaire.

3.7.2.2.1 General quality of life

No patient reported general quality of life data was reported by the studies that provided data towards this comparison.

3.7.2.2.2 Swallowing and oral intake

Judy (2018) reported on the swallowing domains of the EORTC QLQ-H&N 35 tool. This study reported a reduction in problems swallowing liquids and purees at 2-years post treatment when compared to pre-treatment. Within the same cohort however it was noted patients were having more problems swallowing solids and choking with swallowing.[91] These results have been summarized in Table 12. Results were not stratified by radiation therapy treatment dose.

Table 12: EORTC QLQ-H&N 35 swallowing domains as reported by Judy 2018

Swallowing domain	Pre-treatment score	2-years post-treatment
Problems swallowing liquids	1.4	1.2
Problems swallowing purees	1.2	1.1
Problems swallowing solids	1.5	1.7
Choking when swallowing	1.0	1.3

3.8 Modifications made to the published protocol

The a-priori systematic review protocol was published prior to commencing this systematic review and meta-analysis. As discussed earlier, one modification to the original systematic review protocol was made during the study selection process. Given the limited number of experimental and quasi-experimental studies identified we have also included observational analytical studies. No other modifications were made during the review to the methods discussed in our protocol.

Chapter 4. Discussion

The treatment of Oropharyngeal Squamous Cell Carcinoma has evolved significantly over time. Improved understanding of the pathophysiology of this condition along with advances in surgical and non-surgical treatment options have continued to contribute to this evolution. This systematic review has identified sixteen publications that report on the use of reduced dose radiation therapy for the management of HPV+ OPSCC. Herein the results of this systematic review and meta-analysis will be discussed in relation to the existing literature and current guidelines. The main findings of this review were that there was no significant difference in survival when comparing standard versus reduced dose radiation therapy. Additionally, reduced dose radiation therapy was in general associated with better objective and subjective swallowing outcomes, reduced gastrostomy tube requirement and improved quality of life. The limitations of this review as well as the implications on both clinical practice and future research will subsequently be discussed.

This systematic review has contributed to a body of literature and existing reviews assessing de-escalated treatment for HPV+ OPSCC.[20, 46, 66, 67] The existing reviews have all highlighted the promising nature of de-escalated primary and adjuvant chemoradiotherapy. This review has followed thorough JBI methodology to provide an up to date synthesis and meta-analysis of the currently available evidence. These findings have been presented in a GRADE summary of findings table. Despite this, given the heterogeneity of included studies and lack of long-term follow-up to assess treatment related toxicity and survival, no recommendations have been made to change standard of care guidelines.

4.1 Surgery and adjuvant standard versus reduced dose (chemo)radiotherapy

This review has included five studies that assessed post-operative adjuvant standard versus reduced dose (chemo)radiotherapy. For this group, our meta-analysis has shown a RR of 0.94 (95% CI 0.65 to 1.34; GRADE certainty: very low) and RR of 1.04 (95% CI 0.96 to 1.12; GRADE certainty: very low) for 2- and 3-year overall survival respectively. 2- and 3-year progression free survival reflected an RR of 0.99 (95% CI 0.40 to 2.42; GRADE certainty: very low) and RR of 0.97 (95% CI 0.87 to 1.08: GRADE certainty: very low) respectively. The results of the meta-analysis favoured reduced dose radiation therapy for 2-year overall survival as well as 2- and 3-year progression free survival.

Standard dose radiation therapy was favorable for 3-year overall survival. These findings were again not clinically significant and limited by imprecision due to small sample sizes.

Only one of the included studies reported on treatment related adverse effects across varying radiation therapy doses.[90] Miles (2021) assessed 53 patients who underwent primary TORS and neck dissection for stage I-IVa (AJCC 7th edition) HPV+ OPSCC. Adjuvant therapy was delivered based on identified prognostic factors. Patients with favorable prognostic factors received surgery alone. Among this group the most common adverse effects were dysphagia in 37%, severe pain in 30% and xerostomia in 11%.[90] Patients with intermediate prognostic features received 50Gy adjuvant radiation therapy. Among this group, dysguesia, xerostomia and severe pain was reported in 100%, 67% and 67% respectively with no grade 3 or worse effects.[90] The group with poor prognostic factors was treated with 56Gy adjuvant radiation therapy with concurrent cisplatin. As has been discussed previously, worse adverse effects were again seen with the addition of concurrent chemotherapy.[90] Dysphagia and pain were reported in 100% of this cohort with grade 3 mucositis reported in 50%. These differences may however be secondary to patients with more advanced disease undergoing more extensive surgical resections. In general, patients treated with single modality treatment had the least severe toxicity profile while those who underwent trimodality treatment experienced more severe toxicity.[90]

The use of surgery with adjuvant (chemo)radiotherapy requires consideration of the associated benefits and risks. One of the main benefits of primary surgery in the management of OPSCC is to obtain tissue for pathological staging that could guide the need for adjuvant treatment or to be able to avoid the need for any adjuvant treatment. In stage I-III HPV+ OPSCC (AJCC 8th edition) the NCCN guidelines suggest that in the absence of ENE, positive margins or other adverse features, patients may not require adjuvant treatment.[23] This would reduce the risks associated with undergoing adjuvant (chemo)radiotherapy. On the other end of the spectrum, patients with adverse features are generally recommended to undergo adjuvant radiation therapy +/- systemic therapy. These adverse features include; extranodal extension, positive or close surgical margins, meeting pathological T3 or T4 size criteria, one positive lymph node >3cm or multiple positive nodes, level IV or V nodal disease, perineural invasion and/or lymphovascular invasion.[23]

In comparison to undergoing primary chemoradiotherapy, provision of trans-oral robotic surgery is reliant on multiple different factors. Prior to considering patients for TORS requires approval at both an institutional level as well as for the individual surgeon. In Australia, the Australian Society of Otolaryngology Head and Neck Surgery guidelines require a minimum of 20 robotic procedures performed per year. Ten of these must also have been performed as the primary surgeon.[101] During the work-up of patients with OPSCC, important contraindications to undertaking TORS must also be assessed, as highlighted in Table 13.[102] The final consideration in regards to implementation of TORS is the associated costs. The approximate instalment costs of the da Vinci® robot is around AUD $3.25million with an associated annual AUD $100,000 for maintenance and AUD $2,000 per case for equipment.[101] These implementation and maintenance costs are however typically shared amongst multiple specialties that use the robotic device including but not limited to Urology, Colorectal and Gynecology.[103-105]

Table 13: Contraindications to undertaking TORS for oropharyngeal cancer as described by Weinstein (2015)

Category	Contraindication
Vascular	- retropharyngeal carotid artery - location of tumor risks bilateral lingual arteries - proximity to carotid bulb and internal carotid artery risks exposure if resected
Functional	- >50% of deep tongue base musculature requiring resection - >50% of posterior pharyngeal wall requiring resection - up to 50% of tongue base and entire epiglottis requiring resection
Oncological	- all T4b cancers - fixation of tumor to pre-vertebral fascia - multiple distant metastases - unresectable neck disease - neoplastic related trismus
Non-oncological	- inability to hold antiplatelet or anticoagulant medication - comorbidities associated with unacceptable perioperative or anaesthetic risks - non-cancer related trismus precluding TORS access - cervical spine pathology interfering with appropriate TORS positioning

Another important factor in guiding treatment planning is the presence or absence of ENE. The presence of ENE has been shown to be associated with a higher risk of regional recurrence and poorer prognosis across HNSCC in general.[23, 106] Evidence for a prognostic impact of ENE in HPV+ OPSCC however is lacking. One recent retrospective analysis of patients identified through the NCDB suggested that ENE might only have a limited prognostic impact in patients with HPV+ OPSCC.[107] An alternative to the use of surgery to identify ENE is the utilization of medical imaging. A recent systematic review and meta-analysis of radiographic ENE assessment in HPC+ OPSCC reported on the utility of various different imaging modalities.[108] The sensitivity and specificity for detecting ENE on CT was 77% and 60%, PET/CT was 37.5% and 97% and on CT and MRI was 62% and 78% respectively.[108] Methods to identify ENE and the impact this has on treatment planning for patients with HPV+ OPSCC still requires further research.

The evolution of primary surgery for management of HPV+ OPSCC has enabled the reduction in treatment associated adverse effects for two main reasons. Firstly, compared to open surgery there is less treatment-associated morbidity. Secondly, in patients with favorable prognostic factors, treatment may be limited to surgery alone whilst avoiding the need for and effects associated with adjuvant (chemo)radiotherapy.

4.2 Non-surgical radiation therapy de-escalation options for HPV+ OPSCC

This systematic review assessed two non-surgical radiation therapy de-escalation options. The first was to assign standard versus reduced dose radiation therapy based on individual response to induction chemotherapy. For this group, our meta-analysis has shown a HR of 1.26 (95% CI 0.11 to 14.43; GRADE certainty: low) for 2-3-year overall survival and HR of 1.46 (95% CI 0.13 to 16.40; GRADE certainty: low) for 2-3-year progression free survival. The second was to randomize patients to primary standard or reduced dose chemoradiotherapy. For this group our meta-analysis has shown a RR of 1.02 (95% CI 0.96 to 1.09; GRADE certainty: low) for 2- and 3-year overall survival. Despite favouring standard dose radiation therapy, none of these findings were shown to be clinically significant and were assessed to have low or very low certainty in the evidence, due to issues with risk of bias and imprecision. When considering the use of induction chemotherapy with standard or reduced dose radiation therapy it is important to assess the associated risks and benefits.

The main benefit of induction chemotherapy in relation to this review is the identification of patients suitable for de-escalated radiation therapy. Two studies used response to induction chemotherapy to guide de-escalation of subsequent (chemo)radiotherapy.[96, 97] Of the 105 patients included, 74 (70%) received reduced dose radiation therapy based on partial or complete response.[96, 97] Data comparing overall survival and progression free survival for these cohorts were unfortunately not available and performing a meta-analysis was not possible. For this reason, we are not able to assess from this review if de-escalated radiation therapy following induction chemotherapy results in improved survival outcomes.

The beneficial effects of induction chemotherapy in general have been reported in relation to the treatment of locally advanced head and neck cancer.[23, 109-111] When comparing patients treated with induction chemotherapy with subsequent concurrent chemoradiotherapy to those treated with concurrent chemotherapy alone, no significant difference has been identified in overall survival.[111] The utility of induction chemotherapy is however in helping to reduce distant metastasis free survival.[109] Brockstein (2004) performed a multi-institutional review of 337 patients to assess locoregional control, distant control, overall survival and progression free survival. The only significant finding was that induction chemotherapy might reduce the occurrence of distant metastases by 30-40%.[109] When considering the data available in this review, none of the included studies using concurrent chemoradiotherapy alone reported on distant metastasis free survival. Two included studies assessing de-escalated treatment following induction chemotherapy did report on DMFS.[96, 97] Chen (2017) reported a 98% one-year DMFS in patients treated with reduced dose radiation therapy following induction paclitaxel/carboplatin. Seiwert (2019) also reported a 100% two-year DMFS in patients treated with induction chemotherapy, results were not separated by radiation therapy dose. The results from these studies are however limited by the short follow-up period as well as small sample sizes.[96, 97] For this reason it is unclear from our results whether the beneficial long-term effects of induction chemotherapy extend to the patients included in this review.

Adverse effects of chemotherapy can occur during induction chemotherapy as well as during concurrent chemoradiotherapy. Chemotherapy in general, when combined with radiation therapy has been noted to increase treatment related toxicity. In a study by Adelstein (2003), patients treated with concurrent chemoradiotherapy were found to have a higher rate of grade 3 or worse toxicity compared to those treated with radiation

therapy alone. This does however have to be balanced with the known beneficial effects of combining chemotherapy with radiation therapy on 5-year survival.[38] Two studies in our review commented on tolerance of induction chemotherapy.[85, 96] Chen (2017) reported that only 1 of 44 included patients did not tolerate induction chemotherapy. This was secondary to an allergic reaction to paclitaxel for which they were switched to carboplatin. Five patients in the study by Misiukiewicz (2019) had adverse effects from induction chemotherapy. Two patients were hospitalized, one for neutropenia with cholangitis and one with mucositis. The other three patients developed febrile neutropenia, urinary retention and cisplatin related acute hearing loss.[85]

One of the main concerns related to induction chemotherapy are the downstream effects on subsequent treatment.[23] Two randomized phase III trials have assessed the effects of induction chemotherapy in patients with advanced head and neck cancer. Cohen (2014) reported on a cohort of 114 patients where 1/3 of patients developed grade 2 or worse mucositis and four patients died. The study by Hitt (2014) reflected similar adverse effects. Hitt (2014) reported grade 3-4 febrile neutropenia in 1.9% of patients undergoing induction chemotherapy with cisplatin and fluorouracil (PF). This increased to 17% in those undergoing induction with cisplatin, fluorouracil and docetaxel (TPF).[113] 30% and 27% of those undergoing induction chemotherapy with TPF and PF respectively also did not proceed to definitive chemoradiotherapy.[113]

In regard to adverse events noted during concurrent chemoradiotherapy in this review, there was a general trend favoring the reduced versus standard dose radiation therapy treatment arms. Adverse effects reported using the CTCAE found a significantly lower rate of grade III/IV mucositis and dermatitis in those treated with reduced versus standard dose radiation therapy.[97] Foster (2020) reported on the MBS assessments of patients recruited in this same study. Patients treated with reduced dose radiation therapy had lower post-treatment aspiration as well as a lower rate of requiring diet/swallowing precautions.[55]

Despite no significant differences in survival outcomes, the improved toxicity profile of patients treated with reduced dose radiation therapy warrants consideration of use in the future. Open discussions with patients about the potential effects of induction chemotherapy and the impact this may have on definitive treatment will be an important factor. Further research is required however to clarify the long-term survival outcomes (overall survival, progression free survival, distant metastasis free survival) in

those treated with induction chemotherapy with subsequent reduced dose radiation therapy.

4.3 Patient reported outcome measures

The assessment of patient reported outcome measures from the studies included in this review was very heterogeneous in nature. Of the sixteen included studies, only six reported on quality of life measures.[55, 90, 91, 98-100] For these six studies, eight different quality of life scales were utilized, of which only two (FACT-H&N, EORTC QLQ-H&N-35) were reported across multiple studies.[91, 98, 99] For this reason, assessment of quality of life measures between studies was limited. The patient reported outcomes including; general quality of life, dysphagia and xerostomia declined most significantly between 1-3months after treatment. These effects were generally temporary in nature with quality of life measures returning to baseline within 12-24months.[90, 98, 99] Only one study compared patient reported outcomes measures between patients treated with standard versus reduced dose radiation therapy.[55] Foster (2020) reported on the results of the PSS-H&N scale that showed patients who underwent reduced compared to standard dose radiation therapy were less likely to have diet, speech and public eating restrictions.

In order to help guide research and clinical decision-making, the validity of each PROM should be considered for the specific population being investigated. For example, the FOIS was initially developed to assess oral intake in patients' who have suffered a stroke.[59] For patients being treated for head and neck cancer, validity testing for the FOIS has not been undertaken. Consequently, when used in this setting, differences in FOIS scores between treatment arms is of unknown significance. A validated instrument for the assessment of swallowing dysfunction in patients being treated for head and neck cancer is the MDADI tool.[64] Miles (2021) was the only study to use this tool in their assessment of de-escalated adjuvant radiation therapy following TORS as discussed earlier. Patients who underwent surgery alone had no significant change in swallow function compared to their pre-treatment baseline. For those who underwent adjuvant (chemo)radiation therapy, a significant reduction in their mean score was found at 3 months that returned to baseline by 6-months.[90] These findings can be considered more reliable compared to tools that have been used where validity testing has not been performed for this population.

In regards to general quality of life, the most commonly utilized instruments in this review include the EORTC QLQ-H&N 35, UW-QOL, PSS-H&N and FACT-H&N. All four of these tools have been validated for use in assessing quality of life for patients with head and neck cancer.[61, 114-117] The most concise instrument would be the PSS-H&N. This tool uses three questions to assess normalcy of diet, public eating and understandability of speech.[61] This tool is however limited in its ability to assess multiple other symptoms and quality of life concerns of patients undergoing treatment for head and neck cancer. The UW-QoL tool assesses more head and neck related symptoms and quality of life concerns including appearance, recreation, shoulder, taste, saliva, mood and anxiety.[62] Similar to the PSS-H&N tool however, the UW-QoL tool is limited by the detail in which each domain is assessed. The two QoL tools that thoroughly assess both general QoL and head and neck specific domains include the EORTC QLQ-H&N 35 and FACT-H&N. The benefit of the EORTC QLQ-H&N 35 is the detail in which it assesses each domain. For example, there are four questions assessing each of; type of pain, dysphagia with various food consistencies, social eating and nutrition. This questionnaire also assesses issues including; dentition, trismus, coughing as well as sense of taste and smell.[118] In comparison, whilst the FACT-H&N assesses similar social and family wellbeing, there is a clearer focus on physical, emotional and functional wellbeing with this tool.[119] Assessments of physical wellbeing include; feeling ill/bedbound, lacking energy, nausea and being bothered by adverse effects. Emotional wellbeing domains include; feeling sad, not coping, losing hope and worry about death/progression. Functional domains include; sleep, hobbies, work and illness acceptance.[119]

The non-significant differences in survival between patients undergoing treatment with standard versus reduced dose radiation therapy for HPV+ OPSCC has highlighted the importance of PROMs as an adjunct to this assessment. Two thorough QoL tools have been identified, the EORTC QLQ-H&N35 and FACT-H&N, each of which may play its own unique role in assessing specific head and neck cancer related concerns.

4.4 Limitations of the review

Despite rigorous methods being undertaken to ensure the quality of this review, limitations have been identified. During the process of data collection, all corresponding authors were contacted regarding additional data. Unfortunately only two corresponding authors responded. One response provided up to date long-term data regarding their study cohort.[120] Takahashi (2022) provided five-year prospective data

on the 20 patients enrolled by Misiukiewicz (2019) in the Quarterback Trial. The results of this study showed a significantly smaller impact on quality of life among the reduced dose compared to standard dose radiotherapy group as measured with multiple EORTC domains comparing scores at baseline to the end of chemoradiotherapy.[120] Results at three and six months were combined due to small response numbers and again showed significantly higher quality of life recovery among the reduced dose radiotherapy cohort. These results must however be analysed with caution given comparisons may have been made between one intervention at three-months and the comparator at six-months or vice versa.[120] No additional patients had progression of disease with five-year PFS and OS rates the same as when recorded at three-years post treatment by Misiukiewicz (2019).[120] These results in general reflect the favourable toxicity profile of reduced compared to standard dose radiotherapy. No additional data was available from the second respondent. The limitation arises in regards to the missing data that could not be retrieved from the remaining corresponding authors. Additional data may have either contributed to the sample sizes of existing findings or provided data for additional meta-analysis or narrative synthesis. Alongside this, information from authors regarding safeguards implemented to reduce risk of bias may have also increased the quality of the included studies and the certainty of our findings.

The data that was synthesised in this review was identified to have all originated from the United States. The age-standardized rate of oropharyngeal cancer reported in the United States in 2020 was around 2.4 per 100,000 individuals.[121] In comparison, some European countries have a higher age-standardized rate such as Denmark, Romania and France with 5, 4.3 and 4.3 per 100,000 respectively.[121] The consequence of this is that the findings of this review may not be applicable to countries outside the United States.

Another significant demographic factor was the occurrence of tobacco smoking. Unfortunately insufficient data was available in the included studies to comment on the effects active smoking, ex -smoking or never-smoking has on our outcomes. Previous studies have used a cut off of >10 pack years to stratify patients as either low or high risk.[86, 98] The importance of this has been shown in previous studies of patients with OPSCC where smoking has been associated with a reduction in overall survival and progression free survival irrespective of HPV status.[122] These findings were supported by Marur (2017) where de-escalated treatment had less clinical effect for patients with a >10 pack-year smoking history.

In regards to stage of OPSCC at time of diagnosis, this contributed another limiting factor for this review. For the included reviews, heterogeneous patient groups were used across the included studies. The lack of sufficient data for individual patient groups resulted in an inability to perform a subgroup analysis of these patients based on stage of disease.

Heterogeneity was also noted in the dosage of radiation therapy delivered across the included studies for both the standard and reduced dose cohorts. For those who underwent primary surgery, adjuvant radiation therapy ranged from none to 56Gy.[90] For those treated with standard dose adjuvant radiation therapy, this dose also ranged from 60Gy to 70Gy.[92] The lower limit of radiation therapy delivered that still provides safe and acceptable survival outcomes whilst optimising treatment associated quality of life is still unknown.

The final limitation of this review was associated with the limited experimental and quasi-experimental trials. Where available, some trials were heterogenous in patient selection and in delivery of treatment. For example, when comparing patients undergoing primary surgery, the cohort recruited by Miles (2021) assessed only TORS where the cohort recruited by Riaz (2021) assessed any surgical resection with TORS not mandatory. As guided by our protocol, observational analytic studies were included in the review. The inclusion of these observational studies that had retrospectively assessed their data was in turn associated with its own risk of bias and limitations.

4.5 Implications for clinical practice

The findings of this review did not support the use of either reduced or standard dose radiation therapy over the other with regard to overall survival or progression free survival. The appraisal of the included studies also identified a low level of certainty in these findings. One previous study by Misiukiewicz (2019) was conducted to assess for non-inferiority of reduced dose radiotherapy compared to standard dose radiotherapy for HPV+ OPSCC. This study however was limited by their small sample size. For this reason they were unable to demonstrate non-inferiority of reduced dose radiotherapy for this cohort.[85] Given there is no significant evidence to show whether reduced dose radiotherapy is either superior or non-inferior to standard dose radiotherapy, no changes to current practice is recommended at this stage.

For patients' undergoing primary surgery, we also found no significant difference in overall survival or progression free survival between those treated with reduced versus standard dose radiation therapy. One of the important findings from this review however is the reduction in toxicity and improved quality of life noted among patients treated with reduced dose radiation therapy. These findings based on heterogeneous data support the importance of considering these outcomes. The most important consideration for these patients however is obtaining negative surgical margins. Positive surgical margins are not only associated with a higher risk of death but also a requirement for further adjuvant chemoradiotherapy and the toxicity associated with this.[34] The treatment related toxicity noted amongst patients undergoing trimodality therapy (surgery, radiation therapy and chemotherapy) in this review was significantly greater than those undergoing surgery with or without adjuvant radiation therapy. For patients where negative surgical margins may be difficult to obtain, the possibility of trimodality treatment and the associated toxicity must be strongly considered prior to offering this treatment option. Given the various radiation therapy de-escalation strategies available, the associated risks and benefits of each require discussion at a multidisciplinary meeting as well as when counselling patients.

4.6 Implications for research

A number of recommendations can be made for future studies based on the results of the critical appraisal. One of the major sources of bias was in the randomization of patients to treatment groups. Within the experimental studies this arose secondarily as the allocated radiation therapy dose was based on either response to initial treatment or post-operative prognostic factors. For this reason, patients with good prognostic factors being treated with reduced dose radiation therapy were in some instances being compared to patients with poorer prognostic factors being treated with higher doses of radiation therapy. Adjustments could be considered in futures studies to randomize patients with similar responses to induction chemotherapy or similar prognostic factors to standard versus reduced radiation therapy. The next significant domain causing risk of bias was in measurement of the outcome. This was primarily in relation to patient reported outcome measures. The homogenous use of PROMs across future studies as well as blinding of assessors of these outcomes would reduce the associated risk of bias. These could be assessed pre-treatment as a baseline, at 3-months to assess for acute toxicity as well as regular intervals thereafter to assess for recovery. For the reasons discussed earlier, the quality of life outcome measures recommended would include:

- Dysphagia: MDADI
- General QoL: EORTC QLQ-H&N 35 or FACT-H&N
- Adverse events: CTCAE

Subgroup analysis would be supported with the reporting of further detailed demographic data. In regards to smoking history, reporting of current smoking status as well as a quantification of a more or less than ten pack year history is relevant. Clear documentation of the stage of disease, updated with the AJCC 8th edition would also support this analysis. Finally, conducting more rigorous randomized controlled trials that address the above recommendations will also improve the quality of evidence and increase the certainty of findings.

Addressing some of the other limitations identified earlier. Broadening the scope of HPV+ OPSCC research outside of the United States will contribute for multiple reasons. Recruiting patients being treated for HPV+ OPSCC outside of the United States will improve sample sizes, broaden the demographics as well as provide an insight into the surgical results from other countries. The data and results of which may aid in determining the generalizability of the findings.

The length of follow-up is another factor to be considered for two main reasons. Firstly, when considering patients undergoing induction chemotherapy, it will be important to assess if the long term distant metastasis free survival extends to this subgroup of HNSCC. Secondly, the long-term treatment related adverse effects of reduced versus standard dose radiation therapy or even when comparing to primary surgery is not currently known.

The final considerations are in relation to the ongoing change being seen in the delivery of radiation therapy and systematic therapy. In terms of radiation therapy, intensity modulated proton therapy (IMPT) has been considered as an alternative to intensity modulated radiation therapy. Two studies of IMPT have already shown promising results in relation to sparing normal tissue and organs at risk whilst avoiding negative impacts on locoregional control, progression free survival and overall survival.[124, 125] In addition to this, TORPEdO, a phase III multi-center RCT being conducted out of the United Kingdom is currently enrolling patients to compare curative intent standard dose IMPT versus IMRT among patients with OPSCC, irrespective of HPV status.[126] The results

of this research may impact the ongoing need to investigate the effects of reduced dose IMRT.

4.7 Conclusion

There were no statistically significant differences in survival outcomes between patients treated with reduced versus standard dose radiation therapy. These findings were similar when assessed across three treatment options for HPV+ OPSCC. In relation to radiation therapy related toxicity, it was noted that patients treated with reduced dose radiation therapy in general had better quality of life scores and reduced treatment related toxicity. The certainty in these findings were low given the retrospective nature of most of the included studies and the randomization processes associated with the experimental studies.

Appendices

Appendix 1: American Joint Committee on Cancer (AJCC) TNM Staging System for HPV (p16) Associated Oropharyngeal Cancer (8th ed., 2017)

From: "AJCC Cancer Staging Manual. 8th ed." Amin et al. 2017.[29]

Definition of Primary Tumor (T)

T Category	T Criteria
T0	No primary identified
T1	Tumor 2 cm or smaller in greatest dimension
T2	Tumor larger than 2 cm but not larger than 4 cm in greatest dimension
T3	Tumor larger than 4 cm in greatest dimension or extension to lingual surface of epiglottis
T4	Moderately advanced local disease Tumor invades the larynx, extrinsic muscles of tongue, medial pterygoid, hard palate, or mandible or beyond*)

Mucosal extension to lingual surface of epiglottis from primary tumors of the base of the tongue and vallecular does not constitute invasion of the larynx.

Definition of Regional Lymph node (N)

Clinical N (cN)

N Category	N Criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	One or more ipsilateral lymph nodes, none larger than 6 cm
N2	Contralateral or bilateral lymph nodes, none larger than 6 cm
N3	Lymph node(s) larger than 6 cm

Pathological N (pN)

N Category	N Criteria
NX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis in 4 or fewer lymph nodes
pN2	Metastasis in more than 4 lymph nodes

Distant Metastases (M)

M Category	M Criteria
M0	No distant metastasis
M1	Distant metastasis

AJCC Prognostic Stage Groups

Clinical

Stage I	T0, T1, T2	N0, N1	M0
Stage II	T0, T1, T2	N2	M0
Stage II	T3	N0, N1, N2	M0
Stage III	T0, T1, T2, T3 or T4	N3	M0
Stage III	T4	N0, N1, N2 or N3	M0
Stage IV	Any T	Any N	M1

Pathological

Stage I	T0, T1, T2	N0, N1	M0
Stage II	T0, T1, T2	N2	M0
Stage II	T3, T4	N0, N1	M0
Stage III	T3, T4	N2	M0
Stage IV	Any T	Any N	M1

Appendix 2: Search strategies

Search strategy for CINAHL – performed on 07/05/2021

((MH Pharynx OR MH Oropharynx OR MH Tonsil OR MH "Squamous cell carcinoma of head and neck" OR TX Tonsil*) AND (MH Neoplasm OR TX Cancer) OR (MH "Oropharyngeal neoplasms" OR MH "Tonsillar neoplasms" OR TX "Oropharyngeal neoplasm*" OR TX "Oropharyngeal cancer" OR TX "Oropharyngeal carcinoma" OR TX "Oropharyngeal SCC" OR TX "Oropharyngeal Squamous cell carcinoma" OR TX "Oropharyngeal tumo*" OR TX "oropharynx cancer*" OR TX "Oropharynx neoplasm*" OR TX "Oropharynx carcinoma" OR TX "Oropharynx tumo*" OR TX "Oropharynx squamous cell carcinoma*" OR TX "Oropharynx SCC" OR TX "Tonsillar Neoplasm*")) AND (TX Deescalat* OR TX "De escalat*" OR TX "De-escalat*" OR TX "De-intensif*" OR TX "De intensif*" OR TX "Deintensif*" OR TX "Dose reduc*") AND (MH Radiotherapy OR MH "Radiation dosage" OR MH "Radiotherapy, adjuvant" OR MH Chemoradiotherapy OR MH "Chemoradiotherapy, adjuvant" OR TX Chemoradi* OR TX Chemo-radi* OR TX Radiochemotherapy OR TX Radio-chemotherapy OR TX "Radiation therapy")

Search strategy for EMBASE – performed on 07/05/2021

(((‘Oropharynx’/exp OR ‘Palatine tonsil’/exp OR ‘Head and neck squamous cell carcinoma’/exp OR Throat:ti,ab OR Tonsil:ti,ab) AND (Neoplasm/exp)) OR (‘Oropharynx tumor’/exp OR ‘Oropharyngeal neoplasm*’:ti,ab OR ‘Oropharyngeal cancer’:ti,ab OR

‘Oropharyngeal carcinoma’:ti,ab OR ‘Oropharyngeal SCC’:ti,ab OR ‘Oropharyngeal Squamous cell carcinoma’:ti,ab OR ‘Oropharyngeal tumo*’:ti,ab OR ‘Oropharynx cancer*’:ti,ab OR ‘Oropharynx neoplasm*’:ti,ab OR ‘Oropharynx carcinoma’:ti,ab OR ‘Oropharynx tumo*’:ti,ab OR ‘Oropharynx squamous cell carcinoma*’:ti,ab OR ‘Oropharynx SCC’:ti,ab OR ‘Tonsillar Neoplasm*’:ti,ab))AND (Deescalat*:ti,ab OR ‘De escalat*’:ti,ab OR ‘De-escalat*’:ti,ab OR ‘De-intensif*’:ti,ab OR ‘De intensif*’:ti,ab OR ‘Deintensif*’:ti,ab OR ‘Dose reduc*’:ti,ab) AND (Radiotherapy/exp OR Chemoradiotherapy/exp OR Chemoradi*:ti,ab OR ‘Chemo-radi*’:ti,ab OR Radiochemotherapy:ti,ab OR ‘Radio-chemotherapy’:ti,ab OR ‘Radiation therapy’:ti,ab)

Search strategy for WEB of science – performed on 31/05/2021
(((Pharynx OR Oropharynx OR “Palatine tonsil*” OR “Squamous cell carcinoma of head and neck” OR Throat* OR Tonsil*) AND (Neoplasms OR Cancer)) OR (“Oropharyngeal neoplasms” OR “Oropharyngeal neoplasm*” OR “Oropharyngeal cancer” OR “Oropharyngeal carcinoma” OR “Oropharyngeal SCC” OR “Oropharyngeal Squamous cell carcinoma” OR “Oropharyngeal tumo*” OR “oropharynx cancer*” OR “Oropharynx neoplasm*” OR “Oropharynx carcinoma” OR “Oropharynx tumo*” OR “Oropharynx squamous cell carcinoma*” OR “Oropharynx SCC” OR “Tonsillar Neoplasm*”)) AND (Deescalat* OR “De escalat*” OR “De-escalat*” OR “De-intensif*” OR “De intensif*” OR Deintensif* OR “Dose reduc*”) AND (Radiotherapy OR Chemoradiotherapy OR Chemoradi* OR Chemo-radi* OR Radiochemotherapy OR Radio-chemotherapy OR “Radiation therapy” OR “Radiotherapy Dosage” OR “Radiation Dosage”)

Search strategy for MEDLINE (OVID) – performed on 31/05/2021
(((Exp Pharynx OR exp Palatine tonsil OR exp "Squamous cell carcinoma of head and neck" OR Throat*.ti,ab OR Tonsil*.ti,ab) AND (Exp Neoplasms OR Cancer.ti,ab)) OR (Exp Oropharyngeal neoplasms OR Oropharyngeal neoplasm*.tw OR Oropharyngeal cancer.tw OR Oropharyngeal carcinoma.tw OR Oropharyngeal SCC.tw OR Oropharyngeal Squamous cell carcinoma.tw OR Oropharyngeal tumo*.tw OR oropharynx cancer*.tw OR Oropharynx neoplasm*.tw OR Oropharynx carcinoma.tw OR Oropharynx tumo*.tw OR Oropharynx squamous cell carcinoma*.tw OR Oropharynx SCC.tw OR Tonsillar Neoplasm*.tw)) AND (Deescalat*.ti,ab OR De escalat*.ti,ab OR De-escalat*.ti,ab OR De-intensif*.ti,ab OR De intensif*.ti,ab OR Deintensif*.ti,ab OR Dose reduc*.ti,ab) AND (Exp Radiotherapy OR exp Chemoradiotherapy OR Chemoradi*.ti,ab OR Chemo-radi*.ti,ab OR Radiochemotherapy.ti,ab OR Radio-chemotherapy.ti,ab OR Radiation therapy.ti,ab OR exp Radiotherapy Dosage OR exp Radiation Dosage)

Search strategy for SCOPUS – performed on 31/05/2021
((TITLE-ABS-KEY(Pharynx OR Oropharynx OR "Palatine tonsil*" OR "Squamous cell carcinoma of head and neck" OR Throat* OR Tonsil*)) AND (TITLE-ABS-KEY(Neoplasms OR Cancer))) OR (TITLE-ABS-KEY("Oropharyngeal neoplasms" OR "Oropharyngeal neoplasm*" OR "Oropharyngeal cancer" OR "Oropharyngeal carcinoma" OR "Oropharyngeal SCC" OR "Oropharyngeal Squamous cell carcinoma" OR "Oropharyngeal tumo*" OR "oropharynx cancer*" OR "Oropharynx neoplasm*" OR "Oropharynx carcinoma" OR "Oropharynx tumo*" OR "Oropharynx squamous cell carcinoma*" OR "Oropharynx SCC" OR "Tonsillar Neoplasm*")) AND (TITLE-ABS-KEY(Deescalat* OR "De escalat*" OR "De-escalat*" OR "De-intensif*" OR "De intensif*" OR Deintensif* OR "Dose reduc*")) AND (TITLE-ABS-KEY(Radiotherapy OR Chemoradiotherapy OR Chemoradi* OR Chemo-radi* OR Radiochemotherapy OR Radio-chemotherapy OR "Radiation therapy" OR "Radiotherapy Dosage" OR "Radiation Dosage"))

Appendix 3: Reasons for study exclusion at first full text review

Study	Reason for exclusion
Posner 2020	Conference abstract – no associated full text
Sample 2021	Wrong intervention
Cheng 2016	Conference abstract – no associated full text
Pearlstein 2019	Review
Melotek 2017	Conference abstract – no associated full text
Chera 2015	Conference abstract – no associated full text
Hwang 2018	Conference abstract – no associated full text
Marur 2013	Single arm trial
Gabani 2019	Conference abstract – no associated full text
Bahig 2018	Conference abstract – no associated full text
Marur 2017	Wrong study design
Seiwert 2018	Conference abstract – no associated full text
Pearlstein 2018	Conference abstract – no associated full text
Shaverdian 2017	Wrong study design
Ruhle 2021	Wrong study design
Fried 2013	Single arm trial
Quon 2013	Conference abstract – no associated full text
Price 2018	Conference abstract – no associated full text
Bahig 2020	Wrong study design
Chera 2019	Single arm trial
Riaz 2017	Conference abstract – no associated full text
Chen 016	Conference abstract – no associated full text
Melotek 2017	Conference abstract – no associated full text
Swisher-McClure 2020	Single arm trial
Quon 2012	Conference abstract – no associated full text
Rosenberg 2020	Conference abstract – no associated full text
Deek 2019	Conference abstract – no associated full text
Autorino 2017	Conference abstract – no associated full text
Rainey 2017	Conference abstract – no associated full text

Appendix 4: Reasons for study exclusion at second full text review

Study	Reason for exclusion
Chen 2016	Conference abstract – no associated full text
Chera 2018	Conference abstract – no associated full text
Chera 2013	Conference abstract – no associated full text
Cramer 2018	Conference abstract – no associated full text
Echevarria 2019	Conference abstract – no associated full text
Gamez 2015	Conference abstract – no associated full text
Ma 2017	Conference abstract – no associated full text
Melotek 2015	Conference abstract – no associated full text
Nguyen 2020	Conference abstract – no associated full text
Nguyen 2020	Conference abstract – no associated full text
Rocco 2020	Conference abstract – no associated full text
Tam 2017	Conference abstract – no associated full text
Vera 2018	Conference abstract – no associated full text
Yang 2018	Conference abstract – no associated full text

Appendix 5: Requests for additional data from corresponding authors

Study	Response
Misiukiewicz, K, Gupta, V, Miles, BA, Bakst, R, Genden, E, Selkridge, I, Surgeon, JT, Rainey, H, Camille, N, Roy, E, Zhang, D, Ye, F, Jia, R, Moshier, E, Bonomi, M, Hwang, M, Som, P & Posner, MR 2019, 'Standard of care vs reduced-dose chemoradiation after induction chemotherapy in HPV+ oropharyngeal carcinoma patients: The Quarterback trial', *Oral Oncology*, vol. 95, pp. 170-177.	5-year follow-up results provided
Miles, BA, Posner, MR, Gupta, V, Teng, MS, Bakst, RL, Yao, M, Misiukiewicz, KJ, Chai, RL, Sharma, S, Westra, WH, Kim-Schulze, S, Dayal, B, Sobotka, S, Sikora, AG, Som, PM & Genden, EM 2021, 'De-Escalated Adjuvant Therapy After Transoral Robotic Surgery for Human Papillomavirus-Related Oropharyngeal Carcinoma: The Sinai Robotic Surgery (SIRS) Trial', *Oncologist*.	Failed delivery
White, R, Abel, S, Hasan, S, Verma, V, Greenberg, L, Colonias, A & Wegner, RE 2020, 'Practice patterns and outcomes following radiation dose de-escalation for oropharyngeal cancer', *Laryngoscope*, vol. 130, no. 4, pp. E171-E176.	No response
Tam, M, Wu, SP, Gerber, NK, Lee, A, Schreiber, D, Givi, B & Hu, K 2020, 'Radiotherapy dose and survival outcomes in human papillomavirus positive oropharyngeal cancer', *Journal of Laryngology and Otology*, vol. 134, no. 6, pp. 533-540.	No response
Smith, RV, Goldman, SY, Beitler, JJ & Wadler, SS 2004, 'Decreased short- and long-term swallowing problems with altered radiotherapy dosing used in an organ-sparing protocol for advanced pharyngeal carcinoma', *Archives of Otolaryngology - Head and Neck*	No response

Surgery, vol. 130, no. 7, pp. 831-836.	
Seiwert, TY, Foster, CC, Blair, EA, Karrison, TG, Agrawal, N, Melotek, JM, Portugal, L, Brisson, RJ, Dekker, A, Kochanny, S, Gooi, Z, Lingen, MW, Villaflor, VM, Ginat, DT, Haraf, DJ & Vokes, EE 2019, 'Optima: A phase II dose and volume de-escalation trial for human papillomavirus-positive oropharyngeal cancer', *Annals of Oncology*, vol. 30, no. 2, pp. 297-302.	No response
Foster, CC, Seiwert, TY, MacCracken, E, Blair, EA, Agrawal, N, Melotek, JM, Portugal, L, Brisson, RJ, Gooi, Z, Spiotto, MT, Vokes, EE & Haraf, DJ 2020, 'Dose and Volume De-Escalation for Human Papillomavirus-Positive Oropharyngeal Cancer is Associated with Favorable Posttreatment Functional Outcomes', *Int J Radiat Oncol Biol Phys*, vol. 107, no. 4, Jul 15, pp. 662-671.	No response
Riaz, N, Sherman, E, Pei, X, Schoder, H, Grkovski, M, Paudyal, R, Katabi, N, Selenica, P, Yamaguchi, TN, Ma, D, Lee, SK, Shah, R, Kumar, R, Kuo, F, Ratnakumar, A, Aleynick, N, Brown, D, Zhang, Z, Hatzoglou, V, Liu, LY, Salcedo, A, Tsai, CJ, McBride, S, Morris, LGT, Boyle, J, Singh, B, Higginson, DS, Damerla, RR, Paula, ADC, Price, K, Moore, EJ, Garcia, JJ, Foote, R, Ho, A, Wong, RJ, Chan, TA, Powell, SN, Boutros, PC, Humm, JL, Shukla-Dave, A, Pfister, D, Reis-Filho, JS & Lee, N 2021, 'Precision Radiotherapy: Reduction in Radiation for Oropharyngeal Cancer in the 30 ROC Trial', *Journal of the National Cancer Institute*, vol. 12, p. 12.	No further data available on response
Moore, EJ, Van Abel, KM, Routman, DM, Lohse, CM, Price, KAR, Neben-Wittich, M, Chintakuntlawar, AV, Price, DL, Kasperbauer, JL, Garcia, JJ, Hinni, ML, Patel, SH, Janus, JR, Foote, RL & Ma, DJ 2021, 'Human papillomavirus oropharynx carcinoma: Aggressive de-escalation of adjuvant therapy', *Head and Neck*, vol. 43, no. 1, pp. 229-237.	No response
Ma, DJ, Price, KA, Moore, EJ, Patel, SH, Hinni, ML, Garcia, JJ, Graner, DE, Foster, NR, Ginos, B, Neben-Wittich, M, Garces, YI, Chintakuntlawar, AV, Price, DL, Olsen, KD, Van Abel, KM, Kasperbauer, JL, Janus, JR, Waddle, M, Miller, R & Shiraishi, S 2019, 'Phase II Evaluation of Aggressive Dose De-Escalation for Adjuvant Chemoradiotherapy in Human Papillomavirus-Associated Oropharynx Squamous Cell Carcinoma', *Journal of Clinical Oncology*, vol. 37, no. 22, pp. 1909-1918.	No response
Judy, GD, Green, R, Aumer, SL, Amdur, RJ, Tan, X, Sheets, N, Weissler, M, Zanation, A, Patel, S, Hackman, T, Mendenhall, WM & Chera, BS 2018, 'Preservation of swallowing function with de-intensified chemoradiation therapy for HPV-associated oropharyngeal squamous cell carcinoma', *Advances in Radiation Oncology*, vol. 3, no. 3, pp. 356-365.	No response
Gabani, P, Lin, AJ, Barnes, J, Oppelt, P, Adkins, DR, Rich, JT, Zevallos, JP, Daly, MD, Gay, HA & Thorstad, WL 2019, 'Radiation therapy dose de-escalation compared to standard dose radiation therapy in definitive treatment of HPV-positive oropharyngeal squamous cell carcinoma', *Radiotherapy and Oncology*, vol. 134, pp. 81-88.	No response
Cramer, JD, Ferris, RL, Kim, S & Duvvuri, U 2018, 'Primary surgery for human papillomavirus-associated oropharyngeal cancer: Survival outcomes with or without adjuvant treatment', *Oral Oncology*, vol. 87, Dec, pp. 170-176.	No response
Chen, AM, Felix, C, Wang, P-C, Hsu, S, Basehart, V, Garst, J, Beron, P,	No response

Wong, D, Rosove, MH, Rao, S, Melanson, H, Kim, E, Palmer, D, Qi, L, Kelly, K, Steinberg, ML, Kupelian, PA & Daly, ME 2017, 'Reduced-dose radiotherapy for human papillomavirus-associated squamous-cell carcinoma of the oropharynx: a single-arm, phase 2 study', *Lancet Oncology*, vol. 18 1077-4114 (Print), no. 6, pp. 803-811.	
Hegde, JV, Shaverdian, N, Felix, C, Wang, P-C, Veruttipong, D, Hsu, S, Riess, JW, Rao, SD, Daly, ME & Chen, AM 2018, 'Functional Outcomes After De-escalated Chemoradiation Therapy for Human Papillomavirus-Positive Oropharyngeal Cancer: Secondary Analysis of a Phase 2 Trial', *International Journal of Radiation Oncology, Biology, Physics*, vol. 100, no. 3, pp. 647-651.	No response
Shaverdian, N, Hegde, JV, Felix, C, Hsu, S, Basehart, V, Steinberg, ML & Chen, AM 2019, 'Patient perspectives and treatment regret after de-escalated chemoradiation for human papillomavirus-positive oropharyngeal cancer: Findings from a phase II trial', *Head and Neck*, vol. 41, no. 8, pp. 2768-2776.	No response

Appendix 6: Data extraction sheet – primary outcomes

Reference study	Data extracted from	Type of study	Number (I)	Intervention (reduced dose)	Number (C)	Comparator (standard dose)	Overall survival	Progression free survival	Locoregional control	Distant control	DFS	DSS	CTCAE version 5	SPS	PAS	Gastrostomy tube insertions
Chen 2017	Chen 2017	Single arm phase II trial	24	54Gy IMRT	20	60Gy	N/A	N/A	N/A	N/A	N/A	N/A	no reported grade 4 or worse - 26 (39%) of 44 patients had grade 3 adverse events - most common grade 3 during CRTx was dysphagia in 4(9%) and mucocytosis in 4(9%). 2-year freedom of grade 3 mucosal-oesophageal AE 54Gy: 85%, 60Gy 86%	N/A	N/A	3 (7%) had gastrostomy tubes secondary to grade 3 dysphagia. Only 1(2%) were dependent on gastrostomy tube at 3 months after treatment, nil at 6months
Chen 2017	Hedge 2018	Retrospective cohort	24	54Gy IMRT	20	60Gy	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Chen 2017	Shaverdian 2019	Retrospective cohort	14	54Gy IMRT	10	60Gy	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Misiukiewicz 2019	Misiukiewicz 2019	Phase III trial	12	56Gy IMRT	8	70Gy	3 year: - DDRTx: 83.3 (95% CI 0.65-1.0) - SDRTx: 87.5 (95% CI 0.67-1.0) 2 year: - DDRTx: 83.3 (95% CI 0.65-1.0) - SDRTx: 87.5 (95% CI 0.67-1.0)	3 year: - DDRTx: 83.3 (95% CI 0.65-1.0) - SDRTx: 87.5 (95% CI 0.67-1.0) 2 year (plotdigitizer): - DDRTx: 83.3 (95% CI 0.65-1.0) - SDRTx: 87.5 (95% CI 0.67-1.0)	3 year: - DDRTx: 83.3 - SDRTx: 87.5	No distant failures	N/A	N/A	N/A	N/A	N/A - 4RD had gastrostomy tube - 2 SD had gastrostomy tube - nil further information
Seiwert 2019	Seiwert 2019	Phase II trial	50	45-50Gy	11	75Gy	N/A	N/A	N/A	N/A	N/A	N/A	acute grade 3+ mucositis and dermatitis were significantly lower in reduced dose group: - mucositis: 30% RT50, 63% CRT45, 91%CRT75, p=0.004 - dermatitis: 0%RT50, 20%CRT45, 55%CRT75, p<0.0001 - anorexia: 0% RT50, 7% CRT45, 9%CRT75 - neutropenia: 0% RT50, 23% CRT45, 18%CRT75	N/A	N/A	liklihood of ever requiring a PEG tube was significantly lower in the de-escalated treatment arms (0%(0/50) RT50, 31%(9/30) CRT45, 82%(9/11) CRT75, p<0.0001)
Seiwert 2019	Foster 2020	Retrospective cohort	50	45-50Gy	11	75Gy	N/A	N/A	N/A	N/A	N/A	N/A	N/A	- DDRTx: 1-2: 18(46%); 3: 13(33%); 4-5: 8(21%); 6-7: 0(0%) - SDRTx: 1-2: 2(22%); 3: 1(11%); 4-5: 4(44%); 6-7: 2(22%)	Penetration/aspiration scale: - DDRTx: 1-6: 37(95%); >/=7: 2(5%) - SDRTx: 1-6: 6(67%); >/=7: 3(33%)	No patient underwent prophylactic PEG placement 3 months: DDRTx vs SDRTx: 10% vs 64%, p=0.0005) - the difference was not significant at 6 and 12 months - receiving DDRTx: independently associated with a lower 3 month PEG tube dependence (odds ratio 0.10, 95% CI 0.01-0.90, p=0.002) - CRTx75 median PEG duration 6.3months, CRTx45 median duration 3.2months"
Cramer 2018	Cramer 2018	Retrospective cohort	673	58.9Gy	1004	59.7	2yOS: S alone: 98.1%, S+<50Gy: 94.7%, S+50Gy: 96.9, S+60Gy: 98.3%, S+70Gy: 96.8% 3yOS: S alone: 97.0%, S+<50Gy: 91.6% , S+50Gy: 94.9%, S+60Gy: 97.3%, S+70Gy: 94.7%	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Ma 2019	Ma 2019	Phase II trial	36	30Gy	43	30Gy	2yOS: 98.7% 3yOS: overall: 96.2%	2yPFS: overall: 91.1% 3yPFS: overall: 84.8%	2 year LRC: cohort A: 100%, cohort B: 93%	2 year:cohort A: 97%, cohort B: 93%	N/A	N/A	grade 3 or worse AE at timepoints; pre-RT, 1 and 2 years, 0%, 6.7% and 0% respectively	swallow impairment profile: - 5.8 +/- 3.8 vs 4.5 +/- 3.6; p=0.01		1 patient had a PEG placed immediately after RTx and removed within 1month post treatment.
Moore 2021	Moore 2021	Retrospective cohort	79	30Gy	115	60Gy	3 year OS: DDRTx: 96%, SDRTx: 93%	3 year PFS: - DDRTx: 87% (95%CI 79-95%) - SDRTx: 90% (95%CI 84-96%) - HR 1.18, 95% CI 0.50-2.75 2 year PFS: - DDRTx: 91% (95%CI 85-98%) - SDRTx: 90% (95%CI 84-96%)	3 year LRC - DDRTx: 96% (95%CI92-100) - SDRTx: 99%(95%CI 97-100)	3 year DMFS: - DDRTx: 91% (95%CI85-98%) - SDRTx: 91% (95%CI 86-97%)	N/A	N/A	N/A	N/A	N/A	N/A
Miles 2021	Miles 2021	Phase II trial	29	50-56Gy	N/A	N/A	N/A	2-5yPFS group 1: 91.3%, group 2: 86.7%, group 3: 93.3%	90.70%	98.1%	98.10%	100%	group 1: most common AE: dysphagia in 10/27 (37%), severe pain in 8/27 (29.6%), xerostomia in 3/27 (11.1%). group 2: altered taste/dysgeusia in 15/15 (100%), xerostomia in 10/15 (66.6%), severe pain in 10/15 (66.6%), group 3 dysphagia in 16/16 (100%), pain in 16/16 (100%), grade 3 mucositis in 8/16 (50%)	N/A	N/A	N/A
Riaz 2021	Riaz 2021	Prospective cohort	15	30Gy	4	70Gy	2 year: DDRTx: 92.9%, 95% CI 80.3-100% - overall (all 19): 94.7%, 95% CI 85.2-100% 3year OS: DDRTx: 92.8%, SDRTx: 75%	2 year: DDRTx: 92.9%, 95%CI 80.3-100% 3year PFS: DDRTx: 92.8%, SDRTx: 75%	2 year: - DDRTx: 100%, 95% CI 100-100%	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Gabani 2019	Gabani 2019	Retrospective cohort	104	50-66Gy	655	>/= 66Gy	3yOS - DDRTx: 83.1%, SDRTx: 79.4%, p=0.63	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Judy 2018	Judy 2018	Retrospective cohort	40	60Gy	25	70Gy	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Post-treatment MBS SD had more laryngeal penetration with both thin and puree consistencies (50% vs 45%, p=0.33 and 18% vs 13%, p=0.32), no aspiration with puree or solids in either cohort		- SD: 63%(mean duration 16weeks) - RD: 55% (mean duration 14weeks)
Smith 2004	Smith 2004	phase I-II clinical trial	11	60Gy	18	74Gy	2yOS: - 74.4Gy: 54%, 60Gy: 65.4%	N/A	N/A	N/A	N/A	N/A	Mucositis scores were similar at the completion of therapy but were significantly less in the 60Gy patients at 4 months (p=0.006) and approached significance at 12 months (p=0.07).	N/A	4month aspiration with: liquids: 81% (13/16) vs 11% (1/9); p<0.001, puree: 69% (11/16) vs 11% (1/9); p=0.004, solids: 69% (11/16) vs 25% (2/8); p=0.03 12month 74Gy vs 60Gy aspiration with: liquids: 60% (6/10) vs 11% (1/9); p<0.04, puree: 60% (6/10) vs 11% (1/9); p=0.03, solids: 60% (6/10) vs 0% (0/8); p=0.007	Overall prevalence of gastrostomy tubes was reduced from 78% (14/18) following 74.4Gy to 18% (2/11) following 60Gy (p=0.002, log rank test)
Tam 2020	Tam 2020	Retrospective cohort	124	>50Gy but <66Gy	2049	>/=66Gy to <80Gy	3yOS: >/=66Gy: 88.5% (95%CI 87.0-90.1%), 50-<66Gy: 89.9% (95%CI 84.0-96.2%)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
White 2020	White 2020	Retrospective cohort	104	54Gy but <66Gy	513	>/=66Gy to <80Gy	3y OS: 54-<66Gy: 83%, >/=66Gy: 83%	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Appendix 7: Data extraction sheet – secondary outcomes

Data extracted from	Hospital readmissions	EORTC QLQ-H&N 35	PSS-H&N	FACT-H&N	UW-QOL	FOIS	EAT-10	MDADI	XeQoLS	Chicago priorities scale	Decision regret scale
Chen 2017	2 readmissions - aspiration pneumonia - anxiety and panic attacks	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Hedge 2018	N/A	N/A	N/A	median baseline score was 34 (17-40) - median 1-year: 32 (20-40) - median 2-year: 29 (16-38)	swallowing domain: baseline: 94.3, 4weeks: 69.0, 1-year: 87.0, 2-year: 83.0 physical baseline: 93.9, 4weeks: 62.7, 1-year: 79.5, 2-year: 80.3 social: baseline: 78., 4weeks: 69.9, 1-year: 89.4, 2-year: 88.6	N/A	N/A	N/A	N/A	N/A	N/A
Shaverdian 2019	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	- 22 of 24 (92%) had 'being cured of my cancer" as number 1 overall treatment priority, other 2 had "living as long as possible" and "having no pain" as top when assessing those who chose de-escalated radiotherapy reasons were: 1st: 63%"being able to swallow all foods and drinks", "having no pain', 'returning to my regular activities as soon as possible', 'having a comfortably moist mouth' and 'keeping my normal sense of taste and smell'	-20/24, 83% selected they were 'totally satisfied' with their treatment and its result, remaining were 'somewhat satisfied', none were 'neither satisfied nor dissatisfied' or any level of dissatisfaction - 92% chose 'strongly disagree' to "I regret the choice I made" - 18/24 (75%) whose 'strongly agree" to 'i would go for the same choice if i had to do it again'
Misiukiewicz 2019	5 in 4 patients: - 3 in 2pts in SD arm, syncope, dehydration, mucositis - 2pts in RD, opioid overdose, mucositis/pain management	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Seiwert 2019	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Foster 2020	N/A	N/A	PSS-HN diet score: p=0.33 - DDRTx: <100: 16(43%); 100: 21(57%) - SDRTx: <100: 8(89%); 100: 1(11%) PSS-HN speech score: - DDRTx: <100: 0(0%); 100: 37(100%) - SDRTx: <100: 1(11%); 100: 8(89%) PSS-HN public eating score:- p=0.18 - DDRTx: <100: 8(22%); 100: 28(78%) - SDRTx: <100: 5(71%); 100: 2(29%)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Cramer 2018	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Ma 2019	N/A	1 year post vs pre: 106.3+/- 10.7 vs 111.4 +/- 9.2, p<0.001	N/A	1 year post vs pre: 116.9+/- 17.2 vs 127.2 +/- 17.7, p<0.001	N/A	. Pre vs 12months post .- FOIS: 6.0 +/- 0.9 vs 6.3 +/- 1.0; p=0.01	N/A	N/A	- XeQoLS - xerostomia - worsened in the 1month post treatment period then returned to baseline at 12months: 0.3 +/- 0.4 v 0.6+/-0.5; p<0.001 --> 12 months 0.3+/-0.4; p=0.67	N/A	N/A
Moore 2021	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Miles 2021	N/A	N/A	N/A	N/A	N/A	N/A	N/A	group 1: TORS alone: no difference pre(89)/post-op(always above 89) group 2 TORS+50Gy: mean composite score decreased to 76 3months post RTx (p-0.027) but returned to 85 after 6months group 3 TORS/Cisplatin/56Gy: decreased to 63 at 3months (p=0.0001), slow improvement. 71 at 6months (p=0.011). 78 at 1 year. 88 at 2 years.	N/A	N/A	N/A
Riaz 2021	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Gabani 2019	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Judy 2018	N/A	Pre and 2y post EORTC QLQ-H&N35 - problems swallowing liquids - 1.4 and 1.2 (/4) - problems swallowing purees - 1.2 and 1.1 (/4) - problems swallowing solids - 1.5 and 1.7 (/4) - choked when swallowing - 1.0 and 1.3 (/4)	N/A	N/A	N/A	N/A	DDRTx group EAT-10 - mean pre- and 2y post 3.3 and 5.9 respectively	N/A	N/A	N/A	N/A
Smith 2004	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Tam 2020	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
White 2020	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Appendix 8: Results of ROB-2 critical appraisal

Study ID	Treatment group/co-intervention	Radiotherapy treatment dose		Outcome	Bias summary					
		Experimental	Comparator		D1	D2	D3	D4	D5	Overall
Miles 2021	Primary surgery	50Gy or 56Gy	No radiotherapy	Overall survival	-	+	+	+	+	!
Miles 2021	Primary surgery	50Gy or 56Gy	No radiotherapy	Progression free survival	-	+	+	+	+	!
Miles 2021	Primary surgery	50Gy or 56Gy	No radiotherapy	Disease free survival	-	+	+	+	+	!
Miles 2021	Primary surgery	50Gy or 56Gy	No radiotherapy	Disease specific survival	-	+	+	+	+	!
Miles 2021	Primary surgery	50Gy or 56Gy	No radiotherapy	Toxicity	-	+	+	!	+	!
Miles 2021	Primary surgery	50Gy or 56Gy	No radiotherapy	PROM	-	+	+	-	+	!
Misiukiewicz 2019	Induction chemotherapy	56Gy	70Gy	Overall survival	-	+	+	+	+	!
Misiukiewicz 2019	Induction chemotherapy	56Gy	70Gy	Progression free survival	-	+	+	+	+	!
Misiukiewicz 2019	Induction chemotherapy	56Gy	70Gy	Hospital readmissions	-	+	+	!	!	!
Riaz 2020	Primary surgery	30Gy	70Gy	Overall survival	-	!	+	+	+	-
Riaz 2020	Primary surgery	30Gy	70Gy	Progression free survival	-	!	+	+	+	-
Riaz 2020	Primary surgery	30Gy	70Gy	Disease free survival	-	!	+	+	+	-
Riaz 2020	Primary surgery	30Gy	70Gy	Toxicity	-	!	+	+	+	-
Seiwert 2018	Induction chemotherapy	45Gy or 50Gy	75Gy	Overall survival	-	+	+	+	+	!
Seiwert 2018	Induction chemotherapy	45Gy or 50Gy	75Gy	Progression free survival	-	+	+	+	+	!
Seiwert 2018	Induction chemotherapy	45Gy or 50Gy	75Gy	Toxicity	-	+	+	+	+	!
Smith 2004	Primary (chemo)radiotherapy	60Gy	74.4Gy	Overall survival	-	+	-	+	+	!
Smith 2004	Primary (chemo)radiotherapy	60Gy	74.4Gy	Toxicity	-	+	-	-	+	-
Hedge 2017	Induction chemotherapy	54Gy	60Gy	Patient reported outcome measures	-	!	+	-	+	!
Ma 2019	Primary surgery	30Gy or 36Gy	N/A	Overall survival	-	+	+	+	+	!
Ma 2019	Primary surgery	30Gy or 36Gy	N/A	Progression free survival	-	+	+	+	+	!
Ma 2019	Primary surgery	30Gy or 36Gy	N/A	Toxicity	-	+	+	+	+	!
Ma 2019	Primary surgery	30Gy or 36Gy	N/A	Patient reported outcome measures	-	+	+	-	-	-
Chen 2017	Induction chemotherapy	54Gy	60Gy	Overall survival	-	!	+	+	+	!
Chen 2017	Induction chemotherapy	54Gy	60Gy	Progression free survival	-	!	+	+	+	!
Chen 2017	Induction chemotherapy	54Gy	60Gy	Disease free survival	-	!	+	+	+	!
Chen 2017	Induction chemotherapy	54Gy	60Gy	Toxicity	-	!	+	+	+	!

Key to Risk Assessment

+ Low risk
! Some concerns
- High risk

Key to Bias Summary

D1	Randomisation process
D2	Deviations from the intended interventions
D3	Missing outcome data
D4	Measurement of the outcome
D5	Selection of the reported result

Appendix 9: Results of ROBINS-I critical appraisal

		Bias summary							
Reference	Outcome(s)	Confounding	Participant selection	Classification of intervention	Deviations from intended interventions	Missing data	Outcome measurement	Result reporting	Overall
Gabani 2019	Overall survival	LOW	LOW	MODERATE	LOW	LOW	LOW	LOW	LOW
Moore 2020	OS, PFS, DFS	SERIOUS	LOW	LOW	LOW	LOW	LOW	LOW	SERIOUS
Tam 2020	OS	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Cramer 2018	OS	LOW	LOW	LOW	LOW	LOW	LOW	MODERATE	MODERATE
Judy 2018	PROM	MODERATE	LOW	LOW	LOW	MODERATE	MODERATE	LOW	MODERATE
White 2020	OS	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW

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