Oncological and survival outcomes following transoral robotic surgery versus transoral laser microsurgery for the treatment of oropharyngeal squamous cell carcinoma: a systematic review of case series

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Declaration

I 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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Executive summary

Background

Transoral laser microsurgery (TLM) and transoral robotic surgery (TORS) are two principal minimally invasive transoral surgical techniques for the treatment of patients with oropharyngeal squamous cell carcinoma (OPSCC). Currently this increasingly common disease is more often caused by exposure to the human papilloma virus (HPV) rather than tobacco or alcohol. This condition affects younger patients who have a much better prognosis. These minimally invasive techniques have superseded traditional open surgical techniques in the management of head and neck cancer, and also provide a genuine alternative to radiotherapy for definitive treatment. While both TLM and TORS have been shown in case series to have good oncological outcomes, the key differences between both approaches warrant a detailed comparison.

Objectives

The objective of this systematic review was to synthesize the best available evidence regarding the oncological and survival outcomes (as measured by DC, DFS, DSS and OS) of TORS versus TLM for the treatment of oropharyngeal squamous cell carcinoma in adults.

Inclusion criteria

The patient populations studied were male and female adults who had undergone transoral endoscopic surgery with TORS or TLM for the treatment of primary squamous cell carcinoma arising from the oropharyngeal mucosa. The tumor could be of any T-stage and HPV status, but surgical treatment had to have been aimed at curative intent rather than palliation.

Methods

A comprehensive search strategy was employed to find both published and unpublished studies that evaluated local, regional and distant control, tumor margins, and disease free, disease specific and overall survival outcomes. Databases that were searched included PubMed, CINAHL, Embase, Web

of Knowledge and Scopus. Grey Literature was searched through the Cochrane Register of Controlled Trials (CENTRAL), Scirus, MedNar and ProQuest.

Results

Seventeen cases series were included in this review, of which 11 studies had TLM as the intervention of interest and six studies examined TORS. There were a total of 1,257 patients included in this review with ages ranging between 27 and 92 with 65% of patients being male and 35% female. Follow-up periods ranged from one to 132 months and outcomes were measured at one, two, three and five years. Differences in oncological outcomes between TLM and TORS could not be elucidated generally, and with respect to particular patient sub-groups, such as patients with a positive HPV status or patients with different tumor T-stages.

Conclusions

Both TORS and TLM can achieve complete tumor resection. Significant heterogeneity of extracted data and inclusion of studies with low levels of evidence eliminated valid comparison of oncological and survival outcomes between TORS and TLM, therefore there was no means to show superiority of one approach over the other. Operator and institution experience, as well as factors relating to cost and availability, will likely dictate which surgical platform is used. With ever expanding minimally invasive surgical technology and ongoing development of competing surgical platforms, the imperative will lie with leading surgeons around the globe to construct and execute well-designed trials.

Chapter 1: Introduction

1.1. Context of the review

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer worldwide and oropharyngeal squamous cell carcinoma (OPSCC) accounts for about 10% of this burden.[2] The oropharynx is the only site in the head and neck where there is a rising incidence of disease, which in the last decade has been linked with the human papilloma virus (HPV) epidemic.[3] Improved public health measures to reduce tobacco and alcohol use, coupled with a rise in the prevalence of HPV, has seen an increasing proportion of patients with HPV positive OPSCC.[4] These patients tend to be younger and have a better prognosis, which has provided the stimulus for advancements in management to reduce morbidity.[5] These include intensity modulated radiotherapy (IMRT) and minimally invasive transoral endoscopic surgery (TES).

The two principal minimally invasive transoral surgical approaches to the oropharynx are transoral laser microsurgery (TLM) and transoral robotic surgery (TORS), both of which have a different set of advantages and disadvantages. While large case series have shown that both approaches have good oncological and functional results, the two approaches have not been systematically compared to determine if one has significantly better oncological outcomes than the other.[6-8] This thesis presents a synthesis of the best available evidence regarding the oncological and survival outcomes of TORS versus TLM for the treatment of OPSCC.

1.2. Anatomy of the oropharynx

The oropharynx is a complex three-dimensional anatomical subsite of the head and neck, which forms the middle part of the pharynx. It is crucially involved in the functions of swallowing, breathing and speech.[9] The boundary between the oral cavity and the oropharynx is marked by the palatoglossal folds that cover the palatoglossal muscles laterally inside the mouth. The superior boundary of the oropharynx is the hard and soft palate junction. The inferior boundary is the upper margin of the epiglottis (a cartilage in the larynx that acts as a valve to prevent aspiration of food into the airway). The lateral walls of the oropharynx are the palatine tonsils. These are large ovoid collections of lymphoid tissue housed in the tonsillar fossa between the palatoglossal and

palatopharyngeal arches. The posterior extent of the oropharynx is the posterior pharyngeal wall. This is composed of the superior constrictor muscle and the buccopharyngeal and pharyngobasilar fascia covered by the pharyngeal mucosa. The oropharyngeal contents therefore include the soft palate, base of tongue, palatine tonsils and posterior pharyngeal wall (from the hard/soft palate junction superiorly to the tip of the epiglottis inferiorly).[9]

1.3. Oropharyngeal squamous cell carcinoma

1.3.1. Epidemiology

Squamous cell carcinoma is an invasive epithelial neoplasm with varying degrees of squamous differentiation and a propensity to early and extensive lymph node metastases. Head and neck cancer is most commonly of the squamous cell type (HNSCC) and is the sixth most common cancer in the world.[10] Almost 600,000 cases are reported annually and of these, approximately 10% (depending on the geographic location) are oropharyngeal SCC (OPSCC).[10] Tonsillar cancer is the most common type of OPSCC, followed by base of tongue cancer. Together, these two cancers account for 90% of all OPSCCs.[11]

1.3.2. Etiology of OPSCC and the significance of HPV

The risk factors for OPSCC have traditionally been tobacco and alcohol use.[12] The risk of OPSCC is nearly seven times higher in active smokers compared with non-smokers and two-and-a-half times higher in regular drinkers compared to non- or occasional drinkers. [13, 14] Case control studies have shown a super-multiplicative effect in patients with use of both substances.[15] The etiology of OPSCC is of significance in management decisions because the population of patients that it affects and their prognosis are different. Traditional OPSCC, with smoking and alcohol as its risk factors, affects people over the age of 60.[16] It involves the inactivation of the p16 gene, which is used as a prognostic biomarker for OPSCC, and patients tend not to have bulky cervical lymph nodes on presentation. Patients with this HPV-negative disease, who are smokers and/or drinkers, have a poorer prognosis than HPV-positive non-smokers and non-drinkers, with the five-year survival estimated to be between 40% and 60%.[12]

In the last decade, HPV infection transmitted by orogenital sex has become a well-recognized risk factor for OPSCC.[3, 17, 18] Population-level incidence of HPV-positive OPSCC increased by 225% from 1998 to 2004, and if recent trends continue, the annual incidence of HPV-positive OPSCC is expected to surpass that of cervical cancer by the year 2020.[19] The emergence of the HPV-OPSCC has therefore been deemed an epidemic of our times.[18] Patients with HPV associated OPSCC tend to be younger, typically in the age range of 40-60.[16] They do not usually have a history of smoking or

alcohol addiction and epidemiological studies suggest a correlation with multiple sexual partners, sex from an early age, and transmission of the virus via orogenital sex.[20, 21] These tumors overexpress the p16 gene and patients are found to have a small primary tumor at presentation with bulky and cystic cervical nodes. Unlike the traditional group of OPSCC patients, HPV positive OPSCC patients have a good prognosis with five-year survival quoted at 80-90% and infrequent local recurrence.[22, 23]

1.3.3. Clinical presentation and patterns of spread

Patients with OPSCC can present with a neck lump, dysphagia (difficulty swallowing), odynophagia (pain on swallowing), a sore throat, a sensation of a mass in the throat, or referred otalgia (ear pain).[16] Examination involves a close inspection and palpation of the oropharyngeal site as well as examination of the other subsites of the head and neck to exclude a simultaneous primary. The neck is palpated for cervical lymphadenopathy (enlarged neck nodes) to determine if there has been lymphatic spread of cancerous cells from the oropharynx to the neck. Spread from the oropharynx is usually to the level IIa lymph nodes at the upper aspect of the internal jugular vein (jugulodigastric or tonsillar node).[16] Spread of cancer cells to cervical lymph nodes plays a role in staging of patients as it is one of the most accurate predictors of cancer-related outcomes in HNSCC patients.[24, 25] A study which analyzed the American National Cancer Database demonstrated a significant overall survival advantage in patients who are clinically node negative.[26]

1.3.4. Diagnostic evaluation

Diagnosis and assessment of OPSCC requires a thorough clinical evaluation followed by appropriate imaging and tissue sampling. The diagnosis of SCC is confirmed with a tissue sample from the tumor, which can be taken from the primary site under local or general anesthesia. The tissue undergoes histopathological assessment and p16 status is determined as a surrogate marker of HPV tumors by use of immunohistochemistry analysis. [16]

A CT of the head and neck helps to plan treatment, and a staging CT scan of the chest and upper abdomen evaluates the presence of distant metastases.[27] At our institution, examination of the tumor under anaesthesia and rigid endoscopy are used to determine the extent of the disease and

its suitability for trans-oral resection, as well as evaluating the remainder of the upper aerodigestive tract for simultaneous primaries.

1.4. Staging of OPSSC

Oropharyngeal cancer is staged using the American Joint Committee on Cancer (AJCC) Staging system Edition 7.[28] This categorization of head and neck tumors assists with assessing disease status, prognosis and management. The T category indicates tumor size, depth and spread to adjacent structures, the N category indicates the degree of spread to regional cervical lymph nodes and the M category identifies if there is a distant metastasis.

A table is used to give a numerical status of the disease from I to IV based on the TNM classification (Table 1). Stage I-II is considered early disease and stage III-IV is considered advanced. Early stage disease can be treated with a single modality treatment, whereas late disease usually requires multimodality treatment if the intent to treat is curative.

Stage Group	T Stage	N Stage	M Stage
0	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
IVa	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
IVb	T4b	Any N	M0
	Any T	N3	M0
IVc	Any T	Any N	M1

Table 1: Stage grouping for all head and neck sites except the nasopharynx and thyroid

Tis: Tumor in situ, T: Tumor, N: Node, M: Mestastasise

(Adapted from AJCC Cancer Staging Manual, Sixth Edition [2002] published by Springer-Verlag New York, www.springeronline.com)[29]

1.5. Prognostication of OPSCC

Tumor/node/metastasis (TNM) stage as defined by the AJCC has traditionally been the system used as a determinant of HNSCC survival.[28] However, more recently, tumor HPV status has repeatedly been found to be the most influential determinant of HNSCC survival prompting studies to reconfigure how we stage OPSCC.[30] Predicting long-term survival for OPSCC is complex because outside of the AJCC stage and HPV status, there are several other factors such as smoking, lymphovascular invasion and perineural spread that are all associated with adverse survival outcomes.[22] In one of the largest studies examining the long-term survival of patients with OPSCC, generally those with localized disease were found to have a 62% five-year survival, compared to 56% and 27.9% for those with regional and distant disease, respectively (P value < 0.0001).[31]

1.6. Historic perspective on treatment of oropharyngeal SCC

Oropharyngeal SCC is primarily treated with radiotherapy or surgery. Over the years the preference of one treatment modality over the other has shifted back and forth as technology evolved and understanding of the disease progressed.

At the start of the 20th century, early methods of radiation were used. The use of this rudimentary technology resulted in large necrotic wounds requiring carotid artery ligation to prevent life-threatening bleeds, and tracheotomy to allow for breathing below the edematous post-radiated upper aerodigetive tract.[32]

In the 1940s, surgical resection of OPSCC became favored, as there were advances in perioperative medical care that made post-operative management of these patients feasible.[33] Open surgery was again not without significant morbidity, as the lip and mandible (jaw bone) needed to be split and separated for the surgeon to access the tumor for resection. The trauma to the tissue and musculature around the mouth disrupted the patient's ability to swallow and speak, and often left them with temporomandibular joint pain and cosmetic deformity. These patients often required tissue transfer for reconstruction, a percutaneous enteric gastrostomy (PEG) tube for feeding and a tracheotomy for breathing.[33]

In the second half of the 20th century, radiotherapy made a resurgence with improvements in technology allowing for more targeted radiation fields with the ability to deliver higher dosage radiation to specific areas while limiting damage to sensitive surrounding healthy tissue.[34] In 1991 the landmark Veterans' Administration study demonstrated that chemoradiation had equal survival outcomes to surgery and also allowed for preservation of the larynx in patients with advanced laryngeal SCC.[35] These results were extrapolated to the oropharynx, and again chemoradiation swung back into favor, as head and neck clinicians adopted a non-surgical 'organ-preservation' mentality.

1.7. Modern minimally invasive surgical approaches to OPSCC

In the current epidemic of HPV related OPSCC, where patients are being diagnosed younger and are surviving longer, treatment of choice is now focused on providing a cure with the least long-term complications and this has led to the rise of minimally invasive surgical approaches.

Transoral surgery as a management modality has several advantages, all of which, when combined, confer theoretical treatment advantages for the patient, and which are currently being evaluated in several clinical trials.[36] By surgically resecting a tumor, as opposed to treating it with chemoradiotherapy, we can have an accurate pathological diagnosis about tumor size, grade, extent of spread and stage, thereby obtaining diagnostic information as well as providing a therapeutic treatment. Resecting the tumor transorally is the least invasive surgical approach to obtain this pathological information.[37] By having this histopathological diagnosis from the resected tumor, there is a potential to de-intensify further treatment received after surgery (adjuvant therapy) in selected cases with a pathologically favorable profile. By way of example, consider a patient who may have been initially diagnosed with a higher TNM stage based on radiological and clinical findings. Following surgery and pathological examination of the resected specimen, they are actually found to have a lower TNM stage than initially thought, meaning, they are down-staged and treated accordingly. Depending on their new stage, they may not need for further treatment with chemoradiotherapy (also known as adjuvant therapy) according to their institution protocols. [38-40] The benefit of this is of course the elimination of side effects from radiotherapy and chemotherapy of which they would otherwise have been at risk.

The two minimally invasive transoral endoscopic surgical approaches to the oropharynx are transoral laser microsurgery (TLM) and transoral robotic surgery (TORS), which will be elaborated upon further in the following sections.[37]

1.7.1. Transoral laser microsurgery (TLM)

Transoral laser microsurgery was developed in Europe in the 1960s and 1970s and was the first transoral endoscopic surgical approach used by head and neck surgeons.[41] Transoral laser microsurgery uses a laser delivery device (usually a carbon dioxide laser) and a binocular operating microscope to direct a laser beam through the mouth at the area of tissue to be resected. The CO2 laser beam is absorbed by water at the tissue-laser interface and is transformed into thermal energy, which produces a tissue cutting capability.

Initially TLM was developed for early stage laryngeal cancer and found to have good functional and oncological outcomes.[6, 7] Its use has expanded to the pharynx and oral cavity where it has also been shown to have good survival results when compared to other approaches such as open surgery or radiotherapy.[42] This conclusion was based on a prospective multi-center study of 204 patients treated by TLM which demonstrated a good three-year overall survival (OS), disease-specific survival (DSS) and disease-free survival (DFS).[42] Overall survival was defined as the time from surgery to the date of death resulting from any cause. Disease-specific survival was defined as the time from surgery to the date of death from oropharyngeal cancer or direct effects of its treatment. Disease-free survival was defined as the time from surgery to the date of death or recurrence of disease.[42] Transoral laser microsurgery has since become a well-established technique in the treatment of OPSCC.

The use of TLM for OPSCC resection is a particularly unique form of surgical oncological resection. The microscope provides a limited field of view and has diminished illumination deep in the oropharynx and because the laser is projected in a linear fashion there are line-of-site restraints that prohibit the laser from being deployed around curved surfaces. This means that resection of the tumor often requires a segmental, sometimes labeled 'piece-meal', approach to dissection as described by Steiner and colleagues.[43] Removal of each piece of tumor results in easy visual access for removal of subsequent segments. This approach was initially thought to go against traditional Halstedian surgical oncological principles of removing a tumor *en bloc*, as it posed a theoretical risk of leaking tumor and disseminating cancerous cells.[44] Several case series of patients with head and

neck SCC at various sub-sites treated with TLM have shown good oncological results and have since been used to establish the oncological safety of this approach.[45-47] These case series have been included in this review and the results are presented in the results section.

The minimally invasive TLM approach spares the patient the need for splitting of the lip and mandible required in open surgical tumor resection. The benefit of this is that the patient is spared trauma to the tissue and musculature around the mouth, as well as disruption to swallowing and speech that results from this. It also eliminates side effects of temporomandibular joint pain and cosmetic deformity that are also adverse effects of the open approach. [33]

However there are noticeable limitations of TLM. The surgeon is required to use one hand to hold the instrument while the other manipulates the laser. As a consequence, this technique has a steep learning curve. The laser is not an ideal tool for haemostasis, so the TLM procedure requires alternations between the laser and a cautery instrument or surgical clips to achieve haemostasis, . thus making TLM a complex procedure. The technique also relies on uniplanar instruments being used through the laryngoscope, which act as a fulcrum, leading to accentuation of tremor at the distal tip, as well as counter intuitive movements (moving the hand holding the instrument to the right moves the instrument in the resection field to the left).[48]

1.7.2. Transoral robotic surgery (TORS)

The surgical robot was initially designed with the goal of performing telesurgery and eliminating human tremor, but it became better recognized for its effectiveness in minimally invasive surgical approaches in the abdomen and pelvis.

The da Vinci Surgical System (intuitive Surgical Inc., Sunnyvale, CA) was the first robotic platform described for TORS and has become the established device for robotic surgery, with almost all of the literature to date reporting on outcomes from this system. [49, 50] New robotic surgical devices are being developed, and there has been a recent release of the Medrobotics flex system (Medrobotics, Raynham, Massachusetts, USA) in the market, with published early case series demonstrating feasibility.[51, 52] The da Vinci system comprises a surgeon console and a patient side cart consisting of a 30-degree maneuverable binocular scope, a vision system and two arms for attachment of instruments.[53] The surgeon sits away from the robot at the surgeon console, which provides a three-dimensional high definition image of the operating area and a wide field of vision. From this

position, the surgeon manipulates the movement of the robotic arms and camera in a 'master-slave' fashion with controls that de-escalate movement and filter tremor. The two robotic arms allow for bimanual handling of tissue and give greater range of motion of the robotic instruments.

In 2005 Hockstein demonstrated on a mannequin that a robot could be used through the natural orifice of the mouth to gain access to the larynx and pharynx.[49, 50] Weinstein and O'Malley refined the use of oral retractors and instrumentation in canine and cadaveric models, thereby paving the way for US Food and Drug Administration (FDA) approval in 2009 for transoral otolaryngological use of a robot in humans.[53-55] It has since gained significant momentum, with studies showing good oncological and functional outcomes.[8] A prospective single institution case series of 66 TORS patients showed three-year local control and regional control of 97% and 94%, respectively, and two-year disease-specific survival and recurrence-free survival of 95.1% and 92.4%, respectively. The authors of this study concluded that these outcomes were equivalent or superior to the results of other surgical and non-surgical treatments.[8] While it is not the purpose of this review to compare TES with open surgery or non-surgical treatments, a comparison of survival outcomes between these modalities is elaborated upon in the discussion section.

One major advantage of TORS over TLM is that the robot eliminates the line-of-sight issues and one-handed surgery that make TLM particularly challenging, which means that Halstedian principals of *en bloc* tumor resection can more easily be upheld. The major drawbacks of TORS relate to the high expense of robot set-up and ongoing use, which limits its uptake to hospitals and departments that can afford it.[56, 57] Furthermore, training and accreditation requirements restrict which surgeons can use this operating system and the robot is often shared between various other surgical subspecialties, impeding its day-to-day availability.

1.8. Alternatives to surgery for treatment and adjuvant therapy

Radiotherapy continues to be a widely used technique for treating OPSCC. Oncological outcomes from surgical and radiotherapy protocols are deemed to be comparable based on case series, while we await the results of RCTs.[58-61]

While early stages of OPSCC can be successfully treated with either modality alone, surgical candidates with more advanced stages, such as stage III or IV disease, usually require a combination of both to achieve satisfactory local regional control.[62] Furthermore, enhancement of radiotherapy with simultaneous application of chemotherapy has been shown to be advantageous in randomized trials, especially in the presence of risk factors such as positive or close resection margins and nodal involvement with extracapsular spread (ECS).[38, 39, 63]

Some of the risks associated with radiotherapy relate to adverse effects of delayed toxicity, such as mucositis (painful ulceration of the mucous membranes in the mouth), xerostomia (dry mouth), fibrosis, dysphagia (difficulty swallowing), trismus (inability to open the mouth fully) and osteoradionecrosis (bone death) of the jaw, which can occur many years after the initial treatment.[64] Oral mucositis has a high incidence, ranging from 97% to100%, depending on the type of radiotherapy regimes used.[65] Osteoradionecrosis is one of the most devastating consequences of late toxicity, with chronic painful necrosis and deformity of the jaw, but is much less frequent, with incidences quoted between 1.2% to 2.3%.[66]

1.9. Justification of need for evidence synthesis in this area

Transoral laser microsurgery and TORS are both well-established transoral endoscopic surgical approaches for management of OPSCC with individually proven acceptable oncological and functional outcomes as already outlined. There are however no studies systematically comparing these two approaches for the treatment of OPSCC. Currently there are no randomized control trials or quasi-experimental studies comparing TORS with TLM. Almost all of the studies looking at clinical outcomes following TORS and TLM are retrospective or prospective case series.

A preliminary search of the *JBI Database of Systematic Reviews and Implementation Reports*, the Cochrane Library, MEDLINE, Embase and CINAHL found several literature reviews on TES for OPSCC.[32, 48, 67-69] These reviews were performed by experts in the field and describe some of the oncological and functional results of both TORS and TLM; however there are no systematic reviews in this area.

There are some key differences in the surgical techniques used between TORS and TLM that might lead to differences in oncological and survival outcomes. Transoral robotic surgery can be described

as an anatomical dissection, while TLM can be described as a tumor dissection. When using TORS for OPSCC resection, the surgeon performs an *en bloc* oropharyngectomy where the tumor in the oropharynx is aimed to be completely resected in one large piece with a cuff of normal surrounding oropharyngeal tissue (i.e. a tumor free margin).[53-55] In comparison, when using TLM for OPSCC resection, a piecemeal laser resection approach is used and this is deemed complete once tumor is no longer detected under the operating microscope, therefore, the surgeon does not necessarily resect the pharyngeal musculature in its entirety. This might mean that microscopic disease is left behind.[43, 44]

A further point of difference that has also been described, and theoretically could give an oncological advantage, is that during TLM surgery, the laser may seal the lymphatics surrounding the tumor site during resection which may prevent further spread of microscopic metastases and recurrence. [43, 44] There is no literature to suggest that the cautery systems used in TORS may have this effect.

The purpose of this systematic review was to take these differences into account and to compare TORS and TLM with respect to their oncological and survival outcomes as defined by disease control (DC), disease free survival (DFS), disease specific survival (DSS) and overall survival (OS).

Chapter 2: Systematic review protocol

This systematic review was conducted according to the Joanna Briggs Institute (JBI) methodology for performing systematic reviews and meta-analysis. A systematic review protocol was prepared and defended in a panel with two experts in the field of academic surgery. It was subsequently peer reviewed and published in the *JBI Database of Systematic Reviews and Implementation Reports*.[70]

2.1. Objective and statement of review questions

The objective of this systematic review was to synthesize the best available evidence regarding the oncological and survival outcomes (as measured by DC, DFS, DSS and OS) of TORS versus TLM for the treatment of OPSCC in adults (aged 18 or older).

The specific questions that this review sought to address were:

Is there a difference in oncological outcomes between a traditional 'Halstedian' *en bloc* tumor resection technique used in TORS versus the segmental tumor dissection technique used in TLM?

Does one surgical approach confer better oncological outcomes with respect to a particular patient or tumor sub-group? For example, could one technique provide better oncological and survival results for tumors that are p16 positive? Or could one technique been shown to provide better oncological and survival outcomes for patient's with different tumor T-stages?

2.2. Inclusion criteria

2.2.1. Types of participants

The patient populations studied were male and female adults (aged 18 or older) who had undergone TES for the treatment of primary SCC arising from the oropharyngeal mucosa (confirmed pathologically). The tumor could be of any T-stage and HPV status. Surgical treatment had to be aimed at curative intent, rather than for palliation.

This review did not consider studies that included:

- Pedeatric populations/animal studies
- Non-English studies
- Patients with non-SCC lesions
- Patients with lesions of the oral cavity, hypopharynx, nasopharynx and larynx
- Patients treated with other forms of treatment (e.g. primary chemoradiotherapy or neoadjuvant chemoradiotherapy)
- Patients treated with novel surgical approaches such as curved lasers, or combining laser instruments with robotic technology
- Patients who underwent salvage surgery (i.e. surgery performed after failed primary treatment with other modalities such as chemotherapy and/or radiotherapy).

2.2.2. Types of interventions

This review considered primary TORS with or without adjuvant radiotherapy or adjuvant chemoradiotherapy as the intervention of interest.

The comparator intervention considered was primary TLM with or without adjuvant radiotherapy or adjuvant chemoradiotherapy.

As this review sought to compare TES treatment of OPSCC only, re-intervention was not considered. The interventions were included regardless of the experience of the person delivering them. The authors were aware that the intensity and dosage of the adjuvant therapy would not be able to have been controlled for and would be dependent upon the treatment protocols used at any individual institution.

2.2.3. Types of outcomes

This review considered studies that included the following oncological and survival outcomes at 1-10 years:

- **Disease control (DC) – local, regional and distant**

Defined as the time from surgery to the date of recurrence of the disease. Recurrence can be classified as occurring locally (at the site of resection), regionally (elsewhere in the head and neck) and distantly (elsewhere in the body).

- **Disease free survival (DFS)**
  Defined as the time from surgery to the date of death from the disease or recurrence of the disease.

- **Disease specific survival (DSS)**
  Defined as the time from surgery to the date of death from disease or the direct effects of treatment of the disease.

- **Overall survival (OS)**
  Defined as the time from surgery to the date of death resulting from any cause.
  The type of data that will be extracted is the percentages of patients (with confidence intervals) from individual case series that have achieved DC/DFS/DSS/OS at time intervals between one and 10 years. This time period will be variable depending on length of follow-up practiced at different institutions and included in their case series. Sub-group analyses may be undertaken to group results at similar time intervals.

The above oncological and survival outcomes definitions were derived from the included studies, which were found during the preliminary search. [42, 71-73]

2.2.4. Types of studies

This review sought both experimental and epidemiological study designs including randomized controlled trials (RCTs), non-randomized controlled trials, quasi-experimental trials, before and after studies, prospective and retrospective cohort studies, case control studies and analytical cross sectional studies. Given the only recent emergence of randomization in clinical surgical research, quasi-experimental studies and other studies were considered for review in the absence of randomised controlled trials.[36] It was thought from preliminary searches that the majority of included studies would likely comprise case series. Literature review articles and conference abstracts were not included.

2.3. Search strategy

A comprehensive three-step search strategy was employed to find both published and unpublished studies. An initial limited search of MEDLINE was undertaken followed by an analysis of the text words contained in the title and abstract, and of the index terms used to describe the article. A second search using all identified keywords and index terms was then undertaken across all included databases (Appendix I) on 26th March 2016. Finally, the reference list of all identified reports and articles was searched for additional studies. Databases were searched from 1960 (the decade in which TLM was first used) until the date of the last search (26th March 2016) for studies published in English. Non-English studies were excluded due to limited funding for translational services.

The databases that were searched included:

- MEDLINE (PubMed)
- CINAHL
- Embase
- Web of Knowledge
- Scopus.

Grey Literature was searched through the Cochrane Register of Controlled Trials (CENTRAL), Scirus, MedNar and ProQuest.

2.4. Study selection

All identified studies were entered and sorted in Endnote™ into groups based on the database the study was extracted from. An automated scanning function of Endnote™ facilitated removal of duplicate studies. A three-step screening process was employed that involved initially screening of titles alone, followed by screening of titles and abstracts, of all identified studies to assess for inclusion and exclusion based on the pre-determined inclusion criteria (Figure 2). The last step was retrieval and full text assessment of remaining studies. If it was unclear as to whether a study fitted the inclusion or exclusion criteria based on the title and abstract alone, the full text was retrieved for further analysis. Excluded studies that underwent full text screening were organized into subgroups based on reasons for exclusion (Appendix XI).

2.5. Critical appraisal

Papers selected for retrieval were assessed by two independent reviewers for methodological validity prior to inclusion in the review using standardized critical appraisal instruments from the Joanna Briggs Institute Meta Analysis of Statistics Assessments and Review Instrument (JBI-MAStARI) (Appendix II). Any disagreements that arose between the reviewers were resolved through discussion, and in the case that no resolution could be found between two, it was proposed that a third reviewer could be consulted, although this was not required in this study.

2.6. Data extraction

Data was quantitative and comprised percentages of patients from case series (with confidence intervals) who achieved DC/DFS/DSS/OS at time intervals between one and 10 years. This was extracted from papers included in the review using the standardized data extraction tool from JBI-MAStARI (Appendix III). The data extracted also included specific details about the interventions, populations, study methods and outcomes of significance to the review question and specific objectives. The authors of the included studies were contacted where important data relevant to the review was missing from the published papers (Appendix XII). Data extraction was undertaken by the author.

2.7. Data synthesis

Attempts were made to pool quantitative data into a statistical meta-analysis using the JBI-MAStARI software. All results were subjected to double data entry to minimize the risk of error during the data entry. Where appropriate, relative risks and odds ratio and their associated 95% confidence interval were calculated for analysis of categorical data. It was planned that a random effects model would be used, with heterogeneity to be assessed statistically using the standard Chi square test and I^2.

Ultimately, statistical meta-analysis and sub-group analysis was not possible due to the significant heterogeneity of data as elaborated upon in the discussion. Findings have therefore been presented

in narrative form including tables and figures to aid in data presentation. Data was split into sub-groups based on years following treatment during which the survival outcome was assessed.

Chapter 3: Results

3.1. Search results

The search identified a total of 3,750 studies. Following removal of duplicates, 2,914 studies remained. Screening of titles lead to the removal of 2,854 studies and a further 27 were removed following screening of abstracts. This left 33 studies for full-text retrieval and detailed examination. Of the 33 studies, 16 were excluded, as they did not meet the strict inclusion criteria. Reasons for exclusion of each of these studies are provided in Appendix XI. No studies were excluded after assessment of methodological quality (discussed in the next section). Seventeen studies were included in the systematic review and we identified these as case series based on the JBI's preferred definition described by Dekker et al.[74] Of these 17 included studies, 11 studies had TLM as the intervention of interest and six studies examined results from use of TORS. These search results have been summarized in the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow diagram as illustrated in Figure 2.

3.2. Assessment of methodological quality

Following the screening and review of full texts, 17 studies underwent critical appraisal by two reviewers trained in the use of JBI-MAStARI (Appendix II). Any disagreements were resolved by discussion between both reviewers. Given the fact that all studies included were case series, therefore had a generally low quality of evidence, it was agreed upon by both reviewers that each study was to be judged on its own merit if it fulfilled a minimum of four of the possible nine points (Appendix II). Ultimately all 17 studies were included in this systematic review.

Methodological quality was fairly similar across all studies ranging between 5 to 7 points, with an average score of 6.47. The individual question scores for each study from the critical appraisal checklist are outlined in Table 2. Question 1, on whether the series was based on a pseudorandom or random sample was answered as 'no' in all of the included studies as they were all consecutive series of patients. Criteria for selection of patients was generally well defined across all studies as demonstrated by a positive response rate of 88.2% in question 2, as was reporting of confounding factors and strategies to deal with them, which also had a positive response rate of 88.2% in

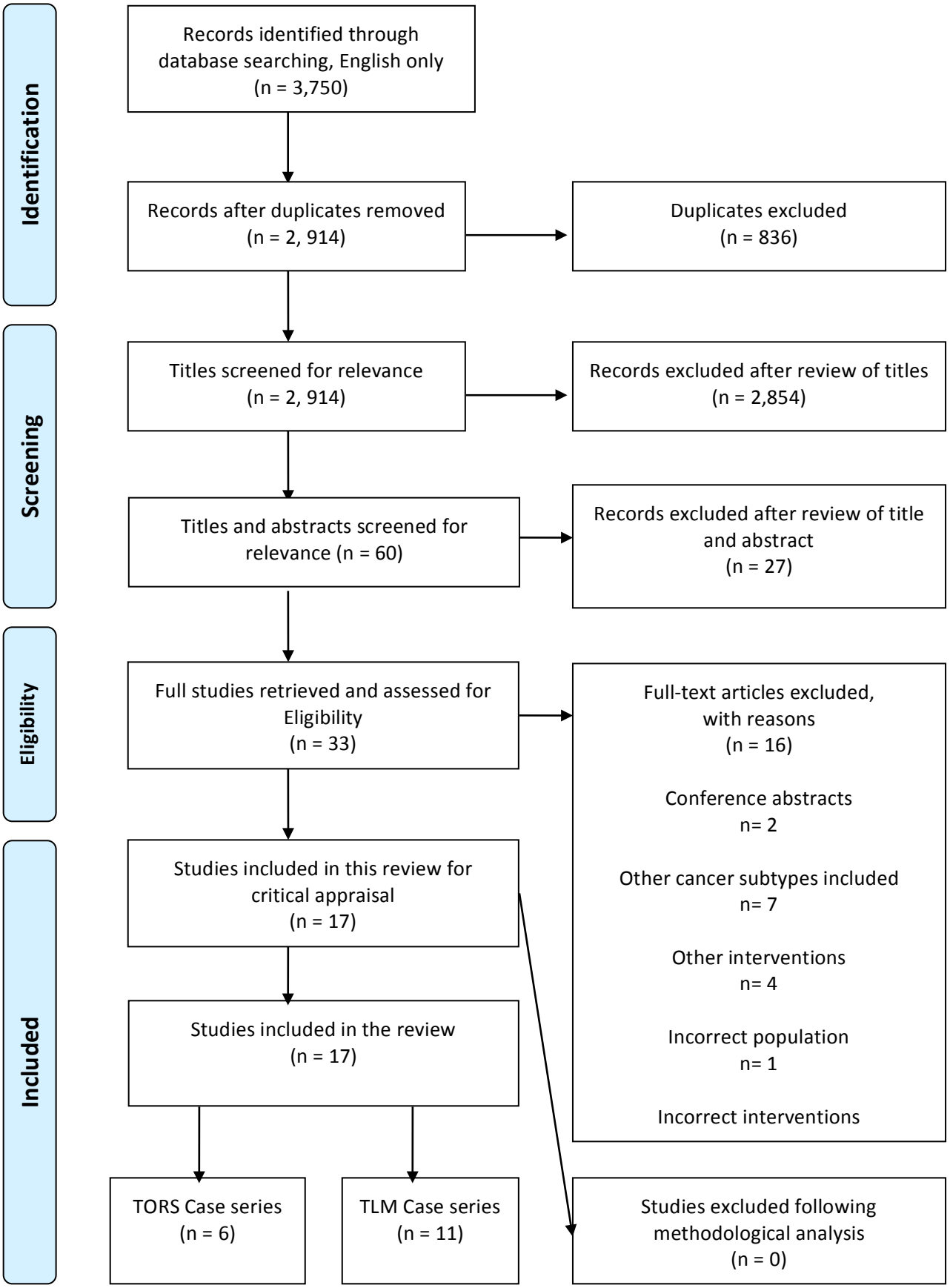

Figure 1: PRISMA flow diagram illustrating the process of including and excluding studies from the systematic review[1]

question 3. In all cases the outcomes assessed were related to at least overall survival, as defined by our inclusion criteria, as well as other measures of survival and oncological success. All studies stated objective criteria by which outcome assessment was made and generally measured these reliably whether the data was collected retrospectively or prospectively, resulting in 100% positive response rates for both question 4 and 8. All studies also scored a 100% positive response rate for question 6 related to the duration of the study as we defined a minimum outcome assessment time of one year as part of the inclusion criteria for study selection, and the majority of studies (nine out of 17) had up to five year outcomes. All studies used the Kaplan-Meier[75] method for analysis of survival data and survival analysis was performed appropriately across all included studies, as reflected by a 100% positive response rate in question 9. Question 5 was mostly inapplicable as there were only three studies[59, 71, 76, 77] that included a comparison group and in these cases sufficient descriptions of the groups were made. Perhaps the poorest performed question was question 7, with a positive response rate of only 58.8% reflecting a variable level of reporting of outcomes of people who withdrew from the study and incorporation of this into analysis.

Table 2: Results of critical appraisal of case series

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Total
Camp et al.[78]	No	Yes	Yes	Yes	N/A	Yes	U	Yes	Yes	6
Canis et al.[76]	No	Yes	Yes	Yes	N/A	Yes	U	Yes	Yes	6
Canis et al.[79]	No	Yes	Yes	Yes	N/A	Yes	U	Yes	Yes	6
Cohen et al.[59]	No	Yes	No	Yes	Yes	Yes	No	Yes	Yes	6
Grant et al.[80]	No	Yes	Yes	Yes	N/A	Yes	Yes	Yes	Yes	7
Grant et al.[81]	No	Yes	Yes	Yes	N/A	Yes	Yes	Yes	Yes	7
Haughey et al.[42]	No	Yes	Yes	Yes	N/A	Yes	Yes	Yes	Yes	7
Haughey et al.[73]	No	Yes	Yes	Yes	N/A	Yes	No	Yes	Yes	6
Henstrom et al.[82]	No	Yes	Yes	Yes	N/A	Yes	No	Yes	Yes	7
Moore et al.[60]	No	Yes	Yes	Yes	N/A	Yes	Yes	Yes	Yes	6
Park et al.[83]	No	Yes	Yes	Yes	N/A	Yes	Yes	Yes	Yes	6
Patel et al.[84]	No	Yes	Yes	Yes	N/A	Yes	Yes	Yes	Yes	7
Rich et al.[58]	No	Yes	Yes	Yes	N/A	Yes	Yes	Yes	Yes	7
Smith et al.[77]	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	7
Steiner et al.[43]	No	Yes	No	Yes	N/A	Yes	No	Yes	Yes	5
Weinstein et al.[72]	No	U	Yes	Yes	Yes	Yes	Yes	Yes	Yes	7
Weinstein et al.[71]	No	Yes	Yes	Yes	N/A	Yes	Yes	Yes	Yes	7
%	0.0	88.2	88.2	100.0	17.6	100.0	58.8	100.0	100.0	

N/A: Not applicable, U: Unclear

(Derived from the JBI critical appraisal checklist for systematic reviews and research syntheses)[85]

JBI Critical Appraisal Checklist of Descriptive/Case Series

Q1. Was study based on a random or pseudorandom sample?
Q2. Were the criteria for inclusion in the sample clearly defined?
Q3. Were confounding factors identified and strategies to deal with them stated?
Q4. Were outcomes assessed using objective criteria?
Q5. If comparisons are being made, was there sufficient descriptions of the groups?
Q6. Was follow up carried out over a sufficient time period?
Q7. Were the outcomes of the people who withdrew described and included in the analysis?
Q8. Were outcomes measured in a reliable way?
Q9. Was appropriate statistical analysis used?

3.3. Description of included studies

All of the 17 case series included in this review were published in a four-year period (from 2009 to 2013) with the study timeframes ranging from 1986 to 2011. All except four studies were undertaken in the USA, with three being completed in Germany[86-88] and one in the Republic of South Korea.[83] There were two two-center studies[80, 81] and one three-center study[89], with the rest being single-center studies. Some single institutions were also involved in producing more than one included study in this review. All three studies from Germany originated from the University of Goettingen[86-88], three studies were undertaken at the University of Pennsylvania[59, 71, 72], three studies came from the Mayo Clinic Florida and Arizona[42, 80, 81], and three studies came from the Washington University School of Medicine.[42, 58, 73] The data was collected prospectively in 10 studies and retrospectively in seven studies as outlined in Appendix V.

There were a total of 1,257 patients included in this review with ages ranging from 27 to 92, with 65% of patients being male and 35% female. Follow-up periods ranged from one to 132 months. Outcomes were measured at one year in threestudies, two years in nine studies, three years in five studies and five years in nine studies, as illustrated in Appendix VI.

Subsites involved ranged across the studies and included the base of tongue, tonsil, soft palate and the posterior pharyngeal wall. Human papilloma virus status was not reported in 11 studies. Across the six studies[42, 58-60, 77, 84] that reported the HPV status, the HPV positivity rate ranged from 67% to 90% of the cohort. Three of these studies[58, 77, 84] reported HPV status based on a proportion of patients within their cohort that had this data available. Smoking and alcohol use was reported in seven studies.[58, 60, 71, 73, 77, 82, 84] Five studies[43, 60, 73, 76, 79] specified that TNM stages were based on

pathological results, and where there was no specification within the study it was assumed that TNM stages were based on clinical and radiological findings. The type and number of neck dissections performed as well as the number of cases and types of adjuvant chemoradiotherapy performed were reported in all but one study.[83] While each study reported the levels of the neck dissected and criteria for this, as well as their adjuvant chemoradiotherapy protocols, there was heterogeneity between studies in these areas, depending on individual institution-accepted protocols.

Reported outcomes and timing of outcome assessment varied across the included studies. All studies reported overall survival, albeit at different time points, and in 13 studies, across multiple time points, as illustrated in Appendix VI. Other outcomes assessed included disease control, disease free survival and disease specific survival, and these outcomes followed similar definitions between studies allowing for comparison of results. Some studies also reported other outcomes such as post-operative speech and swallowing function, tracheotomy and gastrostomy dependence rates and complications, which are demonstrated in Appendix VI, although this data was not extracted or analyzed for the purpose of this review.

3.4. Oncological outcomes

The longest available follow-up outcome data available for TORS came from one study published by Smith et al.[77] This study showed a local control rate of 81% at five years. In comparison there were eight TLM case series[42, 43, 58, 73, 76, 79-81] that had oncological outcomes at five years and the local control rates in these studies ranged from 85.4% to 98.8%. Five[43, 58, 73, 76, 81] of these eight studies also had data for regional and distant control rates at five years with results ranging from 83.3% to 97.7% and 94% to- 99%, respectively, as demonstrated in Appendix VII.

There were two TORS studies and three TLM studies with three-year outcome data. Moore et al. demonstrated in their series of 66 patients treated with TORS three-year local, regional and distant control rates of 97%, 94% and 98.4%, respectively.[60] In comparison, Haughey et al., in one study comprising 204 patients with advanced stage OPSCC treated with TLM, also had a three-year local control rate of 97%.[42] Haughey et al. also demonstrated, in a second case series of 171 patients with HPV-positive OPSCC treated with TLM, local, regional and distant control rates of 98.8%, 97.7 and 96.5%, respectively.[73] Patel et al.[84], in their retrospective review of 80 patients with stage III/IV

OPSCC treated primarily with TLM followed by adjuvant radiotherapy, demonstrated a three-year regional control rate of 98.6% and distant control rate of 95%.

Weinstein et al.,[72] in their case series of 47 patients with advanced OPSCC who were treated with TORS, demonstrated that, at the two-year follow-up period, the local, regional and distant control rates were 98%, 96% and 91%, respectively. In comparison, the TLM case series, with outcomes at two years[42, 43, 58, 78, 81, 82], showed local control rates ranging from 83.6% to 98.8%, regional control rates ranging from 83.3% to 100% and distant control rates ranging from 94% to 96%. There were three TORS case series that had outcomes at one year[59, 71, 72], but no included TLM case series with outcomes at this time point for comparison.

The definition of margin status was relatively consistent across all studies that included this data. A positive margin was defined as histological evidence of tumor at the resection margin, a close margin was tumor within 2-5mm of the inked margin and negative margin was tumor outside 5mm of the inked margin. The rate of positive margins in the included TLM case series ranged from 3% to 19%, compared to a range of 1.5% to 14% in the included TORS case series as reported in Table 3.

Table 3: Comparison of available margin outcomes

Study	Positive margins (N)	%
TLM		
Camp et al.[78]	8/71	11.3%
Patel et al.[84]	8/80	10%
Rich et al.[58]	10/84	12%
Grant et al.[81]	2/59	3%
Haughey et al.[42]	15/204	7%
Haughey et al.[73]	14/171	8%
Henstrom et al.[82]	2/20	10%
Steiner et al.[43]	9/48	19%
TORS		
Moore et al.[60]	1/66	1.5%
Park et al.[83]	2/32	5%
Smith et al.[77]	6/42	14%
Weinstein et al.[72]	1/47	2%
Weinstein et al.[71]	1/30	3%

TORS: Transoral robotic surgery, TLM: Transoral laser microsurgery

3.5. Survival outcomes

Smith et al.[77] demonstrated an OS of 86% and DSS of 91% at five years in their case series of 42 patients. There were eight TLM case series[42, 43, 58, 73, 76, 79-81] that reported this data at five years with OS ranging from 52% to 91%, DSS ranging from 68% to 94.4% and DFS ranging from 60% to 88%.

Moore et al.[60] added further TORS survival data at three years with their study of 66 patients which demonstrated an OS of 95.5%, DSS of 95.1% and DFS of 92.4%. In comparison there were three TLM case series[42, 73, 84] which showed OS, DSS and DFS ranges of 86%-93.7%, 88%-95.5%, and 82%-91.1% at three years, respectively.

There were four TORS case series[59, 72, 77, 83] and six TLM case series[42, 43, 58, 78, 81, 82] with survival data at two years. The OS in the TORS studies ranged from 80.6% to 96% compared with 52%-94% in the TLM studies, the DSS in the TORS studies ranged from 90% to 92.6% compared with 91%-96% in the TLM studies, and the DFS in the TORS studies ranged from 79%-92% compared with 73%-91% in the TLM studies. There were three TORS case series[59, 71, 72] with one-year survival data and the OS results from these studies were 95.7%, 96% and 100%.

Chapter 4: Discussion

4.1. Overview of findings

The results of this systematic review have demonstrated that the two current minimally invasive transoral endoscopic surgical approaches for the treatment of this disease can both achieve complete tumor resection and also have highly comparable oncological and survival outcomes, with no strong evidence to prove superiority of one approach over the other in this domain. Significant heterogeneity of data and study designs limited meaningful pooled analyses and subgroup analyses to statistically compare oncological outcomes between the two platforms with respect to HPV status, tumor T stage or AJCC stage.

There are several expert literature reviews on the use of transoral endoscopic surgery for OPSCC[32, 48, 67-69]; however, as far as we are aware, this is the first systematic review comparing the oncological and survival outcomes of TORS with TLM for OPSCC. This review did not seek to compare TES with other modalities of treatment such as radiotherapy or chemotherapy, although it is worthwhile at this point to understand the oncological and survival results of TORS and TLM in the context of other modalities. Parsons et al.[90] reviewed survival outcomes between open surgery and radiation therapy for OPSCC and found no change in overall or cause-specific survival between the two modalities, but they did see a significant ($P < .001$) reduction in severe and fatal complications in patients treated primarily with radiotherapy. Moncrief et al.[91] reported a five-year local control rate of 87% and a DSS of 83% in 92 patients with OPSCC treated primarily with open surgery, while De Arruda et al.[92] reported an overall two-year survival of 98% and a local progression free rate of 98% in 50 patients with OPSCC treated with definitive chemoradiotherapy. These results suggest that both TORS and TLM have good survival outcomes in relation to other forms of treatment, although one must take into consideration the fact that survival in OPSCC has probably risen over the years due to advances in adjuvant treatment technology, as well as an evolving etiology of disease and better public health measures to reduce alcohol and tobacco use.

Some of the findings in this review probably relate to the history of the development of the two surgical platforms. Our search identified more TLM case series than TORS case series for inclusion in this review, which likely reflects the earlier establishment of TLM, which was described almost four decades prior to the earliest descriptions of TORS. This is also reflected in the difference in number of case series with long-term outcomes between the two platforms. Our study found only one TORS

case series[77] with five-year outcomes, compared to eight TLM case-series[42, 43, 58, 73, 76, 79-81] with data at this time-point. Conversely, there were three TORS case series[59, 71, 72] and no TLM case series with one-year outcomes.

The centers from which our included studies were derived are reflective of the geography of where the two platforms were established. Transoral laser microsurgery was championed by Wolfgang Steiner of Germany and, of the four included studies published outside of the USA, three TLM studies came from the University of Goettingen in Germany.[86-88] Similarly, there were three included studies from University of Pennsylvania published by Gregory Weinstein[59, 71, 72], who was the earliest champion of TORS. All of the studies, irrespective of geographical location, came from highly academic university affiliated institutions, which is likely reflective of factors such as cost of this technology, availability of the surgical platforms, surgeon experience and institution experience. This may impact outcomes such that a high level of expertise and resourcing may optimize the results, regardless of surgical approach.

4.2. Limitations to the study

There were significant limitations to this study related to heterogeneity of data, low levels of evidence and inherent biases.

Comparison of surgical platforms by way of valid meta-analysis was not possible due to substantial heterogeneity of data across all studies, ranging from tumor factors such as involved oropharyngeal subsites, HPV status and size of tumor, to patient factors such as age, sex, comorbidities, smoking use and alcohol intake, and additional treatment factors such as extent of neck dissections and nature of adjuvant chemo radiotherapy protocols.

It is important to interpret the results of this review in the context of the heterogeneity of data related to HPV status. Human papilloma virus status has repeatedly been found to be the most influential determinant of HNSCC survival[30] and has strong independent prognostic value, irrespective of modality.[93] Human papilloma virus status was unknown in 11 of the 17 included studies, and of the six studies[42, 58-60, 77, 84] that did report HPV status, three studies[58, 77, 84] reported HPV status based on only a proportion of patients within the cohort that had this data available, given the fact that the earlier studies included in this review pre-dated the consistent testing for

HPV. Unfortunately, this lack of HPV data eliminated the possibility of performing subgroup analyses of oncological outcomes in relation to HPV status and therefore we cannot say that one treatment approach provides better oncological outcomes than the other with respect to HPV status.

Similarly, subgroup analysis based on tumor T stage as well as AJCC stages was challenging. There was a variety of TNM staged tumors across the included studies and, while there were three studies that specified the inclusion of only advanced stage disease (AJCC III/IV)[58, 72, 84], different outcome time-points across these studies precluded comparison of outcomes between them. Furthermore, there was inconsistency in the reporting of TNM staging, with only five studies[43, 60, 73, 76, 79] specifying that TNM stages were based on pathological results. Smith et al.[77] found in their TORS case series that 18 out of 42 patients (43%) had some change in stage following surgical resection and pathological examination, and in nine of these cases there was a resultant change in their adjuvant treatment plan.

Reported outcomes and timing of outcome assessment varied across the included studies, so that only studies with outcomes captured at the same time points could be compared. Outcomes were measured at one year in three studies and two years in nine studies, and it could be argued that these studies with less than three-year end-point measures may not have captured late recurrences. This is especially critical in HPV driven disease, which is thought to have later presentation of distant metastases than HPV negative disease. [94] While this was not shown in studies focusing on patients treated with primary surgery, one study did show HPV positive disease to have significantly later distant metastases, as well as involving a greater number of subsites and metastatic sites infrequently seen in HNSCC, after completion of chemoradiotherapy, compared to patients with HPV negative disease.[94]

This systematic review by nature is retrospective and observational and heavily reliant on the data reporting of others, and hence was at risk of replicating biased results. There was inherent case selection bias in the included studies related to the fact that TES requires adequate transoral access as a prerequisite, and therefore patients with higher T-stage tumors or patients with tumors that cannot be exposed or resected through the natural orifice of the mouth were excluded.[95] This is especially true for TLM, which requires line of site for resection, whereas TORS with its angled, intraoral camera does allow better access to the tongue base as previously discussed. Further risk of 'surgeon' bias stems from the fact that all of the included studies were retrospective in their evaluation of data, including those case series where data was collected prospectively, with

potential for bias toward demonstrating surgical success.[96] Finally, it is likely that there was some element of financial bias, as all studies required significant investment in time, resource and money by performing institutions, thereby influencing the imperative for successful outcomes.

The exclusion of foreign language articles was another limitation of this review particularly as non-English speaking units in Europe have been the vanguard of the development of TLM. However, this may have been offset by the fact that three of the included articles on TLM came from Germany.

As a final point, it should be noted that the intention of this review was not to compare other types of outcomes between TORS and TLM, such as post-operative patient functional outcomes, complication rates, cost or technical ease of the operating platform. While the outcomes addressed in the review are of critical importance, decisions as to the effectiveness and appropriateness of which platform to use must be based on a wide range of factors and therefore, this review on its own cannot be used to direct practice.

4.3. Implications for practice

It is not possible to make recommendations to influence practice from this study as this systematic review extracted a low level of evidence data from compiled case series and was unable to make a valid comparison of oncological and survival outcomes between TORS and TLM due to the heterogeneity of included data. Despite this, there are a few areas of discussion relating to implications for practice that are worth exploring. Completely removing cancer is one of the most important goals of curative surgical resection because positive margins contribute to increased local recurrence and decreased survival rates.[97] Haughey et al. showed that the presence of positive margins after surgery in 7% of their patients raised the risk of death two-and-a-half- to three-fold compared with that for patients with negative margins.[89]

Although we were not able to perform pooled analysis, we can conclude from the results of this study that the oncological and survival outcomes between the traditional 'Halstedian' *en bloc* tumor resection technique used in TORS and the modern segmental tumor dissection technique used in TLM are comparable. Our findings suggest therefore that whether tumor is removed *en bloc* via TORS or in a systematic comprehensive piecemeal fashion via TLM is not important, as long as complete tumor removal is accomplished. This is in keeping with the recent publication of an expert

analysis of treatment outcomes of piecemeal removal of sinonasal, laryngeal oropharyngeal and hypopharyngeal cancer that reached consensus on the safety of this surgical approach.[44]

4.4. Implications for research

Given the findings from this study and the inherent challenges we faced in conducting meta-analysis, we recommend the establishment of study guidelines specific to head and neck oncological research, along the lines of other established guidelines for the reporting of observational studies, with standardized reporting of core data and defined outcomes in order to allow for pooling and comparison of data to better guide evidence where RCTs are not possible.[98]

Chapter 5: Conclusion

5.1. Future directions

Minimally invasive transoral endoscopic surgical technology continues to evolve to overcome technical limitations and provide the surgeon with the best chance of achieving oncological success for their patients. Improvements in surgical laser technology have led to the development of flexible lasers that offer the ability to work around the base of the tongue, overcoming previous line-of-sight limitations.[99] In a similar fashion, the new da Vinci single port surgical platform (Intuitive, Inc.) is being designed with transoral oropharyngeal surgery in mind, with three smaller robotic arms delivered through a single port to the resection site improving access and minimizing instrumentation collision, as well as allowing for improved and less restricted maneuverability of the equipment around the contoured surgical field.[100] Research is currently underway to combine both laser and robotic technology in a transoral robot-assisted carbon dioxide laser platform, with promising results in early feasibility studies.[101]

Increasing surgeon acceptance and adoption of robotic technology globally is currently leading to the development of new robotic platforms such as the Medrobotics flex system (Medrobotics, Raynham, Massachusetts, USA) that is already gathering momentum, with published early case series demonstrating feasibility.[51, 52] This system has been specifically designed to reach subsites in the upper aerodigestive tract such as the hypopharynx, larynx and nasopharynx that is almost impossible to achieve with the current DaVinci surgical platform.[102] Increased commercial competition between technical systems will drive scientific improvement of tools, decrease financial burdens and improve availability of equipment.

5.2. Recommendations

There is a lack of high quality research in the literature comparing minimally invasive transoral endoscopic surgical techniques related to the fact that randomized controlled trials comparing different surgical platforms have ethical and logistical challenges.

The application of JBI methodology for systematic reviews has allowed synthesis of current knowledge based on case series only, and although a pooled analysis comparing oncological and survival outcomes of TORS versus TLM has not been possible, synthesizing the current evidence can still help inform clinical decisions until further higher level evidence is available.

This study has found that both TORS and TLM are minimally invasive transoral endoscopic surgical approaches with good oncological and survival outcomes for the management of patients with OPSCC.

The piecemeal approach used in TLM does not result in poor survival outcomes when compared to the *en bloc* resection of oropharyngeal cancers employed in TORS. This finding supports the ongoing use and expansion of laser technology, as well as the development of combined laser and robotic technology that will allow for better operating platforms and improved surgical treatment options for patients in the future.

It is currently not possible to say whether one platform is more likely to be effective than the other with regards to HPV status or tumor T-stage, and it is more likely that operator and institution experience, as well as factors relating to cost and availability, will dictate which surgical platform is used.

With continuously expanding minimally invasive surgical technology and ongoing development of competing platforms, the imperative will lie with leading surgeons around the globe to construct and execute well-designed trials to allow for statistically strong comparison of these new technologies across a variety of domains including technical ease, learning curve, cost-utility, set-up and operating time, patient functional outcomes and of course oncological success. An agreed upon set of head and neck research guidelines will ensure strength and unity in observational evidence to best guide clinical practice for the treatment of patients.

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Appendices

Appendix I: Search strategy for different databases

PubMed (Searched 26th March 2016)

Oropharyngeal neoplasms[mh] OR Oropharynx neoplas*[tw] OR Oropharynx cancer*[tw] OR Oropharynx carcinoma*[tw] OR Oropharynx tumo*[tw] OR Oropharynx malignan*[tw] OR Oropharyngeal neoplas*[tw] OR Oropharyngeal SCC[tw] OR Oropharyngeal cancer*[tw] OR Oropharyngeal carcinoma*[tw] OR Oropharyngeal tumo*[tw] OR Oropharyngeal malignan*[tw] OR OP-SCC[tw] OR OPSCC[tw] OR OPC[tw] OR SCCOP[tw]

AND

Robotics[mh] OR robotic surgical procedures[mh] OR TORS[tw] OR Robotic*[tw] OR Robot*[tw] OR Laser therapy[mh:noexp] OR Surgical Procedures Minimally Invasive[mh:noexp] OR Laser*[mh] OR Microsurgery[mh] OR Transoral laser microsurgery[tw] OR TOLS[tw] OR TLM[tw] OR Transoral*[tw] OR Trans-oral*[tw] OR Trans oral*[tw]

CINAHL (Searched 26th March 2016)

MH Mouth neoplasms OR TI Mouth neoplasm* OR AB Mouth neoplasm* OR TI Mouth cancer* OR AB Mouth cancer* OR TI Mouth tumo* OR AB Mouth tumo* OR MH Tongue neoplasms OR TI Tongue neoplasm* OR AB Tongue neoplasm* OR TI Tongue cancer* OR AB Tongue cancer* OR TI Tongue tumo* OR Tongue tumo* OR MH Pharyngeal neoplasms OR TI Pharyngeal neoplasm* OR AB Pharyngeal neoplasm* OR MH Papilloma virus infections OR TI Papilloma virus infection* OR AB Papilloma virus infection* OR MH Oropharynx OR TI Oropharynx OR AB Oropharynx OR TI Oropharyngeal neoplasms OR AB Oropharyngeal neoplasms OR TI Oropharynx neoplas* OR
AB Oropharynx neoplas* OR TI Oropharynx SCC OR AB Oropharynx SCC OR TI Oropharynx cancer* OR AB Oropharynx cancer* OR TI Oropharynx carcinoma* OR AB Oropharynx carcinoma* OR TI Oropharynx tumo* OR AB Oropharynx tumo* OR TI Oropharynx malignan* OR AB Oropharynx malignan* OR TI Oropharyngeal neoplas* OR AB Oropharyngeal neoplas* OR TI Oropharyngeal SCC OR AB Oropharyngeal SCC OR TI Oropharyngeal cancer* OR AB Oropharyngeal cancer* OR TI Oropharyngeal carcinoma* OR AB Oropharyngeal carcinoma* OR TI Oropharyngeal tumo* OR AB Oropharyngeal tumo* OR TI Oropharyngeal malignan* OR AB Oropharyngeal malignan* OR TI OPSCC OR AB OP-SCC OR TI OPSCC OR AB OPSCC OR TI OPC OR AB OPC OR TI SCCOP OR AB SCCOP

AND

MH Minimally invasive procedures OR TI Minimally invasive procedure* OR AB Minimally invasive procedure* OR TI Minimal access surger* OR AB Minimal access surger*

OR TI Minimally invasive surger* OR AB Minimally invasive surger* OR MH Laser therapy OR TI Laser therap* OR AB Laser therap* OR TI Laser surger* OR AB Laser surger* OR MH Microsurgery OR TI Microsurger* OR AB Microsurger* OR MH Robotics OR TI Robot* OR AB Robot* OR TI TORS OR AB TORS OR TI Transoral laser microsurgery* OR AB Transoral laser microsurgery* OR TI TOLS OR AB TOLS OR TI TLM OR AB TLM OR TI Transoral* OR AB Transoral* OR TI Trans-oral* OR AB Trans-oral* OR TI Trans oral* OR AB Trans oral*

EmbaseE (Searched 26th March 2016)

"Oropharynx cancer":ti,ab OR "Oropharynx cancers":ti,ab OR "Squamous cell carcinoma":ti,ab OR "Squamous cell carcinomas":ti,ab OR "Human papillomavirus associated oropharyngeal squamous cell carcinoma":ti,ab OR "Mouth squamous cell carcinoma"/syn OR "Oropharyngeal squamous cell carcinoma":ti,ab OR "Oropharyngeal squamous cell carcinomas":ti,ab OR "Oropharynx carcinoma"/syn OR "Oropharynx carcinoma":ti,ab OR "Oropharynx carcinomas":ti,ab OR
"Pharynx squamous cell carcinoma"/syn OR "Oropharyngeal neoplasm":ti,ab OR "Oropharyngeal neoplasms":ti,ab OR "Oropharynx neoplasm":ti,ab OR "Oropharynx neoplasms":ti,ab OR "Oropharynx SCC":ti,ab OR "Oropharynx tumor":ti,ab OR "Oropharynx tumors":ti,ab OR "Oropharynx tumor":ti,ab OR "Oropharynx tumors":ti,ab OR "Oropharynx malignancy":ti,ab
OR "Oropharynx malignancies":ti,ab OR "Oropharyngeal carcinoma":ti,ab OR "Oropharyngeal carcinomas":ti,ab OR "Oropharyngeal tumor":ti,ab OR "Oropharyngeal tumors":ti,ab OR "Oropharyngeal tumor":ti,ab OR "Oropharyngeal tumors":ti,ab OR "Oropharyngeal malignancy":ti,ab OR "Oropharyngeal malignancies":ti,ab OR "OP-SCC":ti,ab OR "OPSCC":ti,ab OR "OPC":ti,ab OR "SCCOP":ti,ab

AND

Robotics/syn OR Robot*:ti,ab OR "Robotic surgical procedure"/syn OR "Robotic surgical procedures":ti,ab OR "Robot assisted surgery":ti,ab OR "transoral robotic surgery":ti,ab OR "TORS":ti,ab OR "transoral laser microsurgery":ti,ab OR "laser surgery"/syn OR "TOLS":ti,ab OR "TLM":ti,ab OR Transoral*:ti,ab OR "Trans-oral":ti,ab OR "Trans oral":ti,ab

Web of Science (Searched 26th March 2016)

"Oropharyngeal neoplasm*" OR "Oropharynx neoplas*" OR "Oropharynx SCC" OR "Oropharynx cancer*" OR "Oropharynx carcinoma*" OR "Oropharynx tumo*" OR "Oropharynx malignan*" OR "Oropharyngeal neoplas*" OR "Oropharyngeal SCC" OR "Oropharyngeal cancer*" OR "Oropharyngeal carcinoma*" OR "Oropharyngeal tumo*" OR "Oropharyngeal malignan*" OR
"OP-SCC" OR "OPSCC" OR "OPC" OR "SCCOP"

AND

Robotic* OR "robotic surgical procedures" OR TORS OR Robot* OR "Laser therapy" OR

"Surgical Procedures Minimally Invasive" OR Laser* OR Microsurgery OR "Transoral laser microsurgery" OR TOLS OR TLM OR Transoral* OR Trans-oral* OR Trans oral*

SCOPUS (Searched 26th March 2016)

"Oropharynx neoplasm" OR "Oropharynx SCC" OR "Oropharynx cancer" OR "Oropharynx carcinoma" OR "Oropharynx tumor" OR "Oropharynx malignancy" OR "Oropharyngeal neoplasm" OR "Oropharyngeal SCC" OR "Oropharyngeal cancer" OR "Oropharyngeal carcinoma" OR "Oropharyngeal tumor" OR "Oropharyngeal malignancy"

AND

Robotic* OR "robotic surgical procedures" OR TORS OR Robot* OR "Laser therapy" OR "Surgical Procedures Minimally Invasive" OR Microsurgery OR "Transoral laser microsurgery" OR TOLS OR TLM

Appendix II: Critical appraisal instruments

JBI Critical Appraisal Checklist for Descriptive / Case Series

Reviewer _____ Date _____

Author _____ Year _____ Record Number _____

	Yes	No	Unclear	Not Applicable
1. Was study based on a random or pseudo-random sample?	☐	☐	☐	☐
2. Were the criteria for inclusion in the sample clearly defined?	☐	☐	☐	☐
3. Were confounding factors identified and strategies to deal with them stated?	☐	☐	☐	☐
4. Were outcomes assessed using objective criteria?	☐	☐	☐	☐
5. If comparisons are being made, was there sufficient descriptions of the groups?	☐	☐	☐	☐
6. Was follow up carried out over a sufficient time period?	☐	☐	☐	☐
7. Were the outcomes of people who withdrew described and included in the analysis?	☐	☐	☐	☐
8. Were outcomes measured in a reliable way?	☐	☐	☐	☐
9. Was appropriate statistical analysis used?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

_____

_____

_____

Appendix III: Data extraction instruments

JBI Data Extraction Form for Experimental / Observational Studies

Reviewer _____ Date _____

Author _____ Year _____

Journal _____ Record Number _____

Study Method

RCT ☐ Quasi-RCT ☐ Longitudinal ☐

Retrospective ☐ Observational ☐ Other ☐

Participants

Setting _____

Population _____

Sample size

Group A _____ Group B _____

Interventions

Intervention A _____

_____

Intervention B _____

_____

Authors Conclusions:

_____

_____

_____

Reviewers Conclusions:

_____

_____

_____

Study results

Dichotomous data

Outcome	Intervention ( ) number / total number	Intervention ( ) number / total number

Continuous data

Outcome	Intervention ( ) number / total number	Intervention ( ) number / total number

Appendix IV: Included studies – study characteristics/participants characteristics

#	Study	TORS/ TLM	(N)	Gender (M:F)	Age (years)	Subsite(s)	HPV +ve (%)	Smoking / ETOH status	T stage	N stage	AJCC stage	Neck dissection	Adjuvant treatment
1	Camp[78]	TLM	71	55:16	38 - 85	BOT	Unknown	Not reported	T0: 4 T1: 13 T2: 36 T3: 15 T4: 3	N0: 11 N1: 6 N2a: 20 N2b: 16 N2c: 12 N3: 6	I: 1 II: 9 III: 7 IVa: 48 IVb: 6	Nil: 3 UL: 24 BL: 44	RT: 68 CTx: 0 CRT: 27
2	Canis[76]	TLM	82	67:15	31 - 86	BOT	Unknown	Not reported	pT1: 5 pT2: 24 pT3: 15 pT4: 38	pN0: 26 pN1: 12 pN2: 44	I: 1 II: 6 III: 14 IV: 16	Nil: 7 UL: 37 BL: 38	RT: - CTx: - CRT: 55%
3	Canis[79]	TLM	102	82:20	30 - 82	Tonsil	Unknown	Not reported	pT1: 22 pT2: 24 pT3: 42 pT4a: 14	pN0: 30 pN1: 16 pN2a: 6 pN2b: 45 pN2c: 5 pN3: 0	I: 3 II: 10 III: 29 IVa: 60 IVb: 0	Nil: 4 UL: 78 BL: 19	RT: - CTx: - CRT: 66%
4	Cohen[59]	TORS	50	47:3	36 - 76	BOT, tonsil, SP, PPW	74%	Not reported	T1: 15 T2: 24 T3: 8 T4a: 3	N0: 9 N1: 21 N2a: 0 N2b: 20 N2c: 0 N3: 0	I: 3 II: 4 III: 20 IV: 23	Nil: 2 UL/BL: 48	RT: 12 CTx: 4 CRT: 27

5	Grant[80]	TLM	69	58:11	x	Tonsil, BOT, PW, SP, vallecula	Unknown	Not reported	T1: 25 T2: 30 T3: 12 T4: 2	N0: 31 N1: 11 N2a: 16 N2b: 6 N2c: 1 N3: 2	I: 12 II: 13 III: 19 IVa: 25	Nil: 10 UL: 46 BL: 13	RT: 0 CTx: 0 CRT: 0
6	Grant[81]	TLM	59	10:1	42 - 92	BOT	Unknown	Not reported	T1: 16 T2: 23 T3: 12 T4: 8	N0: 16 N1: 10 N2a: 17 N2b: 8 N2c: 1 N3: 7	I: 4 II: 7 III: 12 IV: 36	Nil: 10 UL: 25 BL: 24	RT: 28 CTx: 0 CRT: 0
7	Haughey[42]	TLM	204	181:23	Mean 57	BOT, Tonsil, SP	90%	Not reported	T1: 61 T2: 74 T3: 45 T4: 24	N0: 15 N1: 39 N2: 135 N3: 14	I: 0 II: 0 III: 49 IV: 155	Nil: 7 UL: 164 BL: 33	RT:53 CRT: 33
8	Haughey[73]	TLM	171	148:23	27 - 83	BOT, Tonsil	Unknown	Never: 44% Former: 33% Current: 23% ETOH: Not reported	pT1: 68 pT2: 55 pT3: 26 pT4: 14	pN0: 3 pN1: 14 pN2a: 30 pN2b: 70 pN2c: 18 pN3: 11	I: 8 II: 6 III: 22 IV: 135	Nil: 6 UL: 133 BL: 32	RT: 73 CRT: 69
9	Henstrom[82]	TLM	20	17:3	38 - 73	BOT	Unknown	Never: 45% Former: 30% Current: 25% Regular ETOH: 45%	T1: 8 T2: 8 T3: 1 T4a: 3	N0: 1 N1: 3 N2a: 1 N2b: 11 N2c: 4 N3: 0	I: 0 II: 1 III: 3 IVa: 16	Nil: 1 UL: 11 BL: 8	RT: 12 CRT: 4

10	Moore[60]	TORS	66	59:7	36 - 80	Tonsil, BOT	72%	Never: 50% Former: 24% Current: 26% Regular: 36%	pT0: 2 pT1: 22 pT2: 30 pT3: 3 pT4a: 9	pN0: 9 pN1: 8 pN2a: 8 pN2b: 25 pN2c: 8 pN3: 8	I: 3 II: 5 III: 7 IVa: 43 IVb: 8	Nil: 0 UL: 56 BL: 10	RT: 14 CRT: 41
11	Park[83]	TORS	32	28:11	34 - 77	Tonsil, BOT, SP	Unknown	Not reported	T1: 14 T2: 20 T3: 3 T4: 2	N0: 13 N1: 3 N2a: 1 N2b: 20 N2c: 2 N3: 0	x	x	RT: 21 CRT: 4
12	Patel[84]	TLM	80	70:10	31 - 82	Tonsil, BOT	74% *	Smoking >10 pack/years: 50% ETOH: Not reported	T1: 42 T2: 31 T3: 7	N0: 1 N1: 9 N2a: 9 N2b: 49 N2c: 10 N3: 2	I: 0 II: 0 III: 3 IVa: 69 IVb: 2	Nil: 0 UL/BL: 80	RT: 43 CRT: 37
13	Rich[58]	TLM	84	74:10	35 - 81	BOT, tonsil, SP	82% *	Never: 38% Ever: 60% Unknown: 2% Regular ETOH: 56%	T1: 29 T2: 33 T3: 15 T4: 7	N0: 3 N1: 12 N2: 64 N3: 5	III: 13 IV: 71	Nil: 1 UL: 75 BL: 8	RT: 50 CRT: 28
14	Smith[77]	TORS	42	34:8	41 - 88	Tonsil, BOT, palate, lateral pharynx	67% *	Never: 14% Pack/years: < 10: 10% > 10: 76%	T1: 18 T2: 21 T3: 0 T4: 3	N0: 14 N1: 5 N2a: 8 N2b: 13 N2c: 2	I: 5 II: 9 III: 4 IVa: 24 IVb: 0	Nil: 0 UL/BL: 42	RT: 9 CRT: 13

15	Steiner[43]	TLM	48	39:9	38 - 85	BOT	Unknown	Not reported	pT1: 1 pT2: 12 pT3: 7 pT4: 28	pN0: 31 pN1: 9 pN2: 24 pN3: 0	I/II: 3 III/IVa: 45	Nil: 5 UL: 21 BL: 22	RT: 11 CRT: 12
16	Weinstein[72]	TORS	47	43:4	36 - 76	BOT, Tonsil, SP	Unknown	Not reported	T1: 13 T2: 23 T3: 9 T4: 2	N0: 1 N1: 24 N2a: 1 N2b: 19 N2c: 2	III: 24 IV: 23	Nil: 0 UL/BL: 47	RT: 13 CTx: 2 CRT: 27
17	Weinstein[71]	TORS	30	21:9	44 - 75	Tonsil, BOT, GTS, SP, PPW	Unknown	Never: 10% Former: 57% Current: 27% ETOH: Not reported	T1: 9 T2: 16 T3: 34 T4: 1	N0: 15 N1: 10 N2a: 1 N2b: 4 N2c: 0 N3: 0	x	Nil: 3 UL/BL: 27	RT: 0 CTx: 0 CRT: 0

- * Indicates HPV status not available for entire cohort (therefore result given denotes percentage of known HPV positive patients in entire population)
- NB: Pathological TNM staging has been presented where this information was given. If clinical or pathological status of TNM staging was not specified, it has been assumed to be clinical
- N: Number, M: Male, F: Female, HPV: Human papilloma virus, ETOH: Alcohol, UL: Unilateral, BL: Bilateral, RT: Radiotherapy, CTx: Chemotherapy, CRT: Chemotherapy and radiotherapy, BOT: Base of tongue, SP: Soft palate, GTS: Glossotonsillar sulcus, PPW: Posterior pharyngeal wall

Appendix V: Included studies – Bibliographic details and study characteristics

#	Study	Score	Study time frame	Year published	Journal	Retrospective/prospective	Single/multi-center	Country	Institution
1	Camp et al.[78]	6	1995 - 2005	2009	Otolaryngology - Head and neck surgery	Retrospective	Single	USA	Rush University Medical Center
2	Canis et al.[76]	6	1986 - 2007	2013	European archives of otolaryngology	Retrospective	Single	Germany	University of Goettingen
3	Canis et al.[79]	6	1987 - 2006	2013	European archives of otolaryngology	Retrospective	Single	Germany	University of Goettingen
4	Cohen et al.[59]	6	2005 - 2007	2011	Head and Neck	Prospective	Single	USA	University of Pennsylvania Medical Center
5	Grant et al.[80]	7	1996 - 2008	2009	Archives of Otolaryngology Head and Neck Surgery	Retrospective	2-center	USA	Mayo Clinic Florida and Arizona
6	Grant et al.[81]	7	1997 - 2005	2006	The Laryngoscope	Prospective	2-center	USA	Mayo Clinic Florida and Arizona
7	Haughey et al.[42]	7	1996 - 2006	2010	Head and Neck	Prospective	3-center	USA	Mayo Clinic Florida, Arizona and Washington University School of Medicine
8	Haughey et al.[73]	6	1996 - 2010	2012	The Laryngoscope	Prospective	Single	USA	Washington University School of Medicine
9	Henstrom et al.[82]	7	1996 - 2005	2009	Archives of Otolaryngology Head and Neck Surgery	Retrospective	Single	USA	Mayo Clinic Minnesota
10	Moore et al.[60]	6	2007 - 2009	2012	Mayo Clinic Proceedings	Prospective	Single	USA	Mayo Clinic Minnesota
11	Park et al.[83]	6	2008 - 2011	2013	British Journal of Oral and Maxillofacial Surgery	Prospective	Single	Republic of Korea	Yonsei University College of Medicine
12	Patel et al.[84]	7	2000 - 2011	2013	Head and Neck	Retrospective	Single	USA	Mayo Clinic Arizona

13	Rich et al.[58]	7	1996 - 2006	2009	The Laryngoscope	Prospective	Single	USA	Washington University School of Medicine
14	Smith et al.[77]	7	2007 - 2013	2015	The Laryngoscope	Prospective	Single	USA	Albert Einstein College of Medicine
15	Steiner et al.[43]	5	1986 - 1997	2003	Archives of Otolaryngology Head and Neck Surgery	Retrospective	Single	Germany	University of Goettingen
16	Weinstein et al.[72]	7	2005 - 2009	2010	Archives of Otolaryngology Head and Neck Surgery	Prospective	Single	USA	University of Pennsylvania Medical Center
17	Weinstein et al.[71]	7	2005 - 2010	2012	Archives of Otolaryngology Head and Neck Surgery	Prospective	Single	USA	University of Pennsylvania Medical Center

Appendix VI: Included studies – outcomes data summary

#	Study	1 year outcomes	2 year outcomes	3 year outcomes	5 year outcomes	Margins	DC	DFS	DSS	OS	Other outcomes reported
1	Camp et al.[78]		✔			✔	✔		✔	✔	Functional, QOL
2	Canis et al.[76]				✔		✔	✔		✔	Complications, feeding tube dependence
3	Canis et al.[79]				✔		✔	✔	✔	✔	Tracheostomy rate, complications, swallowing function
4	Cohen et al.[59]	✔	✔			✔	✔		✔	✔	Relapse pattern
5	Grant et al.[80]				✔		✔		✔	✔	Complications, swallowing function and feeding tube dependence
6	Grant et al.[81]		✔		✔	✔	✔	✔		✔	Function and communication scales
7	Haughey et al.[42]		✔	✔	✔	✔	✔	✔	✔	✔	Swallowing function
8	Haughey et al.[73]			✔	✔	✔	✔	✔	✔	✔	
9	Henstrom et al.[82]		✔			✔	✔		✔	✔	Speech and swallowing function and treatment related morbidity
10	Moore et al.[60]			✔		✔	✔	✔	✔	✔	Gastrostomy and tracheostomy tube dependence
11	Park et al.[83]		✔			✔		✔		✔	Swallowing function
12	Patel et al.[84]			✔		✔	✔	✔		✔	
13	Rich et al.[58]		✔		✔	✔	✔	✔	✔	✔	Functional outcomes
14	Smith et al.[77]			✔	✔	✔	✔		✔	✔	
15	Steiner et al.[43]		✔		✔	✔	✔	✔	✔	✔	Functional outcomes
16	Weinstein et al.[72]	✔	✔			✔	✔	✔	✔	✔	Gastrostomy tube dependence, safety and efficacy
17	Weinstein et al.[71]	✔				✔	✔			✔	

DC: Disease control, DFS: Disease free survival, DSS: Disease specific survival, OS: Overall survival, QOL: Quality of life
✔: Indicates information available

Appendix VII: Five-year outcome data by technique

TORS

Study	Sample size	Positive Margins*	Local control~	Regional control~	Distant control~	DFS	DSS	OS
Smith[77]	42	6 (14%)	81%	-	-	-	91%	86%

TLM

Study	Sample size	Positive Margins*	Local control~	Regional control~	Distant control~	DFS	DSS	OS
Canis[76]	82	-	90%	93%	99%	69%	-	59%
Canis[79]	102	-	T1 + T2: 78% T3 + T4a: 75%	-	-	T1 + T2: 64% T3 + T4: 60%	T1 + T2: 74% T3 + T4: 68%	T1 + T2: 59% T3 + T4: 56%
Grant[80]	69	-	94%	-	-	-	86%	86%
Grant[81]	59	2 (3%)	90%	88%	96%	84%	-	69%
Haughey[42]	204	15 (7%)	-	-	-	74%	84%	78%
Haughey[73]	171	14 (8%)	98.8% (2)	97.7% (4)	96.5% (6)	88%	94.4%	91%
Rich[58]	84	10 (12%)	98.8% (1)	95.2% (4)	94.0% (5)	87%	92%	88%
Steiner[43]	48	9 (19%)	85.4% (7)	83.3% (8)	95.8% (2)	73%	-	52%

- *Number quoted is the number of participants with positive margins. The percentage in brackets represents percentage of sample size with positive margins
- ~ For Local, regional and distant control: The percentage represents that percentage of the sample size which did not have a local, regional or distant recurrence. The number in brackets represents the number of patients with recurrences (either local, regional or distant).

Appendix VIII: Three-year outcome data by technique

TORS

Study	Sample size	Positive Margins*	Local control	Regional control	Distant control	DFS	DSS	OS
Smith[77]	42	6 (14%)	81%	-	-	-	91%	86%
Moore[60]	66	1 (1.5%)	97%	94%	98.4%	92.4%	95.1%	95.5%

TLM

Study	Sample size	Positive Margins*	Local control~	Regional control~	Distant control~	DFS	DSS	OS
Haughey[42]	204	-	97%	-	-	82%	88%	86%
Haughey[73]	171	14 (8%)	98.8%	97.7%	96.5%	91%	95.5%	93.7%
Patel[84]	80	8 (10%)	-	98.6% (1)	95% (4)	91.1%		93.7%

- *Number quoted is the number of participants with positive margins. The percentage in brackets represents percentage of sample size with positive margins
- ~ For Local, regional and distant control: The percentage represents that percentage of the sample size which did not have a local, regional or distant recurrence. The number in brackets represents the number of patients with recurrences (either local, regional or distant).

Appendix IX: Two-year outcome data by technique

TORS

Study	Sample size	Positive Margins*	Local control~	Regional control~	Distant control~	DFS	DSS	OS
Cohen[59]	50	-	-	-	-	-	92.6%	80.6%
Smith[77]	42	6 (14%)	81%	-	-	-	91%	86%
Park[83]	32	2 (5%)	-	-	-	92%	-	96%
Weinstein[72]	47	1 (2%)	98%	96%	91%	79%	90%	82%

TLM

Study	Sample size	Positive Margins*	Local control~	Regional control~	Distant control~	DFS	DSS	OS
Camp[78]	71	8 (11.3%)	97.2%	97.2%	95.8%	-	94%	90%
Grant[81]	59	2 (3%)	90%	88%	96%	84%	-	91%
Haughey[42]	204	-	97%	-	-	85%	91%	89%
Henstrom[82]	20	2 (10%)	83.6% (3)	100% (0)	94.7% (2)	-	94.7%	90%
Rich[58]	84	10 (12%)	98.8% (1)	95.2% (4)	94.0% (5)	91%	96%	94%
Steiner[43]	48	9 (19%)	85.4% (7)	83.3% (8)	95.8% (2)	73%	-	52%

- *Number quoted is the number of participants with positive margins. The percentage in brackets represents percentage of sample size with positive margins
- ~For Local, regional and distant control: The percentage represents that percentage of the sample size which did not have a local, regional or distant recurrence. The number in brackets represents the number of patients with recurrences (either local, regional or distant)

Appendix X: One-year outcome data by technique

TORS

Study	Sample size	Positive margins*	Local control~	Regional control~	Distant control~	DFS	DSS	OS
Cohen[59]	50	-	-	-	-	-	97.8%	95.7%
Weinstein[72]	47	1 (2%)	98%	96%	91%	96%	98%	96%
Weinstein[71]	30	1 (3%)	97%	90%	100%	-	-	100%

Note: No one-year TLM outcome data

- *Number quoted is the number of participants with positive margins. The percentage in brackets represents percentage of sample size with positive margins
- ~For Local, regional and distant control: The percentage represents that percentage of the sample size which did not have a local, regional or distant recurrence. The number in brackets represents the number of patients with recurrences (either local, regional or distant).

Appendix XI: Excluded studies on full text review

Patel SH, Wong W, Hinni M, Hayden R, Zarka M, Dueck AC, et al. Transoral laser microsurgery (TLM) followed by radiation therapy (RT) for oropharyngeal tumors. International Journal of Radiation Oncology Biology Physics. 2012;84(3):S472.[103]
Reason(s) for exclusion: Incorrect article type (conference abstract)

Lorincz BB, Mockelmann N, Busch CJ, Munscher A, Sehner S, Dalchow CV, et al. Two-Year Survival Analysis of 50 Consecutive Head and Neck Cancer Patients Treated with Transoral Robotic Surgery in a Single European Centre. Annals of surgical oncology. 2015.[104]
Reason(s) for exclusion: Incorrect article type (conference abstract)

Blanco RGF, Fakhry C, Ha PK, Ryniak K, Messing B, Califano JA, et al. Transoral robotic surgery experience in 44 cases. Journal of Laparoendoscopic and Advanced Surgical Techniques. 2013;23(11):900-7. [105]
Reason(s) for exclusion: Incorrect population (laryngeal cancers patients included and benign tumors included), Incorrect procedure (salvage surgery included)

Chauhan P, Byrne H, Taylor E, Sheahan P. Oncological and functional outcomes of transoral surgery for the treatment of oropharyngeal cancer. Irish Journal of Medical Science (1971 -). 2014. [106]
Reason(s) for exclusion: Incorrect intervention (Non-endoscopic transoral surgery included)

Kumar B, Cipolla MJ, Old MO, Brown NV, Kang SY, Dziegielewski PT, et al. Surgical management of oropharyngeal squamous cell carcinoma: Survival and functional outcomes. Head & neck. 2016 Apr;38 Suppl 1:E1794-802. [107]
Reason(s) for exclusion: Incorrect intervention (Open surgery and non-endoscopic transoral surgery included)

de Almeida JR, Li R, Magnuson JS, Smith RV, Moore E, Lawson G, et al. Oncologic Outcomes After Transoral Robotic Surgery: A Multi-institutional Study. JAMA otolaryngology-- head & neck surgery. 2015 Dec;141(12):1043-51. [108]
Reason(s) for exclusion: Incorrect population (Other head and neck subsites included)

Genden EM, Desai S, Sung CK. Transoral robotic surgery for the management of head and neck cancer: A preliminary experience. Head and Neck. 2009;31(3):283-9. Cited in: Scopus. [109]
Reason(s) for exclusion: Incorrect population (Other head and neck subsites included)

Genden EM, Kotz T, Tong CCL, Smith C, Sikora AG, Teng MS, et al. Transoral robotic resection and reconstruction for head and neck cancer. The Laryngoscope. 2011;121(8):1668-74[110]
Reason(s) for exclusion: Incorrect population (Other head and neck subsites included)

Lee SY, Park YM, Byeon HK, Choi EC, Kim SH. Comparison of oncologic and functional outcomes after transoral robotic lateral oropharyngectomy versus conventional surgery for T1 to T3 tonsillar cancer. Head & neck. 2014 Aug;36(8):1138-45. [111]
Reason(s) for exclusion: Incorrect intervention (Open surgery included)

Melong JC, Rigby MH, Bullock M, Hart RD, Trites JR, Taylor SM. Transoral laser microsurgery for the treatment of oropharyngeal cancer: the Dalhousie University experience. Journal of otolaryngology - head & neck surgery = Le Journal d'oto-rhino-laryngologie et de chirurgie cervico-faciale. 2015;44:39. [112]
Reason(s) for exclusion: Incorrect population (Recurrences and second primaries included)

Moore EJ, Henstrom DK, Olsen KD, Kasperbauer JL, McGree ME. Transoral resection of tonsillar squamous cell carcinoma. The Laryngoscope. 2009 Mar;119(3):508-15. [113]
Reason(s) for exclusion: Incorrect intervention (Non-endoscopic transoral surgery included)

Moore EJ, Olsen KD, Kasperbauer JL. Transoral robotic surgery for oropharyngeal squamous cell carcinoma: a prospective study of feasibility and functional outcomes. The Laryngoscope. 2009 Nov;119(11):2156-64. [114]
Reason(s) for exclusion: Incorrect outcomes (Feasibility and functional outcomes included)

Sinha P, Hackman T, Nussenbaum B, Wu N, Lewis JS, Jr., Haughey BH. Transoral laser microsurgery for oral squamous cell carcinoma: oncologic outcomes and prognostic factors. Head & neck. 2014 Mar;36(3):340-51.[115]
Reason(s) for exclusion: Incorrect population (Oral SCC)

van Loon JW, Smeele LE, Hilgers FJ, van den Brekel MW. Outcome of transoral robotic surgery for stage I-II oropharyngeal cancer. European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery. 2015 Jan;272(1):175-83.[116]
Reason(s) for exclusion: Outcomes (No Overall Survival outcome included)

Weinstein GS, O'Malley BW, Jr., Magnuson JS, Carroll WR, Olsen KD, Daio L, et al. Transoral robotic surgery: a multicenter study to assess feasibility, safety, and surgical margins. The Laryngoscope. 2012 Aug;122(8):1701-7.[61]
Reason(s) for exclusion: Incorrect population (other head and neck subsites included and other outcomes included)

White HN, Moore EJ, Rosenthal EL, Carroll WR, Olsen KD, Desmond RA, et al. Transoral robotic-assisted surgery for head and neck squamous cell carcinoma: one- and 2-year survival analysis. Archives of otolaryngology--head & neck surgery. 2010 Dec;136(12):1248-52. [117]
Reason(s) for exclusion: Incorrect population (other head and neck subsites included)
Incorrect intervention (Salvage surgery included)

Appendix XII: Authors contacted

Study	Response
Camp AA, Fundakowski C, Petruzzelli GJ, Emami B. Functional and oncologic results following transoral laser microsurgical excision of base of tongue carcinoma[78]	Failed delivery
Canis M, Ihler F, Wolff HA, Christiansen H, Matthias C, Steiner W. Oncologic and functional results after transoral laser microsurgery of tongue base carcinoma[76]	Unable to obtain data
Canis M, Martin A, Kron M, Konstantinou A, Ihler F, Wolff HA, et al. Results of transoral laser microsurgery in 102 patients with squamous cell carcinoma of the tonsil [79]	Unable to obtain data
Cohen MA, Weinstein GS, O'Malley BW, Jr., Feldman M, Quon H. Transoral robotic surgery and human papillomavirus status: Oncologic results [59]	No response
Grant DG, Hinni ML, Salassa JR, Perry WC, Hayden RE, Casler JD. Oropharyngeal cancer: a case for single modality treatment with transoral laser microsurgery [80]	Failed delivery
Grant DG, Salassa JR, Hinni ML, Pearson BW, Perry WC. Carcinoma of the tongue base treated by transoral laser microsurgery, part one: Untreated tumors, a prospective analysis of oncologic and functional outcomes[81]	No response
Haughey BH, Hinni ML, Salassa JR, Hayden RE, Grant DG, Rich JT, et al. Transoral laser microsurgery as primary treatment for advanced-stage oropharyngeal cancer: a United States multicenter study [42]	No response
Haughey BH, Sinha P. Prognostic factors and survival unique to surgically treated p16+ oropharyngeal cancer[73]	No response
Henstrom DK, Moore EJ, Olsen KD, Kasperbauer JL, McGree ME. Transoral resection for squamous cell carcinoma of the base of the tongue [82]	No response
Moore EJ, Olsen SM, Laborde RR, Garcia JJ, Walsh FJ, Price DL, et al. Long-term functional and oncologic results of transoral robotic surgery for oropharyngeal squamous cell carcinoma [60]	No response
Park YM, Kim WS, Byeon HK, Lee SY, Kim SH. Oncological and functional outcomes of transoral robotic surgery for oropharyngeal cancer [83]	Failed delivery
Patel SH, Hinni ML, Hayden RE, Wong WW, Dueck AC, Zarka MA, et al. Transoral laser microsurgery followed by radiation therapy for oropharyngeal tumors: the Mayo Clinic Arizona experience [84]	Unable to share data
Rich JT, Milov S, Lewis JS, Jr., Thorstad WL, Adkins DR, Haughey BH. Transoral laser microsurgery (TLM) +/- adjuvant therapy for advanced stage oropharyngeal cancer: outcomes and prognostic factors [58]	No response
Smith RV, Schiff BA, Garg M, Haigentz M. The impact of transoral robotic surgery on the overall treatment of oropharyngeal cancer patients [77]	No response
Steiner W, Fierek O, Ambrosch P, Hommerich CP, Kron M. Transoral laser microsurgery for squamous cell carcinoma of the base of the tongue [43]	Failed delivery
Weinstein GS, O'Malley BW, Jr., Cohen MA, Quon H. Transoral robotic surgery for advanced oropharyngeal carcinoma[72]	No response
Weinstein GS, Quon H, Newman HJ, Chalian JA, Malloy K, Lin A, et al. Transoral robotic surgery alone for oropharyngeal cancer: an analysis of local control[71]	No response