Original Article

Outcomes of primary trans-oral surgical management of early tonsillar squamous cell carcinoma with risk-adapted adjuvant radiotherapy

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Background: Transoral robotic surgery (TORS) is an accepted surgical treatment modality for patients with oropharyngeal squamous cell carcinoma (OPSCC). A prospective study was conducted to test patient selection for unimodality TORS in early OPSCC, with the primary endpoint being avoidance of adjuvant radiotherapy (RT) or chemoradiation (CRT) as per recommended guidelines.

Methods: Patients underwent comprehensive evaluation including multidisciplinary team (MDT) review and staging (AJCC 7th edition). Primary TORS was offered to patients with T1–2 lateralized tonsillar tumours, N0–1 with no extracapsular spread (ECS). Adjuvant RT or CRT were recommended if prespecified pathologic criteria were met, including close or positive margins, ECS and N2b disease.

Results: Twenty-six patients underwent TORS, all with negative margins. Seven patients (26.9%) met one or more upstaging criteria, most commonly pN2b (5 patients, 19.2%) and close margin (3 patients, 11.5%). Five patients (19.2%) proceeded to adjuvant therapy with two patients declining further treatment.

Conclusions: Single modality treatment of early tonsillar SCC utilising TORS is feasible amongst patients who undergo comprehensive evaluation including MDT review.

Keywords: Robotic surgery; oropharyngeal carcinoma; surgery

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Introduction

The management of oropharyngeal squamous cell carcinoma (OPSCC) has undergone several paradigm shifts over the past few decades. Historically, primary open surgery with or without adjuvant radiotherapy (RT), was the preferred treatment approach. Although this obtained reasonably high rates of loco-regional control, the functional outcomes were poor and surgical morbidity high (1,2). A meta-analysis demonstrated that primary surgery and RT approaches were similar in terms of survival, but major complications were markedly worse in the primary surgery group (3). As a result of the morbidity and poor functional outcomes of primary surgery, most centres moved towards primary RT for early OPSCC, and chemoradiotherapy (CRT) in advanced stage patients (4).

Despite improvements in modern RT techniques there remains the potential of significant acute and late side-effects including xerostomia and dysphagia (5).

These toxicity risks, along with the development of minimally invasive surgical techniques, have led to a resurgence of interest in the primary surgical management of OPSCC. The ability to avoid open access incisions preserves neuromuscular structures that are critical for speech and swallowing. Although some centres have employed non-robotic transoral resections with and without a laser for many years (6-8), these approaches can be technically difficult which has been a barrier to widespread adoption.

Transoral robotic surgery (TORS) for the oropharynx and larynx has steadily evolved since the early 2000s (9-12). Case series of TORS for OPSCC have demonstrated encouraging oncologic, functional and quality of life outcomes leading to its widespread adoption (13), particularly in early disease where it may be a viable alternative to primary RT.

Rates of HPV-associated OPSCC (HPV-OPSCC) in countries of the developed world are rapidly increasing (14,15), with distinct risk factors including oral sex and marijuana use, and little association with traditional risk factors such as tobacco and alcohol use, or poor dentition. This disease is recognized as a pathological entity distinct from other head and neck SCC in the 2017 American Joint Committee on Cancer (AJCC) 8th edition staging system (16). In contrast to non-HPV head and neck SCC, HPV-OPSCC tends to occur in patients of younger age, of good performance status, with fewer co-morbidities and with greater potential for return to premorbid employment. As a result of these different patient characteristics and improved prognosis after treatment (17), HPV-OPSCC represents a societal challenge in terms of survivorship and management of late effects of therapy.

With an expanded armamentarium of modern treatment options, changing patient demographics and improvement in overall prognosis, the selection of appropriate modality of treatment for individual patients with early OPSCC becomes a key challenge. Early OPSCC is often amenable to primary surgical treatment, which if employed as a sole modality may offer greater convenience than RT, with fewer late effects than multimodality therapy. In contrast, patients who undergo surgery but then require adjuvant RT, or CRT, may have been arguably better served by primary RT alone given the high documented rates of cure from this established modality, and potential for severe and non-overlapping side-effects from multimodality therapy. Appropriate treatment selection may be aided by comprehensive pre-treatment assessment including imaging, and by the expertise of a head and neck multidisciplinary team meeting (HNMDT) which brings together expert oncologists, allied health professionals, radiologists and pathologists to accurately stage the patient and formulate a treatment recommendation.

Aim

This prospective single-arm, multi-centre phase II trial aimed to assess the efficacy of modern patient selection and primary surgical management of patients with early OPSCC. There was an anticipated predominance of HPV-related OPSCC although this was not a specific inclusion criterion. The primary endpoint was the rate of one or more pathologic indications for adjuvant RT or CRT. Secondary endpoints included oncologic outcomes and acute surgical morbidity.

Methods

Ethics

Ethics approval for the current study was obtained from Metro South Research Ethics and Governance Group (HREC/15/QPAH/80) and all patients provided informed consent.

Patients

Potentially eligible patients were invited to participate in the study and those who declined were offered standard treatment options according to current NCCN guidelines. All patients were assessed by clinical examination by a qualified head and neck surgeon, panendoscopy, and computed tomography (CT) of head and neck with intravenous contrast. All patients included in the study had a magnetic resonance imaging (MRI) with intravenous contrast, and fluorine-18-fluorodeoxyglucose positron emission tomography with CT (FDG PET-CT) performed. All findings were reviewed at a tertiary hospital HNMDT, at which time final clinical staging was assigned and patients who met inclusion criteria were offered participation in this study. The main inclusion criteria were biopsy-proven OPSCC, assessed both clinically and radiologically as arising in the lateral pharyngeal wall, T1 or T2, lateralized (>1 cm from the midline excluding exophytic component with no gross invasion) and N0 or N1, with no evidence of distant

Table 1 Pathologic indications for adjuvant treatment

Adjuvant chemoradiation (CRT)
Positive margin (primary or nodal)
Nodal extracapsular spread (ECS) of any extent
Adjuvant radiotherapy (RT) alone
Primary site close margin ≤2 mm
Primary site pT3–4
Primary site lymphovascular invasion positive
Primary site large nerve (>0.1 mm) perineural invasion positive
Nodal stage pN2–3
Nodal tumour spill at time of surgery

Note: all staging refers to AJCC 7th edition [2009].

metastases. Staging was performed according to AJCC 7th edition [2009] criteria (18). Immunohistochemistry (IHC) for p16 was performed on surgical specimens of the primary tumour as a marker of HPV association.

Surgical treatment

Patients meeting criteria above were treated with primary trans-oral robotic resection of the primary lesion using the da Vinci system (Intuitive Surgical Inc., Sunnyvale USA). All surgeons had TORS accreditation either by fellowship training or accredited course completion and logbook submission. Intraoperative frozen sections taken from the specimen were used in all cases to assess clearance, and adequacy (>2 mm), of surgical margins. Neck dissection was undertaken pre-operatively, synchronously or as a staged procedure within 4 weeks of primary surgery dependent on the preference of the treating surgeon.

Decision for adjuvant treatment

Final pathology of both the primary resection and neck dissection was reported by a qualified pathologist and discussed at another HNMDT. Patients meeting criteria for adjuvant treatment (*Table 1*) were offered RT or CRT, with treatment to commence within 6 weeks following completion of surgical management.

Adjuvant treatment

Adjuvant RT was delivered with megavoltage photons on a linear accelerator, employing an IMRT, simultaneous integrated boost technique. A minimum of 60 Gy (range, 60–64 Gy) was prescribed to both the primary site and nodal tumour beds, with integrated dose of 54–57 Gy to the entire surgical bed and elective nodal regions. Treatment was delivered in 30 fractions over six weeks, utilising online image verification. Target volumes and organs at risk were delineated by a radiation oncologist according to standard departmental protocols taking into account preoperative imaging, operation reports and pathological findings. Concurrent chemotherapy, if prescribed, consisted of cisplatin 100 mg/m^2, in weeks one and four of radiotherapy.

Follow-up

Data on acute surgical complications was collected prospectively. Patients had clinical follow up at a minimum, every 3 months following completion of treatment, with PET-CT and MRI performed 3 months following completion of treatment.

Results

Patients and demographics

Twenty-six patients gave informed consent and were recruited to the study between July 2013 and December 2017. Key demographic and clinical staging at time of recruitment are listed in *Table 2*. Mean age was 61 (SD =9.3). Data close out date was December 31, 2017 and follow-up ranged from 6 to 54 months with a median follow up of 36 months (IQR =19 months).

Primary endpoint

All patients underwent protocol specified surgery of TORS to the primary lesion and ipsilateral selective neck dissection (SND). Surgery was performed by at three hospitals by three surgeons (range of cases per surgeon 3–15), with 15 patients receiving SND prior to TORS, 10 synchronously and one after TORS. Based on final pathologic staging seven patients (26.9%) were recommended adjuvant RT due to meeting one or more specified indications (*Table 1*). Of these seven patients, five were recommended adjuvant RT alone (two of whom declined), and two were recommended adjuvant CRT (both of whom proceeded with recommended treatment). Therefore, 5 patients (19.2%) proceeded to adjuvant RT or CRT (*Table 3*).

Table 2 Patient demographics at study entry

Variable	Number
Age, median [range]	63 [41–77]
Gender (%)	
Male	21 (80.8)
Female	5 (19.2)
p16 IHC (%)	
Positive	24 (92.3)
Negative	2 (7.7)
Smoking (%)	
Current	3 (11.5)
Previous	3 (11.5)
Never	20 (76.9)
Clinical T-staging (%)	
T1	16 (61.5)
T2	10 (38.5)
Clinical N-staging (%)	
N0	14 (53.8)
N1	12 (46.2)
Clinical M-staging (%)	
M0	0 (0)
Clinical stage group (%)	
I	12 (46.2)
II	2 (7.7)
III	12 (46.2)

T and N pathologic staging

Pathological evaluation of the primary TORS specimen confirmed pT1 or pT2 SCC in all cases, with 24 patients being p16 positive (92.3%) and two patients p16 negative. Based on frozen section outcomes 4 patients (15.4%) required further margins to be taken intra-operatively. Formal histopathology revealed no positive margins at the primary site and 3 patients (11.5%) had a close (<2 mm) margin.

SND upstaged neck disease in 7 patients (26.9%) to pN2a (2 patients, 7.7%) and pN2b (5 patients, 19.2%), with two of the pN2b patients also having pathologic evidence of microscopic extracapsular spread (ECS) (these patients were recommended, and completed, adjuvant CRT). No patient staged pN1 or pN2a had evidence of ECS. No positive margins were noted from SND.

Acute surgical morbidity

Two patients (7.7%) returned to theatre unexpectedly, both for postoperative bleeding following TORS. Neither required a blood transfusion. Two elective tracheostomies were placed at the time of TORS and patients were decannulated within seven days. No nasogastric feeding was required for any patients beyond post-operative day 2 with all patients resuming at least partial oral intake on the day 1 post TORS. No percutaneous gastrostomy (PEG) tubes were required at any time.

Oncologic outcomes

At the time of analysis, no local, regional or distant failures

Table 3 Adjuvant treatment recommendations

Patient	Pathologic outcomes	Adjuvant treatment recommendation
1	Extracapsular spread (ECS); Nodal stage pN2–3	Chemoradiotherapy
2	Extracapsular spread (ECS); Nodal stage pN2–3	Chemoradiotherapy
3	Primary site close margin ≤2 mm; Nodal stage pN2–3	Radiotherapy
4	Primary site close margin ≤2 mm; Nodal stage pN2–3	Radiotherapy
5	Primary site close margin ≤2 mm; Nodal stage pN2–3	Radiotherapy (declined)
6	Nodal stage pN2–3	Radiotherapy
7	Nodal stage pN2–3	Radiotherapy (declined)

were recorded. One patient died of unrelated causes during follow-up. Disease free survival was 100% and overall survival was 96%.

Discussion

In this prospective multi-centre study, patients with early OPSCC were managed with primary TORS, testing the hypothesis that adjuvant RT or CRT could be avoided if a careful selection process was applied. Following TORS, 26.9% of patients were recommended adjuvant RT or CRT due to meeting pre-specified pathologic criteria, and conversely with only five patients receiving adjuvant treatment, 80.8% of participants avoided the potential morbidity and inconvenience of unplanned multimodality treatment. This represents a low adjuvant treatment rate in a highly selective patient cohort. This also compares favorably with the only similar published study in the literature in which 43% of patients were recommend adjuvant therapy (19). Furthermore, in our study acute surgical morbidity was acceptable, and tumour control was high with no recorded failures. While there is no randomized data to support either upfront RT or TORS for early OPSCC, upfront TORS is increasingly available to patients and our study emphasizes the importance of patient selection if TORS is offered as a planned unimodality approach. The ongoing randomized phase II ORATOR study will provide direct comparative data on the relative efficacy and toxicity of these modalities (20).

One strength of our study was the recruitment of a homogenous patient population in terms of pre-operative disease characteristics, in contrast to other case series of TORS for head and neck cancer (21-23). Critical to this study was rigorous pre-operative clinical and radiological assessment to ensure appropriate patient selection. This included clinical evaluation and panendoscopy performed by the robotic surgeon, radiologic evaluation with CT, MRI and PET-CT, and HNMDT review of all aspects of the case. In the aforementioned study by Rubek *et al.*, a similar number of patients with broadly similar preoperative characteristics were recruited, but ultrasound instead of PET staging of the neck was utilised. In that study, a 40% rate of pathologic nodal upstaging was reported compared to 26.9% in our protocol (19). Acknowledging the difficulties inherent to comparing outcomes between studies, this difference may reflect the added value of PET-CT in neck staging in our protocol, particularly for detecting (and excluding from this study) patients with N2b disease.

One of the rationales for conducting this study was to introduce a new technology, namely TORS, to several centres in a prospective fashion with close follow-up of outcomes. Whilst the lead surgeon (SD) had substantial experience of TORS at other centres prior to commencement of the study, the efficacy of patient selection for unimodality TORS in the participating sites had yet to be tested. Evidence exists for a learning curve in TORS (23,24), and carefully selected patients with early OPSCC may provide an ideal platform for development of surgical skill and confidence. We believe meticulous pre-operative clinical and radiological assessment combined with intra-operative frozen section analysis has helped ensure successful TORS management of the primary lesions in our patient cohort.

The selection of risk factors (*Table 1*) prompting adjuvant RT or CRT was also crucial in development of our study. We based these risk factors on expert opinion, consensus guidelines and published evidence, aiming to be conservative in our approach. We acknowledge that much of the prospective data supporting these risk factors for locoregional recurrence predates the HPV and TORS era (25-28), however we believe our approach still reflects clinical practice in most departments and so forms a useful endpoint in terms of ensuring safety of unimodality treatment. Ongoing studies such as PATHOS may clarify the relative importance of these risk factors in a surgical cohort, and the intensity of adjuvant treatment required (29).

In our study, no patients were upstaged to pT3 or pT4 following surgery, and no positive margins were recorded. This reflects a strict adherence to our inclusion criteria and purposeful exclusion of any patients with borderline pre-operative clinical/radiological staging. In T1–2 OPSCC a high rate of negative margins from transoral surgery is reported in the literature, particularly where frozen section margin mapping is employed (30,31). Surgeon experience may also be an important factor in obtaining negative margins (24), emphasizing the need for adequate training and mentoring in centres newly undertaking TORS. Three patients (11.5%) in our study had close excisions of their primary tumour on final paraffin sections, defined as <2 mm, all at the deep margin. In OPSCC, the margin width which should prompt a recommendation for adjuvant RT is controversial. For tonsillar tumours in particular, the limited depth of pharyngeal constrictor musculature and presence of adjacent fascial plane means that an anatomically adequate excision may be achieved without final pathologic margins >2 mm (31). More recently, excellent local control outcomes are reported in series where no adjuvant

radiotherapy was employed for margins >1 mm (32). For our study, we selected a 2 mm definition of 'close' margin consistent with current institutional practice in other head and neck subsites, and with other ongoing studies (20,29).

Two patients in our study (7.6%) had pathologic evidence of ECS despite no radiologic evidence of this preoperatively, and both were recommended (and underwent) adjuvant CRT. The role of adjuvant CRT in the presence of ECS is supported by two phase III studies and a meta-analysis (33-35). However, HPV status was not tested in these studies, and the role for CRT in HPV-associated nodal disease with ECS has recently been questioned (36,37). The role of CRT *vs.* RT alone for patients with pathologic ECS may be clarified after the results of the PATHOS study are available (29).

Secondary endpoints in our study included acute surgical morbidity and standard oncologic outcomes of locoregional failure-free survival, PFS and OS. Collection of functional outcome endpoints is continuing and these will be reported separately. Two patients (7.7%) required further surgery within the same admission as primary TORS to control minor postoperative haemorrhage. The short duration of nasogastric feeding and lack of long-term PEG placement during follow-up emphasizes the limited acute functional impact of primary surgical intervention. These morbidity outcomes are consistent with published literature of tertiary centres undertaking TORS for oropharyngeal tumours (22,38). As expected for a cohort with early OPSCC, of which 92% were p16 positive, PFS and OS outcomes were excellent with no failures recorded during the follow-up period.

Conclusions

Our study demonstrates that early OPSCC can be safely managed with primary TORS resulting in a low rate of unplanned adjuvant treatment. This provides valuable information for clinicians and patients considering unimodality surgical treatment for early OPSCC. Primary TORS is associated with high rates of progression free and overall survival, and low acute surgical morbidity.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/ajo.2019.02.01). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Ethics approval for the current study was obtained from Metro South Research Ethics and Governance Group (HREC/15/QPAH/80) and all patients provided informed consent.

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