Oncological outcome following de-intensification of treatment for stage I and II HPV negative oropharyngeal cancers with transoral robotic surgery (TORS): A prospective trial

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A B S T R A C T

Objective: This prospective study aimed to see long-term oncological outcome of Transoral Robotic Surgery as single modality treatment for cT1-T2 N0 HPV negative oropharyngeal malignancies.

Method: From March 2013 to October 2015, 57 patients with early stage oropharyngeal carcinoma underwent Transoral robotic surgery (TORS) with neck dissection using daVinci Surgical system. Patients were evaluated for disease free survival, overall survival, locoregional and distant metastasis.

Results: 57 patients (48 males and 9 females) underwent TORS for early stage oropharyngeal carcinoma. All patients underwent ipsilateral neck dissection and 12 patients underwent bilateral neck dissection. 49 patients with final histopathology suggestive of stage I and II disease did not received any adjuvant treatment. Mean age at presentation was 59.4 years (37–88 years). Most common site of involvement was the base of tongue (BOT) in 31 (54.8%) patients. Twenty-four (42.1%) patients were cT1 and 33 (57.9%) were cT2 at presentation. During follow-up, 2 (4.2%) patients recurred locoregionally and 1 (2.1%) patient had distant metastasis. Two patients expired due to causes other than malignancy. Forty-three (89.6%) patients were disease free on an average follow-up of 29 months with an overall survival of 93.8% at mean follow-up of 29 months.

Conclusion: Transoral Robotic Surgery as a single modality treatment is a good option for cure in HPV negative early resectable oropharyngeal malignancies which are relatively unresponsive to radiation. TORS can be used to de-intensify the treatment of early stage oropharyngeal carcinoma and thus avoid the early and late toxicities associated with Radiotherapy/Chemoradiotherapy.

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Introduction

The incidence of oropharyngeal squamous cell carcinoma (OPSCC) is increasing in India. There were estimated 38,691 new cases of oropharyngeal cancers in India in 2012 [1]. As compared to the developed countries, where the increase in the incidence of OPSCC is mainly attributed to the epidemic increase in the incidence of HPV infection, the leading cause of OPSCC in India is still caused due to exposure to tobacco and alcohol. The prevalence of HPV positivity in newly diagnosed cases of OPSCC in developed countries like USA is >60% [2,3]. On the other hand the prevalence of HPV positivity in OPSCC in India ranges from 20–30% in various studies [4,5]. Many studies have shown the HPV status is an important prognostic factor in OPSCC, with HPV positivity conferring a survival advantage over HPV negative oropharyngeal cancers [6–9].

Patients with HPV negative OPSCC tend to present like the “classical” type of squamous cell carcinoma of the oral cavity. HPV negative OPSCC tends to present at an older age and comparatively at a higher stage [6,7,10]. RTOG 0129 trial aimed to study the difference in overall survival or late toxicity with use of accelerated vs standard radiation therapy plus cisplatin in patients with locally advanced head and neck cancer. A secondary analysis of RTOG 0129 showed an increased risk of progression or mortality in HPV negative OPSCC as compared to HPV positive OPSCC after adjusting for demographics, T class, nodal (N) class, and smoking [6]. On comparing 215 patients with p16-positive and 101 with p16-negative oropharyngeal cancer, p16-positive patients had significantly better overall survival (HR = 0.34, 95% confidence interval [CI] = 0.22–0.52), progression-free survival (HR = 0.43, 95% confidence interval [CI] = 0.27–0.68), and locoregional recurrence survival (HR = 0.31, 95% confidence interval [CI] = 0.17–0.57). The results were similar even after adjustment for other variables. This suggests that HPV status can be an important factor in the clinical presentation of HPV negative OPSCC.
CI = 0.29–0.64), and locoregional failure rate (HR = 0.29, 95% CI = 0.17–0.48) but not distant metastases rate (HR = 0.59, 95% CI = 0.26–1.35) after all prognostic covariates were adjusted. Eight-year rates were 70.9% vs 30.2% for overall survival, 64.0% vs 23.3% for progression-free survival, 19.5% vs 52.4% for locoregional failure, and 10.3% vs 16.1% for distant metastases between HPV positive and HPV negative respectively [6]. TAX324 was a randomized, open-label phase 3 trial comparing three cycles of TPF induction chemotherapy (docetaxel 75 mg/m² of body-surface area, followed by intravenous cisplatin 100 mg/m² and 5-fluorouracil 1000 mg/m² per day administered as a continuous 24-h infusion for 4 days) with three cycles of PF (intravenous cisplatin 100 mg/m², followed by fluorouracil 1000 mg/m² per day as a continuous 24-h infusion for 5 days) in locally advanced head and neck cancers. TAX 324 trial included 111 patients with locally advanced OPSCC and revealed increased mortality in HPV negative OPSCC compared to HPV positive OPSCC. Furthermore, a lower incidence of second primary tumours in HPV positive OPSCC contributed to the difference in long term outcomes over time and reduced the mortality as compared to HPV negative OPSCC [7].

Presently there is a trend towards intensification of treatment in HPV negative OPSCC, but the overall prognosis still remains dismal [7,11,12].

Historically, advanced-stage OPSCC was treated with open surgical resection, reconstruction, and postoperative radiotherapy [13,14]. These open approaches to the oropharynx required mandibulotomy or pharyngotomy, resulting in significant morbidity and functional impairments to speech, swallowing, and breathing [15]. In 1991, with the publication of the Veterans Affairs Laryngeal Cancer Study Group trial, there was an increased trend toward nonsurgical therapies to treat other head and neck sites, most notably OPSCC [16]. In 2002, a meta-analysis of patients with OPSCC found similar survival outcomes for patients treated with surgery and postoperative radiotherapy versus primary radiotherapy with salvage neck dissection [13]. Subsequent studies showed comparable oncological and functional outcome between primary surgery and radiotherapy for OPSCC [17,18]. But with the utilization of intensified organ preservation nonsurgical therapies, especially concurrent chemoradiation, there was an increase in treatment-related toxicities including mucositis, xerostomia, loss of taste, tissue fibrosis, stricture, osteoradionecrosis, neuropathy, and fatigue [19–21].

As a result of increased treatment related toxicities associated with chemoradiation (CRT), a number of trials are underway to study de-intensification of treatment for HPV positive OPSCC with transcervoral robotic surgery (TORS) [22–25]. But due the premise that the HPV negative OPSCC have poorer oncological outcomes as compared to HPV positive OPSCC, these patients were not included in the trials [6,7]. The only trial exclusively comparing CRT with surgery followed by CRT for HPV negative OPSCC, RTOG 1221 was stopped due to failure to accrue.

There is no prospective data available in the world literature regarding treatment outcome of HPV negative OPSCC treated with TORS. The aim of this prospective trial was to study the functional and oncological outcomes in cases of early stage HPV negative OPSCC treated with TORS as a single modality.

Material and methods

A prospective study from February 2013 to October 2015 to evaluate the functional outcome and oncological outcome of TORS as a single modality treatment for early (Stage I and II) HPV negative OPSCC after attained the required clearance from the Institutional Ethics Committee was performed. A total of 57 patients were included in the study with the following criteria.

Inclusion criteria:
1. Age ≥ 18 years.
2. Clinically cT1 and cT2 tumours.
3. Mouth opening ≥ 3 cm.
4. Prior treatment naïve patients.
5. Clinically and radiologically cN0 on presentation.

Exclusion criteria:
1. Extensive local extension of disease.
2. Mouth opening < 3 cm.
3. HPV positive status.

The surgical intervention was performed with the patient under general anesthesia with a nasotracheal intubation. Tracheostomy was performed in few patients who were deemed to have higher risk of aspiration and difficult airway. A Nasogastric tube or percutaneous gastrostomy was placed for maintaining adequate feeding in post-op. The da Vinci Surgical System (Intuitive Surgical, Sunnyvale, CA) was set up, as previously described by Weinstein et al. [7,8]. Proper surgical exposure was attained with the use of a Fehy–Kastenbauer retractor (Gyrus-Medical, Tuttingen, Germany). A binocular endoscope of 0° and 30° were used to gain 3D vision. 5 mm diameter instruments namely Maryland dissector and monopolar cautery spatula arms were used. The surgeon was seated at the console of the da Vinci system, while an assistant, positioned at the head of the patient, assisted with the suction and retractor.

All patients underwent ipsilateral neck dissection and twelve patients underwent bilateral neck dissection, performed immediately before TORS. Patients staged as Stage I and II on the final histopathology did not receive any adjuvant treatment in the form of Chemoradiation or Radiation after TORS and were kept under regular follow-up, with clinical examination every three months and radiological examination in the form of a PET-CT every year or when warranted by any clinical suspicion.

The data collected in this study included the demographic characteristics (age and sex) of the patients, tumor site, clinical and pathologic stage (based on the TNM classification system from the Union for International Cancer Control, seventh edition of 2009).

The endpoints of the study were determined according to functional and long term oncological outcome in the form of rate of recurrence, disease free survival and overall survival at a mean follow-up of 29 months (15–47 months).

Results

A total of 57 patients of HPV negative OPSCC underwent TORS from February 2013 to October 2015 were included in the study. The demographic characters and clinicopathological details of the patients are shown in Table 1.

Average Robotic set-up time was 7.4 ± 2 min and average robotic operative time was 31.5 ± 5 min. Average blood loss during surgery was 30 ± 9 ml. Six (10.5%) patients required tracheostomy, and 4 (7.1%) patients underwent percutaneous endoscopic gastrostomy for feeding and rest 53 patients had nasogastric tube placement. All patients were successfully decannulated after surgery. Two (3.5%) patients were dependent on long term nasogastric tube/PEG feeding. Patients started tolerating oral feeds within two week of procedure (mean 7.6 days), with the nasogastric tube removed within two to three weeks post-op (mean 13.4 days). The average hospital stay was 5.8 days (range, 4–9 days) (Table 2).

Postoperative complications in the form of primary haemorrhage required active intervention in one patient. One patient...
developed aspiration pneumonitis which was managed conservatively by antibiotics.

On final histopathology, 8 patients had pathologically positive lymph node (pN1) for metastasis and thus were upstaged to Stage III and were referred for adjuvant treatment in the form of radiation or chemoradiation and were excluded from the oncological outcome analysis for this study.

Seven patients were pN1 and 1 patient was pN1 with extracapsular spread (ECS) on final histopathology. Seven patients received adjuvant radiotherapy, of which 4 patients are alive without disease on follow-up, 2 patients had locoregional recurrence and 1 patient developed distant metastasis. One patient with ECS on final histopathology received adjuvant chemoradiation and is alive without disease on follow-up.

Remaining 49 (85.9%) patients were pathologically stage I and II and were included for the oncological outcome analysis.

The mean follow-up was 29 months (range, 15–47 months). Of the 49 patients included for analysis, one patient was lost to follow-up of 29 months is 93.8% and disease free survival of 89.6% (Table 3).

**Table 1**

Demographic and clinic-pathological details of the patients (n = 57).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>48 (84.2)</td>
</tr>
<tr>
<td>Female</td>
<td>9 (15.8)</td>
</tr>
<tr>
<td>Mean age</td>
<td>59.4 years (37–88)</td>
</tr>
<tr>
<td>Addictions</td>
<td></td>
</tr>
<tr>
<td>Tobacco</td>
<td>49</td>
</tr>
<tr>
<td>Alcohol</td>
<td>31</td>
</tr>
<tr>
<td>Site of primary</td>
<td></td>
</tr>
<tr>
<td>BOT</td>
<td>31 (54.8)</td>
</tr>
<tr>
<td>Tonsil</td>
<td>22 (38.6)</td>
</tr>
<tr>
<td>Soft palate</td>
<td>3 (5.3)</td>
</tr>
<tr>
<td>Posterior pharyngeal wall</td>
<td>1 (1.8)</td>
</tr>
<tr>
<td>Primary stage</td>
<td></td>
</tr>
<tr>
<td>cT1</td>
<td>24 (42.1)</td>
</tr>
<tr>
<td>cT2</td>
<td>33 (57.9)</td>
</tr>
<tr>
<td>Final pathological staging</td>
<td></td>
</tr>
<tr>
<td>Stage I</td>
<td>19 (33.4)</td>
</tr>
<tr>
<td>Stage II</td>
<td>30 (52.7)</td>
</tr>
<tr>
<td>Stage III</td>
<td>8 (14.1) [Excluded from oncological analysis]</td>
</tr>
</tbody>
</table>

**Table 2**

Functional outcome of the patients (n = 57).

<table>
<thead>
<tr>
<th>Functional outcome</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-operative tracheotomy</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>6 (10.5)</td>
</tr>
<tr>
<td>No</td>
<td>51 (89.5)</td>
</tr>
<tr>
<td>Successful decannulation (n = 6)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>6 (100)</td>
</tr>
<tr>
<td>No</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Average post-op day of decannulation</td>
<td>7 ± 0.8</td>
</tr>
<tr>
<td>Mode of enteral feeding</td>
<td></td>
</tr>
<tr>
<td>Nasogastric tube</td>
<td>53 (92.9)</td>
</tr>
<tr>
<td>Percutaneous gastrostomy</td>
<td>4 (7.1)</td>
</tr>
<tr>
<td>Long-term NG/PEG dependence</td>
<td>2 (3.5)</td>
</tr>
<tr>
<td>Average post-op day of oral intake</td>
<td>7.6 ± 1.3 days</td>
</tr>
</tbody>
</table>

**Table 3**

Oncological outcome of the patients (n = 49).a

<table>
<thead>
<tr>
<th>Oncological outcome</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathological stage</td>
<td></td>
</tr>
<tr>
<td>pT1N0</td>
<td>23 (46.9)</td>
</tr>
<tr>
<td>pT2N0</td>
<td>26 (53.1)</td>
</tr>
<tr>
<td>Disease free survival</td>
<td></td>
</tr>
<tr>
<td>Overall survival</td>
<td></td>
</tr>
<tr>
<td>45 (93.8)</td>
<td></td>
</tr>
<tr>
<td>Mean follow-up</td>
<td>29 ± 14 months</td>
</tr>
</tbody>
</table>

a Excluding 8 patients who were upstaged to stage III in view of metastatic lymphadenopathy.

**Discussion**

In this study we present oncological outcomes of early stage (Stage I and II) HPV negative OPSCC following single modality treatment with TORS. Previously published retrospective data available before the routine HPV testing started was suggestive of long-term disease free survival with single modality treatment for early stage disease [26]. Currently radiotherapy is the most common used single modality treatment for early stage OPSCC, but HPV positive tumours are considered to be more radiosensitive than HPV negative tumours and have better oncological outcome [27,28] as historically these tumours were treatment by open surgical techniques involving mandibulotomy and pharyngotomy resulting in significant morbidity and functional impairments to speech, swallowing, and breathing [15].

Recently there has been a renewed interest in surgical treatment of early stage OPSCC due to the introduction of minimally invasive, transoral robotic surgery. Quality of life and functional outcome form an important component of treatment planning and transoral techniques have shown excellent functional outcomes with comparable oncological outcome when compared to open surgical procedures [29–32].

Compared to traditional open surgical techniques for OPSCC, TORS provides better functional outcomes. Tracheotomy rates with traditional open surgical techniques approaches 100%. With a transoral approach, there is a significant reduction of tracheotomy rates (0–2%), shorter time to decannulation, and shorter hospitalization time [29,33,34]. In our study as well only 10.1% patients underwent tracheostomy during the surgery and all were successfully decannulated within 1 week of surgery. Swallowing function is also improved with transoral approaches when compared to traditional open surgery for OPSCC, with all patients started accepting oral feeds within 1 week of the surgery. Similar to the results seen in other studies, our patients were also discharged within 7 post-op days.

TORS is currently been used for treatment of early stage (T1 and T2) OPSCC, with the main aim of de-intensification of treatment and avoiding adjuvant treatment in the form of radiation or chemoradiation [15]. There are many studies reporting the oncological outcome after TORS for HPV positive OPSCC [29,35–37] but there is no prospective study till date to evaluate functional and oncological outcome of TORS in HPV negative OPSCC.

Moore et al. [29] in a retrospective review of a TORS database, reported the data of 18 HPV negative OPSCC patients and their 3 year disease-specific and recurrence free survival was 89% and 83% respectively. Also there was no significant difference in survival when compared to HPV positive patients. Also in another retrospective review of 364 patients of OPSCC of which 70 patients were HPV negative, De Almeida et al. found no significant overall or disease specific survival difference on the basis of the HPV status.
of the patients. In their series the 2 year locoregional control and overall survival in HPV negative OPSCC was 92% and 94% respectively [37]. Another retrospective study by Cohen et al. reported an overall survival of 80% at 2 years in HPV negative OPSCC, with no significant difference in disease free survival when compared with HPV positive patients [35]. Similar to all these retrospective studies, in our prospective study of HPV negative OPSCC, we attained a disease free survival of 89.6% and overall survival of 93.8% with a single modality, de-intensified treatment using TORS at mean follow-up of 29 months.

**Conclusion**

This is a first of its kind single institutional prospective study which evaluated the functional outcome and oncological outcome in early stage HPV negative oropharyngeal SCC. This study demonstrated that TORS as a single modality treatment is oncologically sound for treatment of early stage HPV negative OPSCC which are relatively unresponsive to radiotherapy. TORS can be used to de-intensify the treatment for early stage HPV negative OPSCC. It has the least morbidity and offers benefits in terms of early airway feeding rehabilitation and can avoid complications resulting from radiation therapy for these patients. Long-term oncological outcome and 5 year survival still needs to be evaluated for TORS.

**Conflict of interest**

None of the authors have any conflict of interest to declare.

**References**


