



Oncological outcome following initiation of treatment for stage III and IV HPV negative oropharyngeal cancers with transoral robotic surgery (TORS)

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ABSTRACT

Objective: To report long-term oncological and functional outcome of Transoral Robotic Surgery escalated treatment including radiotherapy or chemoradiotherapy for Stage III-IV HPV negative oropharyngeal malignancies.

Method: From March 2013 to September 2015, 153 patients with oropharyngeal carcinoma were included in the study. Patients were evaluated for disease free survival, overall survival and post-treatment functional outcomes.

Results: 153 patients (96 males and 57 females) underwent TORS for oropharyngeal carcinoma. 142 patients on final histopathology had stage III and IV disease and received adjuvant treatment based on final histopathology. One hundred and sixteen (81.7%) patients were disease free on average follow-up of 48 months with an overall survival of 91.5% at mean follow-up of 48 months.

Conclusion: TORS can be used to intensify treatment of Stage III/IV oropharyngeal carcinoma and avoid early and late toxicities due to higher doses of upfront RT/CTRT and achieve better oncological outcome.

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Introduction

The incidence of oropharyngeal squamous cell carcinoma (OPSCC) is on an increase in India. There were an estimated 15,529 new cases in males and 2374 new cases in females of oropharyngeal cancers in India in 2018 [1]. The leading cause of OPSCC in India is still exposure to smoking and alcohol, whereas 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 prevalence of HPV positivity in newly diagnosed cases of OPSCC in developed countries like the USA is >60% [2,3]. The prevalence of HPV positivity in OPSCC in India ranges from 20 to 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 present like the “classical” type of squamous cell carcinoma of the oral cavity. HPV negative OPSCC presents at an older age and a higher stage [6,7,10]. A secondary analysis of RTOG 0129 demonstrated a higher 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]. TAX 324 trial included 111 patients with locally advanced OPSCC and showed higher mortality in HPV negative OPSCC as compared to HPV positive OPSCC [7].

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Presently there is a trend towards intensification of treatment in HPV negative OPSCC, with majority studies showing dismal results [6–9], but few studies showing promising results with TORS escalated treatment therapy [7,11–13].

In the past, the main treatment option for advanced OPSCC was open surgical resection with mandibulotomy or pharyngotomy, reconstruction, and postoperative radiotherapy [14,15]. These open approaches resulted in high morbidity rates with severe functional impairments to speech, swallowing, and breathing [16]. In 1991, the Veterans Affairs Laryngeal Cancer Study Group trial leads to an increased trend toward nonsurgical options to treat other head and neck sites, most notably OPSCC [17]. Subsequent studies showed comparable oncological and functional outcome between primary surgery and radiotherapy for OPSCC [18,19].

But with the increased use of intensified organ preservation nonsurgical treatment options, especially concurrent chemoradiation, there was an increase in treatment-related toxicities including mucositis, xerostomia, loss of taste, tissue fibrosis, stricture, osteoradionecrosis, neuropathy, and fatigue with several studies reporting long term feeding gastrostomy dependence after concurrent chemoradiation to the tune of 9–38% [20–25].

Transoral robotic surgery provides the benefit of doing the surgery through the oral cavity with associated low rates of morbidity and quicker functional recovery. TORS has proven to be effective in the management of OPSCC with good oncological outcomes in the past, even in HPV negative OPSCC [13,26–28].

We undertook the present study to report the oncological and functional outcome of TORS for initiation of treatment with adjuvant Radiotherapy/chemoradiotherapy for Stage III-IV HPV negative oropharyngeal SCC.

Material and methods

A prospective study from March 2013 to September 2015 to evaluate the functional and oncological outcome of TORS intensified treatment for Stage III and IV HPV negative OPSCC after having attained the required clearance from the Institutional Ethics Committee and after attaining the required written consents from all the participants and with full accordance with ethical principles, including the World Medical Association Declaration of Helsinki (version 2002) was performed. A total of 153 patients were included in the study with the following criteria.

Inclusion criteria

1. Age \geq 18 years.
2. Mouth opening \geq 3 cm.
3. Prior treatment naïve patients.
4. Clinically or radiologically cN + on presentation.

Exclusion criteria

1. Extensive local extension of disease (cT3 and cT4 disease).
2. Mouth opening $<$ 3 cm.
3. HPV positive status (p16 positive).
4. Unresectable nodal disease.
5. Distant metastasis.
6. Retropharyngeal lymphadenopathy in the assessment imaging.

All the patients underwent a pre-operative biopsy with IHC for p16 as a surrogate marker for HPV status.

According to the biopsy and the p16 status surgical intervention was performed with the patient under general anesthesia with nasotracheal intubation. Tracheostomy was performed in a few

patients who were deemed to have a 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 Si* 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 Feyh–Kastenbauer retractor (Gyrus-Medical, Tuttlingen, Germany). A binocular endoscope of 0° and 30° was 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.

Ninety-two patients underwent ipsilateral neck dissection and 61 patients underwent bilateral neck dissection (Level II to V with preservation of the submandibular gland), performed immediately before TORS. Patients staged as Stage III and IV in the post-op received adjuvant treatment in the form of Chemoradiation or Radiation after TORS based on the final histopathology report. Patients received 60Gy/30# adjuvant radiation in cases which had poor differentiation, multiple lymphadenopathy or higher stage of the tumour. Patients with any positive margin or extra-capsular spread in the lymph node received adjuvant chemo-radiotherapy with 5–6 cycles of weekly Inj. Cisplatin with 60Gy/30# radiation over 6 weeks.

Patients 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 swallowing was assessed both pre-operatively and post-operatively at 1 month and 3 months follow-up using the functional outcome swallowing scale (FOSS) given by Salassa et al. [29]. Stage 0–2 denotes normal swallowing or compensated abnormal function. Stage 3–4 indicates decompensated abnormal function with oral feeding still possible and Stage 5 requires a non-oral mode of feeding.

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 American Joint Commission for Cancer (AJCC), 8th edition) and long term tracheostomy and feeding tube dependence (more than 3 months post surgery).

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 48 months (31–61 months).

Results

A total of 153 patients of HPV negative OPSCC underwent TORS from March 2013 to September 2015. The demographic characters and clinico-pathological details of the patients are shown in Table 1.

Average Robotic set-up time was 10.3 \pm 2 min and average robotic operative time was 43.6 \pm 4 min. Average blood loss during surgery was 50 \pm 9 ml. Sixteen (10.5%) patients required tracheostomy, and 21 (13.7%) patients underwent percutaneous endoscopic gastrostomy for feeding and the remaining 132 patients had nasogastric tube placement. All patients were successfully decannulated after surgery.

All patients had normal swallowing (Stage 0–1) in the pre-operative stage. Seven (4.5%) patients were dependent on long term nasogastric tube/PEG feeding, i.e. at least 3 months post-treatment. Patients started tolerating oral feeds within two weeks of procedure (mean 8.3 days), with the nasogastric tube removed within two to three weeks post-op (mean 14.9 days). Of the 142 patients analyzed, 122 (85.9%) patients had a favorable result on

Table 1
Demographic and clinic-pathological details of the patients. (n = 153).

Characteristics	Number (%)
Gender	
Male	96 (62.7)
Female	57 (37.3)
Mean Age	56.3 years (32–87)
Addictions	
Tobacco	137
Alcohol	96
Site of primary	
Tonsil	86 (56.2)
BOT	42 (27.5)
Soft palate	12 (7.8)
Posterior pharyngeal wall	2 (1.3)
T Stage	
T1	46 (30.1)
T2	67 (43.8)
T3	29 (18.9)
N Stage	
N0	11 (7.2)
N1	56 (36.6)
N2a	12 (7.8)
N2b	56 (36.6)
N2c	18 (11.8)
Final Pathological staging	
Stage II	11 (7.2) {Excluded from oncological analysis}
Stage III	56 (36.6)
Stage IV	86 (56.2)

FOSS assessment (Stage 0–2), 13 (9.2%) had an unfavorable result on FOSS (Stage 3–4) but could tolerate oral feed and 7 (4.5%) had a score of 5 on FOSS and were dependent on tube feeding at 3 months post-treatment. The average hospital stay was 4.8 days (range, 4–9 days) (Table 2).

Postoperative complications in the form of primary hemorrhage required active intervention in four patients. Three patients developed aspiration pneumonitis which was managed conservatively by antibiotics.

On final histopathology, 11 patients had pathologically negative lymph node (pN0) with pT1 or T2 primary and were staged as Stage I or II and were excluded from the oncological outcome analysis of this study.

Of the 142 patients analyzed in the study, 56 patients were staged as Stage III OPSCC on the post-op histopathology. Thirty-five patients either did not require any adjuvant treatment or did not opt for any adjuvant treatment in the post-op and were kept under regular follow-up (Table 3). Twelve of these 35 patients were

Table 2
Functional outcome of the patients. (n = 153).

Functional outcome	Number (%)
Pre-operative tracheotomy	
Yes	16 (10.5)
No	137 (89.5)
Successful decannulation (n = 16)	
Yes	16 (100)
No	0 (0)
Average post-op day of decannulation	8.4 ± 0.8
Mode of enteral feeding	
Nasogastric tube	132 (86.3)
Percutaneous gastrostomy	21 (13.8)
Long-term NG/PEG dependence (at least 3 months post completion of treatment).	7 (4.5)
Average post-op day of oral intake	8.3 ± 1.3 days

Table 3
Treatment details of the patients. (n = 142)^a.

Complete Treatment Strategy	Number (%)
Surgery alone	35 (24.7)
Surgery + RT	59 (41.5)
Surgery + CTRT	48 (33.8)

^a Excluding 11 patients who were down-staged to Stage II on final histopathology report.

pT3N0 on final histopathology with clear margins and no other high-risk factor (LVI/PNI/Poor differentiation etc.) on the histopathology with either advance age or multiple co-morbidities; and after detailed discussion in the Tumour board, these patients were kept under regular follow-up taking into consideration the intended benefit of adjuvant radiotherapy vs. the issue of tolerability and side effects of radiotherapy in these patients. The remaining 13 patients opted out of adjuvant treatment even after detailed counseling explaining the need and intended benefits of adjuvant radiotherapy. These patients were also kept in regular 3 monthly follow-up.

Fifteen patients required adjuvant radiotherapy in view of perineural invasion and lymphovascular invasion. Six patients underwent adjuvant chemoradiation in view of a positive margin or extranodal spread. Of these 56 patients, 50 are alive without disease at the last follow-up, with 5 patients developed loco-regional recurrence or distant metastasis of which 4 are alive with disease and one expired due to disease metastasis. One patient died due to non-oncological cause.

Eighty-six patients were pathologically pN2 with primary pT1–3. Of these 86 patients, 44 patients received adjuvant radiotherapy and 42 patients required adjuvant chemoradiation based on the post-operative histopathology report. Sixty-six patients were disease-free and alive at the last follow-up, 14 patients had a loco-regional or distant recurrence, of which 10 were alive with disease and 4 expired due to disease. Six patients expired due to non-oncological causes during follow-up.

The mean follow-up was 48 months (31–61 months). At the last follow-up, 116 patients were alive and disease free, 19 patients developed recurrence with 10 patients having loco-regional recurrence and 9 patients developed distant metastasis. The recurrences were treated with salvage surgery, radiation, chemoradiation or palliative treatment. Twelve patients died during the follow-up due to oncological and non-oncological causes. The 4-year Overall survival (OS) calculated using Kaplan Meier curves was 91.5%, Disease-specific survival (DSS) was 96.5% and Recurrence-free survival was 81.7%. (Table 4).

Discussion

In the present study we present the results of oncological and functional outcomes of Stage III and IV HPV negative OPSCC undergoing treatment initiation with TORS followed by adjuvant radiation/chemoradiation. Historically these tumors were treated by open surgical techniques involving mandibulotomy and pharyngotomy resulting in significant morbidity and functional impairments to speech, swallowing, and breathing [16].

In view of poor functional outcomes and higher morbidity associated with open surgical procedures, there was a trend towards organ-preservation with increased use of concurrent Chemoradiation for treatment of Stage III and IV OPSCC even in absence of randomized control trials comparing the outcomes with surgery. But even with concurrent Chemoradiation the OS and DFS were very poor especially in HPV negative OPSCC as these tumors are inherently radio-resistant. Various studies using CCRT as the

Table 4
Oncological outcome of patients (n = 142).

Oncological Outcome	Number (%)
Pathological stage	
pT1N1	16 (11.3)
pT2N1	40 (28.2)
pT1-3N2a	12 (8.4)
pT1-3N2b	56 (39.4)
pT1-3N2c	18 (12.7)
Stage III	
Overall survival (OS)	96.4%
Disease specific survival (DSS)	96.4%
Recurrence free survival (RFS)	89.3%
Stage IV	
Overall survival (OS)	88.4%
Disease specific survival (DSS)	95%
Recurrence free survival (RFS)	76.8%
Overall (Stage III and IV)	
Overall survival (OS)	91.5%
Disease specific survival (DSS)	96.3%
Recurrence free survival (RFS)	81.7%
Mean Follow-up	48 months (31–61 months)

treatment modality for Stage III and IV HPV negative OPSCC reported a very dismal OS between 31% and 74% at 2 years follow-up [6–8,30]. Also, the gastrostomy dependence was in the range of 9–38% after CCRT with an increase in treatment-related toxicities including mucositis, xerostomia, loss of taste, tissue fibrosis, stricture, osteoradionecrosis, neuropathy, and fatigue [20–25,31].

But recently there is a renewed interest in surgical treatment OPSCC due to the introduction of minimally invasive surgical approaches like Transoral Laser Microsurgery (TLM), Transoral Endoscope assisted Oropharyngeal resection like Transoral endoscopic Ultrasonic surgery (TOUSS) and transoral robotic surgery (TORS). Quality of life and functional outcome in addition to oncological outcomes constitute an important part of the treatment planning and transoral techniques have shown excellent functional outcomes with the comparable oncological outcome when compared to open surgical procedures [32–35]. TLM has shortened the duration of hospitalization as all patients undergoing TLM do not require tracheostomy. Moreover, patients could be started on oral feeds earlier as compared to open surgery. For oncological outcomes, TLM compares well with open surgery for proper tumor visualization and resection of oropharyngeal cancers [36]. However, TLM has certain inherent problems, as there is a long learning curve associated with the technique. In addition, gaining adequate exposure is of utmost importance with TLM which can become difficult, especially in the South-Asian population due to the high incidence of submucous fibrosis associated with areca nut use.

With the advent of the *da Vinci* robotic surgical system and the use of the same in head and neck as TORS, a lot of the drawbacks of TLM have been eliminated. TORS provides the advantage of four hands (Two surgical instruments and two hands of the bed-side assistant). The endoscopic 0° and 30° vision provides a magnified 3D vision unparallel to the one attained in TLM. TORS also significantly reduces the operating time of the surgery. In addition, the learning curve is much less compared to TLM [37].

Also the various endoscope assisted transoral approaches like TOUSS, have shown promising results when compared to TORS for oropharyngeal resection [38], but still the data is limited and again TORS offers advantages of four hands, magnified 3D vision and wristed instruments over endoscopic approaches.

Compared to traditional open surgical techniques and concurrent CRT for OPSCC, TORS provides better functional outcomes. Tracheotomy rates with traditional open surgical techniques approach 100%. With TORS, there is a significant reduction of tracheotomy rates (0–2%), shorter time to decannulation, and shorter

hospitalization time [26,32,39,40]. In our study as well only 10.5% of 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. Patients started tolerating oral feeds within two weeks of the procedure, with the nasogastric tube removed within two to three weeks post-op. Of the 142 patients, 122 (85.9%) patients had a favorable result on FOSS assessment, 13 (9.2%) had an unfavorable result on FOSS but could tolerate oral feed and only 4.5% had a score of 5 on FOSS and were dependent on tube feeding at least 3 months after completion of treatment.

Currently, TORS is been used for the treatment of early-stage (T1 and T2) OPSCC even HPV negative OPSCC, with the main aim of de-intensification of treatment and avoiding adjuvant treatment in the form of radiation or chemoradiation [16,26]. There are many studies reporting the oncological outcome after TORS for HPV positive OPSCC [13,32,41–43] but there is no prospective study till date to evaluate the functional and oncological outcome of Stage TORS in HPV negative OPSCC.

Park et al. [13] in a retrospective review of Stage III and IV OPSCC reported a 5-year OS of 88.8%, DSS of 89.9% and RFS of 78.3%. On sub-group analysis according to the p16 status, the 5-year DSS of p16 + OPSCC patients was 93.2%, which was higher than the 89.0% for p16- OPSCC patients, but the difference was not significant. Moore et al. [32] in a retrospective review of a TORS database, reported the data of 18 HPV negative Stage I to IV OPSCC patients and their 3 years 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. In another retrospective review of 364 patients of OPSCC of which 70 patients were Stage I to IV 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 [43]. Another retrospective study by Cohen et al. reported an overall survival of 80% at 2 years in HPV negative Stage I to IV OPSCC, with no significant difference in disease-free survival when compared with HPV positive patients when treated with TORS ± Adjuvant treatment [41]. Similar to all these retrospective studies, in our prospective study of Stage III-IV HPV negative OPSCC treated with TORS ± Adjuvant treatment, we attained a 4 year Overall survival (OS) was 91.5%, Disease specific survival (DSS) was 96.5% and Recurrence free survival was 81.7%.

Also of the 86 patients with Stage IV, we could avoid additional chemotherapy in more than half (51.2%) of the patients and also we could also decrease the total dose of radiation to about 60Gy in the whole study population based on the pathological information received after TORS. The avoidance of concurrent chemotherapy and the overall decrease in the dosage of radiotherapy can be believed to decrease the overall adverse effects of Chemoradiation and contribute to better functional outcomes [44,45]. Similar improvement in functional outcomes due to the decreased dose of radiation was also seen in the study by Park et al. [13].

One of the limitations of our study is that the stage III/IV oropharyngeal cancers compared in our study are basically T1-3/N1-3 which are compared to higher percentage of T3-4/N3 patients in few chemoradiation studies [5] thus giving a better oncological outcome in our patients. A more head to head comparison according to the T-stage is required in the future to attain better understanding.

Conclusion

This is a first of its kind single-institutional prospective study

which evaluated the functional outcome and oncological outcome in stage III and IV HPV negative relatively radio-resistant oropharyngeal SCC. TORS based treatment has the benefit of intensifying the treatment in terms of multi-modality treatment improving the oncological outcomes and at the same time decreasing the utility of chemotherapy and decreasing the overall dose of radiotherapy leading to lower acute and late toxicities and better functional outcome. The long-term oncological outcomes and 5-year survival still needs to be evaluated for TORS.

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Conflict of interest

All authors have no conflict of interest to declare.

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