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Outcomes in surgically resectable oropharynx cancer treated with transoral robotic surgery versus definitive chemoradiation☆

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ABSTRACT

Purpose: Optimal treatment strategies for the management of oropharyngeal squamous cell carcinoma (OPSCC) remain unclear. The objective of this study is to examine the role of transoral robotic surgery (TORS) on functional and treatment outcomes.

Materials and methods: A retrospective review of patients with OPSCC (tonsil/base of tongue) who underwent TORS with neck dissection ± adjuvant therapy between January 2011 to December 2016 were compared to a stage matched cohort of patients treated with primary chemoradiation. Demographic, treatment, and outcome data were collected.

Results: 54 patients received primary chemoradiation and 65 patients (surgical group) received TORS ± adjuvant therapy for clinically staged disease meeting study criteria. 25% ($N = 17$) were treated with surgery alone. The remainder of the surgical group received postoperative radiation ($N = 48$), half of which received adjuvant chemotherapy ($N = 24$) in addition to radiation. 63% ($N = 41$) of the patients did not have risk factors for chemotherapy. No differences in overall or disease free survival were observed with TORS compared to chemoradiation ($p = 0.9$), although Charlson Comorbidity Index (CCI) was higher in the surgical group ($p = 0.01$). The strongest predictor of prolonged gastrostomy tube use was not treatment, but rather co-morbidity ($p = 0.03$), with no significant differences beyond 12 months.

Conclusion: Although no significant survival differences were observed across treatment groups, this was maintained despite increased comorbidity index in the surgical patients. Given the ability to de-escalate and/or eliminate adjuvant therapy, particularly in a less healthy population, TORS would appear to be the viable treatment option it has become.

1. Introduction

The incidence of oropharyngeal squamous cell carcinoma (OPSCC) continues to increase as a result of the human papillomavirus (HPV) epidemic, with 16,420 cases diagnosed in the U.S. in 2015 [1–3]. The annual number of cases in the U.S. is expected to double by the year 2030 [4]. As a result of its HPV etiology, the disease affects a much younger, healthier population, with improved therapeutic outcomes relative to its smoking-related, HPV (−) counterparts [5–7].

Traditional open surgical resections of OPSCC have been associated with significant morbidity [8]. External incisions, mandibulotomy, pharyngotomy, tracheotomy, and almost obligate flap reconstruction result in substantial disfigurement and swallowing dysfunction. As a result, patients prefer non-surgical therapy. Radiotherapy or chemoradiotherapy became the mainstay, with emphasis on organ preservation [9]. Although effective, chemoradiation has its own late toxic effects, most commonly pharyngeal dysfunction, xerostomia, and stricture [10,11].

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Concurrent with the rise in incidence of OPSCC, advances in surgical techniques occurred. Refinement of transoral laser microsurgery and the advent of transoral robotic surgery (TORS) allowed a re-introduction of surgery into the management paradigm. These minimally invasive approaches are oncologically effective, with evidence of improved functional outcomes and quality of life [12–16]. Similarly, intensity modulated radiation therapy has significantly improved the therapeutic ratio of radiotherapy [5,17,18]. Combining minimally invasive surgery with intensity modulated radiation therapy provides the opportunity for significant de-intensification of therapy in these patients.

Selection of patients for primary surgery versus non-surgical therapy remains, to some degree, a matter of debate and institutional preference. These preferences continue to shift over time. We present our experience with TORS ± adjuvant therapy (AT) for surgically resectable OPSCC. We compare this to an historical cohort of stage-matched patients treated with primary radiation or chemoradiation. The objective is to compare oncologic and functional outcomes.

2. Methods

Surgical patients were identified through review of institutional operative logs. Adult patients were identified who underwent TORS between January 1, 2011 and December 31, 2016, for primary squamous cell carcinoma of the tonsil or base of tongue Stage criteria for inclusion were clinical T stage 1 or 2, with clinical N stage N2b or less (AJCC 7th Edition) [19]. Seventh Edition staging was used as the implementation of the Eighth Edition took effect January 1, 2017, after conclusion of the study. Contraindications to surgery at the time included extensive involvement of the soft palate, involvement of the hard palate or mandible, extension across the midline of the base of tongue, and invasion through the superior constrictor muscle into the parapharyngeal space. Most of these criteria would have resulted in T3 or T4 staging and would have been excluded from this cohort even if treated surgically. Patients in this cohort underwent neck dissection in conjunction with TORS as a method of treatment. Neck dissection was performed either at the same procedure, or within one week before or after TORS. Indications for postoperative radiation included close margins (< 2 mm), or perineural or lymphovascular invasion, and N2 (a or b) disease. Indications for postoperative adjuvant chemotherapy were the presence of extracapsular extension or the presence of extensive (> 5) nodal disease. During the majority of the study period, adjuvant chemotherapy was given for both microscopic and gross extracapsular extension.

A second cohort for comparison was identified, also clinically staged with T1/T2 tumors, which were treated with primary definitive chemoradiation. Within the timeframe that the above surgical data was collected, the vast majority of patients who were eligible for TORS, were treated with TORS. No randomization occurred. Furthermore, the majority of patients referred to the institution for non-surgical therapy did not meet inclusion criteria, mostly on the basis of more advanced disease. In order to obtain a sufficient number of non-surgically treated patients for comparison, we included patients treated with definitive chemoradiation between January 1, 2007 and December 31, 2016.

Electronic medical records were reviewed for data collection and to confirm inclusion criteria. Demographic information collected included age, gender, race, and smoking status. Comorbity was quantified using the Charlson Comorbity Index (CCI) and Karanofsky performance status [13]. Patients with Karanofsky score ≤ 70 were excluded. Pathologic information included p16 status, when available, pathologic staging, margins, LVI/PNI, and extracapsular extension. Radiation and chemotherapy data were collected as well.

Patients treated with definitive chemoradiation therapy were treated to a high-risk volume to 70 Gy given at 2 Gy per daily fraction. A second, low-risk volume was treated to 56 Gy at 1.6 Gy per daily fraction. Definitive chemoradiation therapy patients received cisplatin at 100 mg/m2 on days 1, 21 and 42 as tolerated. Definitive bio-radiation therapy patients were treated with weekly cetuximab given as a 400 mg/m2 loading dose and weekly maintenance doses of 225 mg/m2 for 8 cycles. TORS patients with high-risk features necessitating post-operative chemoradiotherapy were treated to 66 Gy at 2 Gy daily fractions with low-risk volume receiving 52.8 Gy at 1.6 Gy daily fractions. Patients received adjuvant cisplatin or cetuximab at the discretion of the medical oncologist. TORS patients treated with radiation alone were treated to 60 Gy at 1.8 Gy daily fractions.

The primary outcome measures were overall survival (OS) and disease-free survival (DFS). DFS was calculated from the date of diagnosis to the earliest date of biopsy-proven recurrence, death, or censored at date of last follow up. OS was calculated from date of pathologic diagnosis to date of death, or censored at date of last follow up. Kaplan-Meier methods were used to calculate survival, with log rank testing used for comparison of survival between groups. Categorical data were compared using a two-tailed Fisher's exact test. The secondary outcome of interest was the presence of percutaneous gastrostomy tube (PEG) at 3, 6, 12, and 24 months. Univariate and multivariate logistic regression were used to assess risk factors associated with prolonged PEG tube dependence across groups, and both adjusted and unadjusted odds ratios (OR) are reported, with Wald *p*-values. Statistics were calculated using SAS Software, Version 9.4 (Cary, NC).

3. Results

One hundred and nineteen patients were included in the study. Of those, 65 underwent TORS with neck dissection ± AT, and 54 were treated with definitive primary chemoradiation. Demographic information is outlined in Table 1. No significant differences in age or smoking status were observed across groups, although a larger proportion of females were found in the non-surgical group. Tonsil and base of tongue tumors constituted about half of each group. The vast majority of TORS patients were p16 positive (80%, $N = 52$). A significant number of non-surgical patients (48%, $N = 26$) had unknown

Table 1
Patient demographics.

		Chemoradiation ($n = 54$)	TORS ± adjuvant therapy ($N = 65$)	
Age	Median (Range)	57.9 (25–82)	61 (41–83)	0.3204
Sex	Male	25 (46.3%)	48 (73.9%)	0.0026
	Female	29 (53.7%)	17 (26.1%)	
Smoking	Never	20 (45%)	19 (29%)	0.2584
	Former	10 (23%)	23 (35%)	
	Current	14 (32%)	22 (33.5%)	
	Unknown	11 (20%)	1 (1.5%)	
CCI	Mean (SD)	3.89 (± 1.48)	4.8 (± 1.79)	
	Median (Min, Max)	4.0 (2.0, 7.0)	5.0 (2.0, 10.0)	0.0111
Tumor subsite	Base of Tongue	27 (50%)	31 (48%)	0.5124
	Tonsil	26 (48%)	34 (52%)	
	Other	1 (2%)		
P16 status	Negative	3 (6%)	10 (15%)	< 0.0001
	Positive	25 (46%)	52 (80%)	
	Unknown	26 (48%)	3 (5%)	
T-stage	T1	22 (41%)	20 (31%)	0.2571
	T2	32 (59%)	45 (69%)	
N-stage	N0	6 (11%)	14 (22%)	0.0001
	N1	2 (4%)	13 (20%)	
	N2a	6 (11%)	12 (18%)	
	N2b	25 (46%)	25 (38%)	
	N2c	12 (22%)	0 (0%)	
	N3	3 (6%)	1 (2%)	

TORS: transoral robotic surgery. CCI: Charlson Comorbidity Index.

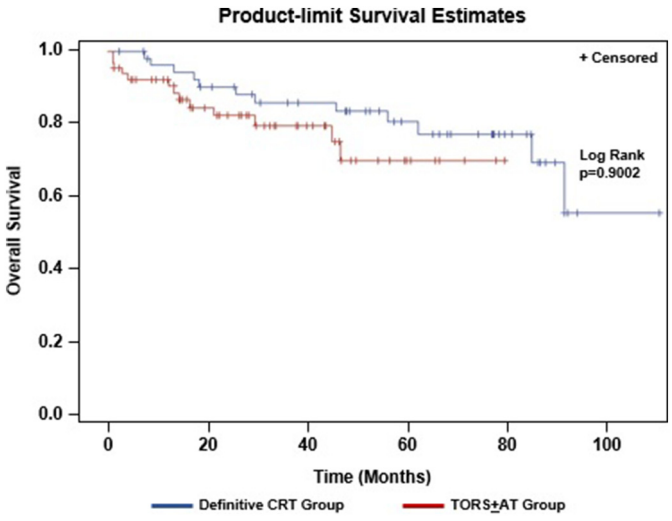

Fig. 1. Overall survival.

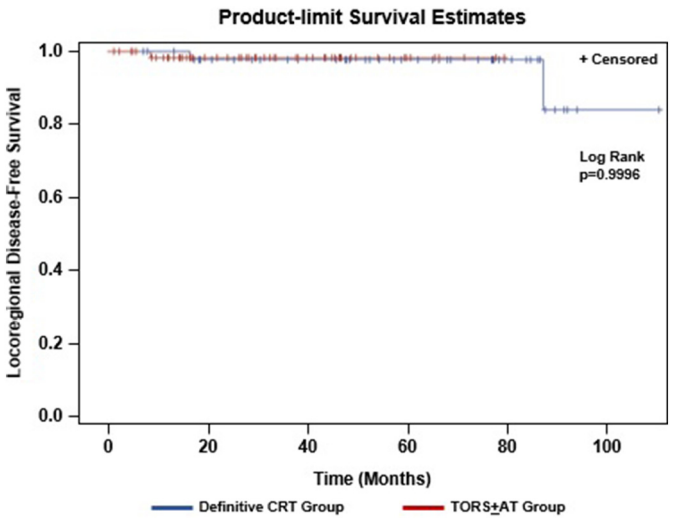

Fig. 3. Locoregional recurrence.

p16 status, likely a function of inclusion from an earlier time period, predating uniform p16 testing. However, it is reasonable to expect that a comparable number of these patients were, in fact, p16 positive, making the groups relatively comparable. There was a slightly increased preponderance of more advanced neck disease (N2c, N3) in the chemoradiation group. Charlson Comorbidity Index was actually higher in the patients treated with TORS.

In the TORS group, 92% ($N = 60$) underwent neck dissection at the time of surgical therapy. 26% ($N = 17$) were treated with surgery alone. The remaining 74% ($N = 48$) patients received postoperative radiation therapy, half of which also received adjuvant chemotherapy. Thus, postoperative chemoradiation was given to 37% ($N = 24$) of TORS patients, sparing chemotherapy to 63% of the surgical cohort. In the non-surgical group, 91% ($N = 49$) were treated with definitive chemoradiation, with the remaining 9%, ($N = 5$) being treated with radiation alone. Four patients (8%) had a neck dissection prior to definitive chemoradiation.

No significant differences in overall (Fig. 1) and disease-free (Fig. 2) survival were observed across treatment groups ($p = 0.9002$, p-0.27, respectively). No significant differences were observed in loco-regional recurrence, as seen in Fig. 3 ($p = 0.9996$). Similarly, distant disease-free survival is seen in Fig. 4, where again no significant differences were observed across treatment groups (p = 0.9002). Overall 2- and 5-year survivals for the TORS group were 82.3% and 70.2% respectively, compared with 90.2% and 80.5% in the chemoradiation group. These differences were not statistically significant ($p = 0.22$, $p = 0.19$). On Cox proportional hazard regression analysis (Table 2) only higher Charlson Comorbidity Index was associated with a lower overall survival ($p = 0.0325$).

No significant differences in the presence of PEG tubes were observed at any time point. Although a greater proportion of TORS patients had feeding tubes at the 3 and 6-month time points, these observed differences were not significant, and the differences disappeared at the 12-month time point and beyond. Multivariate analysis demonstrated that the TORS patients were 51% more likely to have a feeding tube at 3 months post-treatment (OR 1.51, $p = 0.51$), and 84% more

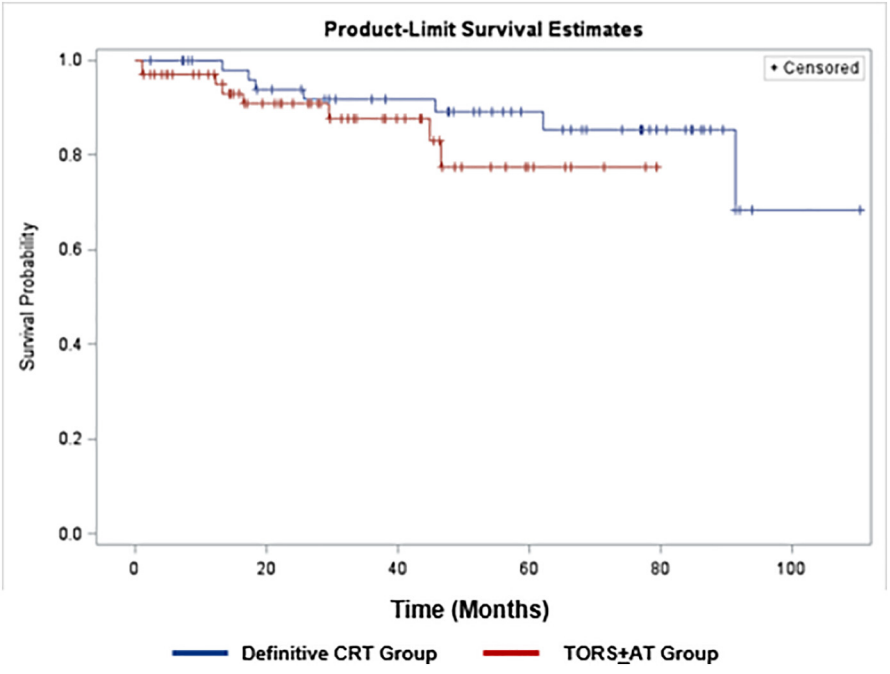

Fig. 2. Disease specific survival.

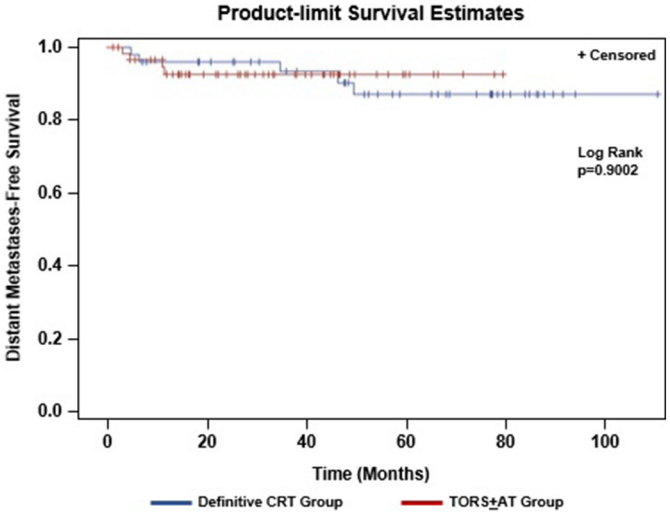

Fig. 4. Distant recurrence.

Table 2
Multivariate Cox proportional hazards modeling for survival.

	Overall survival		Disease-free survival	
	HR	*P* value	HR	P value
TORS ± AT vs. Definitive chemoradiation therapy	2.11	0.2384	1.23	0.9401
P16 positive vs P16 negative	0.54	0.4667	0.113	0.1115
Stage (3 vs 2)	3.561	0.0632	0.883	0.9171
Smoker (current/former vs non-smoker)	1.45	0.5418	2.48	0.6632
Charlson comorbidity index	1.5	0.0325	0.91	0.8662
Age at diagnosis	0.999	0.9844	1.02	0.8723

HR: Hazards ratio. TORS: transoral robotic surgery. AT: adjuvant therapy.

likely at 6 months (OR 1.84, $p = 0.31$). However, they were 62% less likely to have a PEG at 24 months (OR 0.38, $p = 0.36$). None of these were statistically significant. However, the strongest predictor of persistent PEG at 3 and 6 months was not treatment type, but rather CCI. For every one-unit increase in the Charlson Comorbidity Index, the odds of having a PEG at 3 months post-treatment increased by 72% (OR 1.72, $p = 0.03$) and was increased at 6 months by 64% (OR 1.64, p = 0.03). As the morbidity index was actually higher in the surgical group, this may explain the observed preponderance of early persistent PEG tubes in the TORS patients.

4. Discussion

TORS, as well as transoral laser microsurgery, have become accepted modalities in oropharyngeal carcinoma management. Multiple series have demonstrated acceptable oncologic and functional outcomes [12,13,15,20,21]. Primary surgery allows for pathologic staging of the disease, with modification and ideally de-escalation of radiation and chemotherapy based on pathologic features. In this series, 26% ($N = 17$) of patients were able to be treated with TORS alone who otherwise would have been treated with definitive chemoradiation, and 63% ($N = 41$) of patients were able to avoid chemotherapy altogether through the use of TORS.

The primary indication for postoperative chemotherapy in this cohort was the presence of pathologic extracapsular extension. There is some evidence to suggest that traditional indications for adjuvant therapy, such as extracapsular extension, are maintained in the surgical management of oropharyngeal carcinoma [22,23]. However, the impact of extracapsular extension may be more limited in HPV-related disease [24]. Review of patients from the National Cancer Database suggests that while overall survival is reduced in patients with extracapsular extension, survival was not improved with the addition of chemotherapy to the adjuvant postoperative radiotherapy regimen [25]. As such, the role of adjuvant chemotherapy in these patients requires even further refinement.

Optimally, a randomized clinical trial comparing primary chemoradiation to surgery (TORS), with or without adjuvant therapy, could be undertaken, though such a trial has yet to be completed. The ORATOR trial is underway in Australia, comparing primary radiotherapy to TORS with neck dissection alone. This is a Phase II investigation of T1/T2 tumors, N2 or less, with no radiologic evidence of extracapsular extension. It does not address or include postoperative therapy, and the results will not be available for some time. ECOG 3311, a prospective study that has completed accrual, incorporates postoperative adjuvant therapy, but does not include a non-surgical arm.

The resulting reliance on retrospective data has a number of limitations. In this study, the vast majority of patients who were evaluated and eligible for surgery were treated with surgery. Identifying a non-surgical cohort for comparison was difficult, and necessitated inclusion of patients treated prior to the use of TORS. This presents an acknowledged degree of selection bias. However, referral patterns at this institution have remained stable, with the majority of patients treated here having advanced, late stage disease. It is thus reasonable to suggest that the comparably staged patients from the earlier part of the study period who were treated with primary chemoradiation would very likely have been treated with TORS had the technology been available at the time. While this by no means is a substitute for randomization, it does reduce some selection bias that is present when both treatment modalities are equally available. This is reasonably comparable to the treatment cohorts being performed in parallel.

Both TORS and primary chemoradiation appear to be equally and highly effective in achieving loco-regional control and DFS. The results compare favorably with other published series [19,20]. No differences in overall survival were observed. The most interesting observation from this series is that the TORS group had higher CCI compared to the chemoradiation group. This is an encouraging finding to the extent that these patients are able to tolerate the burdens of surgery and potentially trimodality therapy. Furthermore, sicker patients, who may not be able to receive chemotherapy as part of their primary treatment regimen, may still benefit from TORS. TORS with adjuvant radiotherapy may be of some benefit to these patients over radiation alone. The degree to which the increased comorbidity offsets the potential survival advantage of TORS is unclear, and likely difficult to quantify.

Furthermore, the adjuvant radiation received with TORS is not necessarily the same as the radiation received as part of primary therapy. Postoperative doses are generally lower, although this difference is often minimal. However, radiation is not an “all or none” therapy. Patients treated surgically may only receive radiation to the neck alone, depending on margins and pathologic features of the primary tumor. Sparing the oral cavity and laryngo-esophageal segment has a definitive, albeit difficult to measure, impact on swallowing.

No significant differences in PEG removal rates across treatment groups were observed in multivariate analyses. The strongest predictor of persistent feeding tube dependence at 3 and 6 months was CCI. For every one unit increase in the CCI, the likelihood of a PEG tube increased by 72% at 3 months, and 64% at 6 months in multivariate modeling, which included treatment type. A reflection of this is the observed increased early post-treatment prevalence of PEG tubes in the TORS group. Long-term PEG prevalence was actually slightly lower in the TORS group, although these observations were not statistically significant. Additional quality of life measures, such as xerostomia, fibrosis, and esophageal stricture, more commonly seen in primary chemoradiation, are somewhat difficult to capture in this retrospective analysis.

5. Conclusion

TORS with directed adjuvant therapy appears to have comparable outcomes to primary chemoradiation in terms of survival and PEG dependence. TORS provides the opportunity for de-escalation and in some instances the elimination of adjuvant therapy, and is tolerated in the setting of increased comorbidity. PEG tube dependence appears to be less of a function of therapy and more closely associated with patient comorbidity status. Further efforts to refine the interplay of treatment modalities in the management of oropharyngeal cancer are needed.

References

[1] Fujiwara K, Fukuhara T, Kitano H, et al. Preliminary study of transoral robotic surgery for pharyngeal cancer in Japan. J Robot Surg 2016;10(1):11–7.
[2] Mahmoud O, Sung K, Civantos FJ, Thomas GR, Samuels MA. Transoral robotic surgery for oropharyngeal squamous cell carcinoma in the era of human papillomavirus. Head Neck 2018;40(4):710–21.
[3] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016;66(1):7–30.
[4] American Cancer Society. Cancer facts & statistics. https://cancerstatisticscenter.cancer.org/#!/; 2018, Accessed date: 12 April 2018.
[5] Sher DJ, Fidler MJ, Tishler RB, Stenson K, al-Khudari S. Cost-effectiveness analysis of chemoradiation therapy versus transoral robotic surgery for human papillomavirus-associated, clinical N2 oropharyngeal cancer. Int J Radiat Oncol Biol Phys 2016;94(3):512–22.
[6] Fakhry C, Westra WH, Li S, et al. Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. J Natl Cancer Inst 2008;100(4):261–9.
[7] D'Souza G, Kreimer AR, Viscidi R, et al. Case-control study of human papillomavirus and oropharyngeal cancer. N Engl J Med 2007;356(19):1944–56.
[8] White H, Ford S, Bush B, et al. Salvage surgery for recurrent cancers of the oropharynx: comparing TORS with standard open surgical approaches. JAMA Otolaryngol Head Neck Surg 2013;139(8):773–8.
[9] Kao SSM, J; Ofo, E; Edwards, S; Dhatrak, D; Foreman, A; Krishnan, S; Hodge, J-C. A comparison of oncological outcomes between transoral surgical and non-surgical treatment protocols in the management of oropharyngeal squamous cell carcinoma. J Laryngol Otol. 1–7.
[10] Sharma A, Patel S, Baik FM, et al. Survival and gastrostomy prevalence in patients with oropharyngeal cancer treated with transoral robotic surgery vs chemoradiotherapy. JAMA Otolaryngol Head Neck Surg 2016;142(7):691–7.
[11] Machtay M, Moughan J, Trotti A, et al. Factors associated with severe late toxicity after concurrent chemoradiation for locally advanced head and neck cancer: an RTOG analysis. J Clin Oncol 2008;26(21):3582–9.
[12] Leonhardt FD, Quon H, Abrahao M, O'Malley Jr. BW, Weinstein GS. Transoral robotic surgery for oropharyngeal carcinoma and its impact on patient-reported quality of life and function. Head Neck 2012;34(2):146–54.
[13] Chen AMDM, Luu Q, Donald PJ, Farwell DG. Comparison of functional outcomes and quality of life between transoral surgery and definitive chemoradiotherapy for oropharyngeal cancer. Head Neck 2015;37(3):381–5.
[14] Moore EJ, Olsen KD, Kasperbauer JL. Transoral robotic surgery for oropharyngeal squamous cell carcinoma: a prospective study of feasibility and functional outcomes. Laryngoscope 2009;119(11):2156–64.
[15] Iseli TAKB, Iseli CE, Carroll WR, Rosenthal EL, Magnuson JS, Iseli TA, et al. Functional outcomes after transoral robotic surgery for head and neck cancer. Otolaryngol Head Neck Sur 2009;141(2):166–71.
[16] Weinstein GS, O'Malley Jr. BW, Snyder W, Sherman E, Quon H. Transoral robotic surgery: radical tonsillectomy. Arch Otolaryngol Head Neck Surg 2007;133(12):1220–6.
[17] Beadle BM, Liao KP, Elting LS, et al. Improved survival using intensity-modulated radiation therapy in head and neck cancers: a SEER-Medicare analysis. Cancer 2014;120(5):702–10.
[18] Nutting CM, Morden JP, Harrington KJ, et al. Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial. Lancet Oncol 2011;12(2):127–36.
[19] Edge B. AJCC cancer staging manual. vol. 7. Springer; 2010. p. 97–100.
[20] Moore EJ, Olsen SM, Laborde RR, et al. Long-term functional and oncologic results of transoral robotic surgery for oropharyngeal squamous cell carcinoma. Mayo Clin Proc 2012;87(3):219–25.
[21] More YI, Tsue TT, Girod DA, et al. Functional swallowing outcomes following transoral robotic surgery vs primary chemoradiotherapy in patients with advanced-stage oropharynx and supraglottis cancers. JAMA Otolaryngol Head Neck Surg 2013;139(1):43–8.
[22] Routman DM, Funk RK, Tangsriwong K, et al. Relapse rates with surgery alone in human papillomavirus-related intermediate- and high-risk group oropharynx squamous cell cancer: a multi-institutional review. Int J Radiat Oncol Biol Phys 2017;99(4):938–46.
[23] Shevach JB, Adam, Bakst Richard L, Liu Jerry, Misiukiewicz Krzysztof, Beyda Jessica, et al. Extracapsular extension is associated with worse distant control and progression-free survival in patients with lymph node-positive human papillomavirus-related oropharyngeal carcinoma. Oral Oncol 2017:56–61.
[24] Lewis Jr. JSC, Danielle H, Thorstad Wade L, Qin Zhang, Haughey Bruce H. Extracapsular extension is a poor predictor of disease recurrence in surgically treated oropharyngeal squamous cell carcinoma. Mod Pathol 2011;24(11):1413–20.
[25] An Y, Park HS, Kelly JR, et al. The prognostic value of extranodal extension in human papillomavirus-associated oropharyngeal squamous cell carcinoma. Cancer 2017;123(14):2762–72.