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ABSTRACT

Objectives: Trans Oral Robotic Surgery (TORS) is a fascinating new technique that has proved to be a safe and feasible treatment of oropharyngeal squamous cell carcinoma (OPSCC). The aim of this study is to compare oncological outcomes of OPSCC-patients treated with either TORS (with or without adjuvant therapy) or definitive chemoradiation therapy (CRT).

Materials and methods: This study involved 129 patients with OPSCC, treated with TORS or definitive CRT at our Department between 2008 and 2018. Clinicopathological characteristics, treatment specifications and oncological outcomes were evaluated retrospectively.

Results: Definitive CRT was administered in 69 patients (53,5%), while 60 (46,5%) were surgically treated with TORS alone or in combination with adjuvant therapy. Patients who underwent adjuvant therapy after TORS received a lower dosages of cisplatin and radiation than the CRT group ($p < 0.01$). There was no statistical difference in 5-year survival rate and in disease free interval between TORS and CRT groups. Albeit 5-year overall survival in the HPV-related tumours was better, the HPV status did not affect the rate of local and regional recurrence. Treatment groups (TORS vs. CRT) were not found affecting survivals on multivariate analysis. Tube feeding dependency rate was low between both groups (1.7% in TORS vs. 4.8% in CRT groups).

Conclusion: The modern management of OPSCC must be tailored to each patient. Although the definitive CRT remains a milestone, TORS is proving to be a valid and safe treatment option. The choice of single therapeutic strategy requires an evaluation by a multidisciplinary team

Introduction

Trans Oral Robotic Surgery (TORS) is becoming an accepted modality in the management of the oropharyngeal squamous cell carcinoma (OPSCC). Multiple series have demonstrated acceptable oncologic and functional outcomes [1–6]. Further, a previous systematic review [7], comparing outcomes after radiotherapy versus TORS, suggested that, although oncological outcomes were similar with both modalities, TORS appeared to achieve better functional outcomes. However, the addition of concurrent chemotherapy to radiotherapy has improved oncological outcomes and survival [5], at the cost of markedly increased toxicity, with a treatment-related mortality risk of up to 3%. The prognostic importance of HPV-associated OPSCC has generated increasing interest in clinical trials to reduce either radiotherapy dose or substitute chemotherapy for more targeted agents such as cetuximab for HPV positive tumors [8,9] while intensifying therapy for high risk HPV negative tumors. The ORATOR Trial [5] was a phase II randomized trial, recently published, that compared standard-dose radiotherapy with TORS and neck dissection in T1-T2, N0-N2 HPV-positive OPSCC. The trial reported improved swallow function in the radiotherapy group that was not clinically or statistically significant and demonstrated the difference in toxicities between the treatment options. However, the results should be interpreted with caution due to study design that led to 24% of the TORS group receiving trimodality treatment (surgery, radiotherapy, and chemotherapy). Nevertheless, the ORATOR trial took a vital step toward improving functional outcomes for HPV-positive OPSCC.

On the one hand, primary surgery allows for pathologic staging of the disease, with modification and ideally de-escalation of radiation and chemotherapy based on pathologic features; on the other, definitive chemoradiotherapy (CRT) still remains the mainstay, with emphasis on organ preservation, although the consistent risks of early and/or late complication and toxicity [9].

In this current framework, the selection of patients for primary surgery versus CRT remains a matter of debate. Further, the criteria for indicating the best treatment shift over time and are related to the institutional experience on both strategies. Here, we described our 10-year experience in the management of OPSCC with definitive CRT or TORS for surgically resectable tumours. The oncologic comparison is made with a retrospective analysis of historical cohort of stage-matched patients.

Materials and methods

The medical charts of consecutive OPSCC patients who underwent TORS or definitive CRT at our Department between January 2008 and December 2018 were evaluated retrospectively. Clinicopathologic features of interest included age at diagnosis, comorbidity, sex, HPV status, final margin status, clinical/pathologic T and N classifications, overall American Joint Committee on Cancer (AJCC) stage (7th edition), extranodal extension (ENE) and primary treatment. Two treatment groups are defined: one including patients who received definitive CRT and one Surgery group including: TORS alone; TORS with adjuvant radiotherapy (RT); TORS with adjuvant CRT. Tumour HPV status was considered positive if either HPV in situ hybridisation or HPV-p16 was

positive. Additionally, a re-evaluation of tumour staging based on the 8th edition of the AJCC cancer staging was performed.

Exclusion criteria included previous history of head-and-neck cancer within 5 years, previous head and neck radiation at any time (except non-melanoma skin cancer), distant metastases at presentation, primary treatment other than intention-to-cure.

The surgical approach has previously been described [10]. The edges of surgical excision were set at least 1 cm from the tumour. Negative margins or close margins were stated if > 5 mm or < 5 mm of surrounding free tissue was present on microscopic evaluation, respectively. Adjuvant RT was recommended for patients with N2b/N2c/N3 disease, close final margins, and all patients with T3 tumours. Adjuvant CRT was recommended for patients with pathologic ENE and positive margins.

Patients treated with definitive CRT were treated to a high-risk volume, clinical target volume (CTV) with 60 Gy in 30 fractions, 2 Gy daily fraction and a concomitant boost for tumor gross tumor volume (GTV) and nodal GTV to 66 Gy/30 fractions. Low-risk volume CTV was treated with 54 Gy at 1.8 Gy per daily fraction. All patients were treaded using image guided radiotherapy (IGRT) and intensity modulated radiotherapy (IMRT). Further, concurrent chemotherapy with cisplatin was administered at dose of 100 mg/m 2 on days 1st, 21st and 43rd as tolerated.

Recurrence was classified as the time between treatment modality and the date at which a patient was diagnosed with a local recurrence, nodal recurrence, or distant metastases. A second primary tumour was defined as occurring > 5 years after initial treatment or occurring in a unique sub site separate from the original tumour bed. 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. Furthermore, local recurrence-free survival (LRFS), regional recurrence-free survival (RRFS) were registered.

Statistical analysis

For continuous variables, the means are reported with standard deviations (mean ± standard deviation). To test for differences among groups, Fisher's exact test was used for categorical data, while the Student's t-test was used for continuous data. The role of each possible prognostic factor (univariate analysis) and their independent effect (multivariate analysis) was explored using logistic regression model or Cox-proportional hazard model as appropriate. Survival analysis was performed by the Kaplan-Meier method. Probability values lower than 0.05 were considered statistically significant. All analyses were performed with STATA 12.1 software (Stata Corp., College Station, TX, USA).

Results

One hundred and thirty-nine patients were eligible for the study. Definitive CRT was administered in 84 patients. Unfortunately, 15 patients, who had exclusive RT, were excluded from this group for incomplete datas. In the same period, a total of 60 OPSCC were surgically

treated with TORS alone or in combination with adjuvant RT or CRT based on pathologic cancer staging. All patients were treated with intent-to-cure. The patients characteristics of both groups and staging according the 7th and 8th AJCC editions are shown in Table 1. A number of patients in CRT group (30.4%, n = 21) and in Surgery group (10%, n = 6) had not determined/unknown HPV/p16 status. This issue could be explained because most of them are from the earlier series and especially, in CRT group, some might be not determined due to technical problems on the biopsy specimen. Unfortunately, the acquisition of comorbidity data was fragmentary and not easily inferred from medical records. Therefore, in order to avoid potential disrupting factors in statistical analysis, these data were not included.

In the Surgery group, the management strategies included surgery alone in 35% (21/60), TORS-RT in 31.7% (19/60) and TORS-CRT in 33.3% (20/60). Patients undergoing RT after TORS received a mean dose of 58.6 ± 5.2 Gy on the tumour bed (range 50–66 Gy) and a mean of 55.3 ± 11.9 on N (range 0–60). In the CRT group, a mean dose of 62.2 ± 3.7 Gy of radiation was delivered on T, ranging from 51 to 66, and a mean dose of 60.8 ± 2.6 on N (range 54–66). Further in the Surgery group, a mean dose of 252.1 ± 45.2 mg/m 2 cisplatin (range 180–300) was administered to selected patients for adjuvant chemotherapy; whilst, in the CRT group, the mean dose was 389.7 ± 134.2 mg/m2 cisplatin (range 60–636).

These lower dosages in the Surgery group are statistically significant ($p < 0.01$) reflecting the purpose of the adjuvant treatments.

In 15 (25%) cases with supposed high probability of generating fistula, a staged neck dissection was done after a mean of 27.7 ± 13.4 days (range 8–60). These sub-group of patients especially belongs to our preliminary experience when we applied the guidelines in accordance with Penn University [11]. In 6 cases, the considerable delay in carrying out the neck dissection was mainly due to our lack of experience (preliminary phase) in the management of post-TORS complications. As our experience increased, our approach changed in order to minimize post-operative bleeding complications and improve resection with a bloodless surgical field. Thus, neck dissections were recently carried out before TORS in order to ligate selectively branches of/ external carotid artery [6]. In 7 patients (11.7%), the neck dissection was previously done (−28.1 ± 11.5 days; range −41 to −12) because of the high risk of vascular injury or because the patient was referred to our institution for a primary tumour resection after neck dissection (unknown cases). Concurrent neck dissection was performed in 26 patients of Surgery group (43.3%). The extent of dissection most commonly included levels IIa, IIb, III and IV. The ENE was noted in 28.3% of neck dissection.

The mean duration of follow-up for the CRT group was 42.1 ± 35.2 months, whilst 37.8 ± 25.9 in the Surgery group. The 5-year survival rates of both groups are summarized in Table 2. The mean of Disease Free Interval from the onset of a distant metastasis was 22.3 ± 11.1 months in the Surgery group; whilst in the CRT group was 18.2 ± 16.7 ($p = 0.66$). According to the AJCC 8th edition, the survival Kaplan-Meier curves for early stages and advanced stages are shown in Figs. 1 and 2, respectively. No statistical significant differ-

ences among survivals are highlighted between Surgery and CRT groups. However, the tumours not related to HPV had poorer 5-year OS as shown in Fig. 3. Nonetheless, the HPV status did not affect the rate of 5-year DFS, LRFS, RRFS.

Moreover, the 5-year OS, DFS, LRFS, RRFS of patients treated with surgery alone were shown in Fig. 4.

On Cox proportional hazard regression analysis, showed in Table 3, no independent variables are associated with poorer prognosis.

Regarding complications, we did not register any major or life-threatening intra-operative complications in Surgery group (see Table 4). Only one patient, who had concurrent neck dissection, experienced post-operative bleeding into the neck. Eight (13.3%) patients had post-operative bleeding from primary tumour resection field; 5 patients from tonsil and 3 from BOT. Oral bleeding had a mean of 6.2 ± 3.7 days. The secondary intention healing was the predominant choice in simple and no-extensive resection's cases (90%; 54/60). One facial artery myo-mucosal (FAMM) and 1 buccinator-based myomucosal (BMM) flaps were used to cover extensive carotid exposure in two patients with a tonsillar cancer (T2). The temporalis myofascial flap (TMF) was adopted to restore a competent velopharyngeal sphincter and a watertight seal between the pharynx and neck in a case of OPSCC in- volving part of soft palate and the anterior tonsillar pillar (T2). In 3 cases with extensive tumour of BOT involving tonsil and soft palate (T3), the surgical defect was recon- structed with an antero-lateral thigh (ALT) free flap.

No total local or free flap failure were registered; whilst a partial necrosis of temporalis muscle flap that did not affect the healing and two flap dehiscences (1 facial artery muscle mucosa flap and 1 anterolateral thigh flap) that needed a surgical revision were recorded. Only the same patient with anterolateral flap (ALT) dehiscence experienced pharyngocutaneous fistula that was treated with both surgical revision and compressive dressings. Tracheostomy was performed routinely in the first series of patients (15 cases until 2012). Since our experience increased, tracheostomy was reserved only in difficult intubation cases, cT3 tumours, or cases who needed reconstruction with free flaps or local bulky flaps. The mean duration of tracheostomy use was 7.4 ± 2.6 days, and nasogastric tube 14.3 ± 6.9 days. Only one patient (pT3N2b of BOT invading tonsil and soft palate with ALT reconstruction) experienced a post-operative severe dysphagia, needing a permanent tracheostomy tube and percutaneous endoscopic gastrostomy (PEG) feeding.

In the CRT group, 54 patients (78.3%) experienced oral/pharyngeal mucositis. The second common complication was dysgeusia in 76%, followed by xerostomia and dysfagia (50.6% and 48.2%, respectively). Weight loss and cutaneous erythema was present in 56.6% and 67.5%, respectively. Regarding hematological dysfunctions, patients experienced anemia in 4.8%, neutropenia in 27.7%, thrombocytopenia in 3.6%. Rarely alopecia and paresthesia were recorded (2.4% and 1.2%, respectively). Only 3 patients (4.8%) needed PEG.

Discussion

Currently, the choice of the treatment modality for OPSCC is still the subject of strong debate and also makes use of the single centre's ex-

perience. The decision should be passed through a multidisciplinary teamwork for tailoring the best management for single patient. The selection of optimal patients for TORS is of paramount importance and can dictate the ability to achieve excellent oncologic outcomes.

In this series, 35% of patients were able to be treated with TORS alone who otherwise would have been treated with definitive CRT, and 31.7% 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 ENE. These results are similar to those described by Dhanireddy et al. [12]. In this study, 26% of patients were treated with TORS alone 63% of patients with TORS and adjuvant RT. Both TORS and definitive CRT appear to be equally and highly effective in achieving loco-regional control and DFS. Moreover, no differences in overall survival were observed. Other similar findings were encountered comparing definitive RT doses with adjuvant doses; in fact postoperative doses are generally lower.

Data regarding the use of adjuvant RT or CRT in TORS treated patients is limited. A recent systematic review demonstrated that 26% and 41% of TORS treated patients needed adjuvant RT and CRT, respectively [13]. In a retrospective cohort study of 42 patients treated with TORS, 21% required adjuvant RT and 31% required adjuvant CRT [14]. A retrospective study of 410 patients treated with TORS showed rates of adjuvant RT and CRT as 31.3% and 21.3%, respectively. Another large retrospective study, matching 1584 patients, demonstrated 32.7% use of adjuvant CRT in patients treated with TORS [15].

For what concerns survival, our study demonstrated that patients treated with TORS had a similar rates to patients treated with definitive CRT. Albeit the HPV status influence the rate of survival (HPV + patients have better survival outcomes), the choice of treatment (CRT vs. TORS) is not detrimental to survival. These results are encouraging and open the scenario to the choice of tailored treatment. Dhanireddy et al. [12] demonstrated similar outcomes at Cox regression multivariate analysis, except for the Charlson Comorbidity Index as the only independent variable that may affect the overall survival (HR 1.5, $p = 0.03$). Both TORS and definitive CRT appear to be equally and highly effective in achieving loco-regional control and DFS. The results compare favorably with other published series [3,16]. No differences in overall survival were observed. In literature, few studies have incorporated TORS in the treatment of HPV negative OPSCC. In one small cohort study of 13 patients, at two years, there were no local recurrences and only one regional recurrence [17]. Another encouraging study by Moore et al, demonstrated an 89% disease specific survival at 3 years in HPV negative patients treated with TORS [3].

For what concerns the treatments' complication, TORS is usually associated with low morbidity rates and lower blood loss in comparison with open surgical procedures. These associated characteristics also reflect the shorter average hospital stays (4.2 days). The percutaneous endoscopic gastrostomy (PEG) dependency rate following TORS is 0–9.5% in 1 year and 0% in 2 year [1,16]. Another analysis of 177 patients from a multicentre study reported a long-term tracheostomy rate of 2.3%, and a long-term gastrostomy tube rate of 5%. The average duration of tracheostomy use was 7 days, and nasogastric tube

12.5 days [1]. Our study showed overlapping data. Regarding fistula formation, this complication was noted in the series from the Mayo Clinic in 6% of cases. These patients underwent concurrent neck dissection at the time of TORS. In all four cases, the fistulae responded to treatment with daily packing and antibiotics [3]. Postoperative haemorrhage can be a life-threatening event in the case of TORS. The rate of postoperative haemorrhage varied 0% to 9% [18–22]. Chia et al. [23] summarized the common complications in a 2013 multi-institutional survey of all TORS-trained surgeons in the United States.

An electronic survey was sent to 300 TORS-trained surgeons. Forty-five surgeons responded to the survey and reported a postoperative haemorrhage rate of 3.1% requiring readmission. There were a total of 6 deaths among 2015 procedures (0.3%). Other complications included temporary hypoglossal nerve injury (0.9%), lingual nerve injury (0.6%) and tooth injury (1.4%).

Regarding the organ preservation treatment protocols, most concurrent modality, using cisplatin- based CRT, have evolved in the past three decades resulting in improved control rates on survivals with radiotherapy alone [24]. However, the risk of toxicity related to the treatment are inevitably increased. In our series, 36.1% of CRT patients experienced an hematological impairment. The most common complications encountered were mucositis and dysgeusia. These dysfunctions are concomitant in different degrees with xerostomia and dysphagia. Our results are comparable to those of recent clinical review [25].

Improvements in radiation delivery with the use of intensity modulated radiation therapy (IMRT) have been shown to improve sparing of the pharyngeal constrictors and reduce radiation-related dysphagia when compared with conventional radiation therapy in treatment of head and neck cancers. In addition to improvements in radiation delivery, de-intensified treatment for HPV-associated OPSCC is currently being studied in an effort to further improve the treatment toxicity profile without a decrement in tumor response. Several studies have looked at dose to specific swallowing structures, such as the pharyngeal constrictor muscles and larynx, with most finding a mean dose > 50 Gy significantly correlating to occurrence of aspiration [26–28]. In a recent phase II trial [29], de-intensified CRT regimen consisted of 60 Gy (2 Gy/fx, once per day) IMRT with concurrent cisplatin 30 mg/m 2 (cumulative, 180 mg/m 2) once per week for 6 weeks. The clinical outcomes were favorable rather than two randomized phase III trials have evaluated the substitution of cetuximab for cisplatin concurrently with 70 Gy [30,31]. The overall occurrence of late grade 3 to 4 toxicity for these trials was approximately 17% to 30%. Sixty to 70% of patients required a feeding tube, and the 1-year feeding tube dependence rate was approximately 9%. In contrast, in the recent study [29], no patient experienced late grade 3 or higher toxicity, 39% required a feeding tube, and the 1-year feeding tube dependence rate was 1%. Albeit this study did not perform a randomized study to make a direct comparison with standard-intensity therapy, these results are very encouraging.

Unfortunately our study had a limitation regarding subjective and objective swallowing assessments. These informations were impossible to acquire given the retrospective nature of our study due to the lack of continuity in recording these data in medical charts. Although personal

experience holds a low level of evidence, in our cohort we did not experienced significant disrupting swallowing problems in both groups. However, postoperative pain is a factor affecting the resumption of swallowing and may last for more than a month. On the other hand, post-radiotherapy dysgeusia and xerostomia have a negative impact on swallowing functionality, but these disorders usually last longer. The review of the literature allows to obtain a vision on this issue.

Amongst the studies on the quality of life (QOL), two studies included a comparison of QOL outcomes between TORS and RT. More et al. [4] found that the preoperative and 3 month postoperative MD Anderson Dysphagia Index (MDADI) scores were similar between the two groups. However, by 6 months and at the 12-month postoperative follow-up, patients treated with TORS and adjuvant therapy had significantly better MDADI scores. Chen et al. [2] compared QOL scales between patients who underwent initial surgical resection with either transoral laser microsurgery or TORS versus definitive CRT. At 1-year, there was no significant difference between the surgical group and the definitive CRT group except for the swallowing score, which was better in the surgical group.

Conclusion

The modern management of OPSCC may use different approaches that can be tailored to each patient. TORS is a fascinating new tool that is useful in the management of selected cases of OPSCC, whereas definitive CRT still remains a strategic milestone. The choice of single therapeutic strategy requires an evaluation by a multidisciplinary team on a solid scientific basis beside its own experience.

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Declaration of Competing Interest

Claudio Vicini and Filippo Montevecchi are consultants and proctors for Intuitive Surgical Inc. All other authors have nothing to declare.

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