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Trans oral robotic surgery for oropharyngeal cancer: A multi-institutional experience

Armando De Virgilio a, b, 1, Raul Pellini c, 1, *, Giovanni Cammaroto d, Rossella Sgarzani e, Andrea De Vito d, Manlio Gessaroli f , Andrea Costantino a, b
, Gerardo Petruzzi c , Bianca Maria Festa a, b, Flaminia Campo c , Claudio Moretti c, g, Barbara Pichi c ,Giuseppe Mercante a, b , Giuseppe Spriano a, b
, Claudio Vicini d, g , Giuseppe Meccariello d

a Department of Biomedical Sciences, Humanitas University, Via Rita Levi Montalcini, 4, 20090, Pieve Emanuele, MI, Italy
b Otorhinolaryngology Unit, IRCCS Humanitas Research Hospital, Via Manzoni 56, Rozzano, MI, Italy
c Department of Otolaryngology-Head and Neck Surgery, IRCCS Regina Elena National Cancer Institute, Rome, Italy
d Otolaryngology and Head-Neck Surgery Unit, Department of Surgery, Morgagni Pierantoni Hospital, Azienda USL della Romagna, Forlì, Italy
e Plastic Surgery, DIMES Department, University of Bologna, Bologna, Italy
f Maxillo-Facial Unit, Department of Surgery, Maurizio Bufalini Hospital, Azienda USL della Romagna, Cesena, Italy
g University of Ferrara, Ferrara, Italy

A b s t r a c t

Objectives: Trans Oral Robotic Surgery (TORS) has proved to be a safe and feasible treatment for
oropharyngeal squamous cell carcinoma (OPSCC). The aim of this study is to analyse oncological out-
comes of OPSCC patients treated with TORS.

Materials and methods: This study involved 139 patients with OPSCC, treated with TORS between 2008
and 2020. Clinicopathological characteristics, treatment details and oncological outcomes were evalu-
ated retrospectively.

Results: The management strategies included TORS alone in 42.5%, TORS-RT in 25.2% and TORS-CRT in

30.9%. The ENE was noted in 28.8% of neck dissections. In 19 patients clinically classified as unknown
primaries, the primary was found in 73.7%. Rates of local, regional relapses and distant metastasis were
8.6%, 7.2%, and 6.5%, respectively. The 5 year- Overall Survival and Disease Free Survival were 69.6% and
71.3%, respectively.
Conclusion: TORS fits well in the modern management of OPSCC. Although definitive CRT remains a
milestone, TORS is proving to be a valid and safe treatment option. The choice of the therapeutic strategy
requires evaluation by a multidisciplinary team.

1. Introduction

The advancement of trans-oral techniques, especially Trans-Oral Robotic Surgery (TORS), determined the revalidation of surgical treatments for oropharyngeal squamous cell carcinoma (OPSCC). Considering the increasing incidence of Human Papilloma Virus (HPV)-related OPSCC, which mainly affects younger patients, there has been a growing interest in surgical therapy, especially minimally invasive techniques as they may reduce the systemic and long-term toxicity that often follow concomitant chemoradiation therapy (CRT) [1].

In this framework, TORS represents the most advanced technological application in transoral surgery and might be considered the first treatment choice in the presence of an oropharyngeal T1-2 exophytic primary tumour. However, the choice of a minimally invasive surgical approach versus primary radiotherapy (RT) as a single-modality therapy represents a point of debate [2,3]. A recent phase 2, randomised trial (ORATOR trial) [4] tried to definitively compare intensity modulated (IM) RT and TORS in terms of toxicity and quality of life (QOL) although no clinical meaningful differences were recorded, nor specific recommendations were defined. Nevertheless, TORS is usually associated with low morbidity rates and shorter average hospital stays [5], especially when it is used as a monotherapy based on pathological results, which strictly de-

pends on preoperative patient selection [6].

The purpose of this work is to analyse the outcomes of TORS for OPSCC combining data of three Italian centres.

2. Materials and methods

The medical charts of consecutive OPSCC patients who underwent TORS at the Department of Otolaryngology of Morgagni-Pierantoni Hospital in Forlì, Humanitas Clinical and Research Center-IRCCS in Milan and IRCCS Regina Elena National Cancer Institute in Rome, Italy between January 2008 and December 2020 were retrospectively evaluated. Clinicopathological features of interest included: age at diagnosis, comorbidity, smoking and alcohol habits, sex, HPV status, final margin status, clinical/pathologic T and N classifications, overall Union for International Cancer Control (UICC) stage (8th edition) [7], extra-nodal extension (ENE) and primary treatment. Three treatment groups were defined: TORS alone, TORS and adjuvant RT, TORS and adjuvant CRT. The HPV status was considered positive if immunohistochemistry staining of cell blocks, using p16 as a surrogate marker, was positive. The institution review board of each institution waived the need for ethics approval due the retrospective nature of the study not reporting on use of experimental or new protocols besides the international guidelines and agreements.

Exclusion criteria included previous history of head and neck cancer within 5 years (except non-melanoma skin cancer), previous head and neck radiation at any time, distant metastases at presentation, primary treatment other than intention-to-cure. The surgical approach has been previously described [8,9]. The edges of surgical excision were set at least at 1 cm of macroscopically healthy tissue from the tumour. Negative margins and close margins were defined when more than 2 mm or less than 2 mm of surrounding free tissue was present on microscopic evaluation, respectively. Adjuvant RT was recommended for patients with N2a/N2b/N2c/N3 disease, close final margins, and for all patients with T3 and T4 tumours. Adjuvant CRT was recommended for patients with pathologic ENE and positive margins. Re-resection was never

performed to avoid adjuvant treatments in case of close or positive margins.

Patients treated with adjuvant RT were treated to a high-risk, clinical target volume (CTV) with 56e66 Gy in 30 fractions, 2 Gy per daily fraction, and a concomitant boost for gross tumour volume (GTV) and nodal GTV with 50 Gy in 30 fractions. Low-risk CTV was treated with 54 Gy, 1.8 Gy per daily fraction. All patients were treated using image guided radiotherapy (IGRT) and intensity modulated radiotherapy (IMRT). Furthermore, in patients requiring concurrent chemotherapy, cisplatin was administered at a dose of 100 mg/m2 on days 1st, 21st and 43rd as tolerated.

2.1. Outcome measures and statistical analysis

The primary outcome measures were overall survival (OS) and disease-free survival (DFS). OS was calculated from the date of pathologic diagnosis to the date of death, or censored at the date of last follow up. DFS was calculated from the date of diagnosis to the date of biopsy-proven loco-regional recurrence or distant metastasis. Furthermore, local recurrence-free survival (LRFS), regional recurrence-free survival (RRFS), and loco-regional recurrence-free survival (LRRFS) were classified as the time between the end of treatment 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 the initial treatment or occurring in a sub-site separate from the original tumour bed. This was determined as a sub-site (as defined by the UICC [7]) that was originally neither the one of origin of the primary tumor, neither partially involved by it.

Categorical variables were summarised by counts and percentage, while continuous variables were reported as means ± standard deviations (SD), after confirming the normal distribution using the ShapiroeWilk normality test. Differences between groups were compared by Student's t-test for normally distributed continuous variables, while categorical variables were evaluated using the chi-squared test or Fisher's exact test, as appropriate. Univariable analysis was performed using the log-rank test to determine the

impact of clinical stage and treatment on the survival outcomes. Univariable analysis was also done using the Cox proportional hazards regression model to identify factors associated with tumour recurrence and survival. Then, a multivariable Cox regression analysis was performed to identify factors independently associated with the survival outcomes after adjusting for adverse tumour variables that resulted significant ($p < 0.05$) at the Cox univariable analysis. The results were summarised with hazard ratios (HR) and 95% confidence intervals (CIs).

Probability values lower than 0.05 were considered statistically significant. All analyses were performed using the STATA 12.1 software (Stata Corp., College Station, TX, USA).

3. Results

One hundred and thirty-nine patients were eligible for inclusion in the study as they 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 clinical and pathological characteristics are shown in Tables 1 and 2. The p16 status was undetermined/unknown for some patients. This issue could be explained considering that most of these patients came from earlier series, while others might not be determined due to technical problems on the 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, this data was not included. The cumulative rate of smokers and former smokers was 57.6% whilst alcohol consumption of more than 2 drinks per day was registered in 33.1% of patients.

The management strategies included TORS alone in 42.5% (59/139), TORS-RT in 25.2% (35/139) and TORS-CRT in 30.9% (43/139). Unfortunately, two patients refused any adjuvant treatment. Patients undergoing RT after TORS received a mean dose of 58.6 ± 5.2 Gy on the tumour bed (range 50e66 Gy) and a mean of 55.3 ± 11.9 on the neck (range 0e60), whilst a mean dose of 252.1 ± 45.2 mg/m2 cisplatin (range 180e300) was administered to

selected patients when adjuvant chemotherapy was indicated. At the time of analyses, the 2 patients that refused adjuvant treatments were alive and free of disease.

Neck dissection was performed in 128 patients (92.1%). The extent of dissection most commonly included levels IIa, IIb, III and IV. A radical or modified radical neck dissection of the I, II, III, IV and V level was performed on patients with clinically positive nodes. ENE was noted in 28.8% of neck dissections. The median of pathologic nodes was 1 (range 0e33). At presentation, 19 patients out of 139 (13.7%) were classified as unknown primaries, that is having a pathologically proven cervical nodal metastasis from a squamous cell carcinoma (SCC) and no lesion suspect of the primary tumor after performing a complete clinical evaluation with fibre optic examination and narrow band imaging (NBI), a magnetic resonance imaging (MRI) with contrast medium and a positron emission tomography (PET) scan. 17 out of 19 patients classified as unknown primaries were p16-positive (89.5%).

In 14 out of 19 (73.7%) the primary tumour was found either in the palatine tonsil (7/14) or base of tongue (7/14) with the same rate.

Thirty-three patients (23.7%) had close or positive margins at final histopathologic examination. Most of these patients had tumours of the tonsillar fossa (n ¼ 19/33, 57.6%). Adjuvant RT and CRT was administered in 78.8% and 57.6% of patients, respectively. At the time of analyses, 27 out of 33 patients were alive free of disease (81.8%), 1 was alive with disease (3%), 1 was dead of other causes (3%), and 4 were dead of disease (12.1%).

The mean duration of follow-up was 26.3 ± 22.2 months (range 0e124 months). The mean Disease Free Interval (DFI) before the onset of a local recurrence was 14.1 ± 8.7 months (range 3e31 months) in 12 patients (8.6%), while it was 11.2 ± 10.9 months (range 0e35 months) in 10 patients (7.2%) before a regional recurrence; on the other hand, the DFI before a distant metastasis was 14.1 ± 12.5 months (range 1e42 months) in 9 patients (6.5%).

The cumulative 5 year- OS, DFS, LRFS, RRFS and LRRFS were

69.6%, 71.3%, 85.4%, 88.2% and 77.2%, respectively. On the other hand, the 3 year- OS, DFS, LRFS, RRFS and LRRFS were 83.3%, 74.5%, 85.4%, 88.2% and 77.2%, respectively. Table 3 shows the pathological features and survivals within the three groups of treatment (TORS alone, TORS þ RT, TORS þ CRT).

The 5 year- OS, DFS, LRFS, RRFS, LRRFS Kaplan-Meier curves as stratified by the levels of UICC stage or treatment categories are shown in Figs. 1e5. According to disease stage, the rate of 5 year- OS for stage I was 91.7%; stage II 82.4%; stage III, 63.8% and stage IV 44.%. The 5 year- DFS was 82.2%, 75.8%, 70% and 45.8% for stage I, II, II and IV, respectively. The 5-year OS and DFS stratified by p16 or HPV status are shown in Fig. 6, highlighting a statistically significant improvement in survival in p16-positive patients compared to the p16-negative counterpart.

On Cox proportional hazard regression analysis, shown in Table 4, p16-negative tumours slightly influenced the 5 year- LRFS (HR 0.06, 95%CI:0.01e0.49, p ¼ 0.01) as well as alcohol consumption of more than 2 drinks per day (HR0.3, 95%CI:0.1e0.8, p ¼ 0.03, respectively). Advanced stage of disease was related to a poorer 5 year- RRFS (HR 75.8 95%CI:2.3e247, p ¼ 0.02) as well as an age older than 60 years (HR 0.08, 95%CI:0.01e0.74, p ¼ 0.03). ENE positivity and alcohol consumption of more than 2 drinks per day were associated to a reduction in the 5 year- DFS (HR 5.6, 95% CI:1.4e22, p ¼ 0.01; 0.43, 95%CI:0.2e0.9, p ¼ 0.02). A poorer 5 year - LRRFS was related to p16-negative tumours, ENE positivity and older age (HR 0.12, 95%CI:0.01e1, p ¼ 0.05; HR 9.9, 95%CI:1-8-53.6, p ¼ 0.01; HR 0.26, 95%CI:0.07e0.96, p ¼ 0.05, respectively).

4. Discussion

In recent decades, a significantly growing incidence of oropharyngeal squamous cell carcinoma (OPSCC) has been recorded, which nowadays represents about 10% of all head and neck malignant neoplasms worldwide [10]. In particular, OPSCC incidence is mostly increasing in younger white males in western countries [11,12]. OPSCC epidemiologic evolution appears to be linked to its relationship with the HPV infection, while the prevalence of HPV-

negative OPSCC is still essentially related to tobacco-induced carcinogenic mutations, and alcohol abuse. In particular, in the last years a reduction in HPV-negative OPSCC cases has been recorded [13].Our case series confirms the majority of HPV-positive patients over the HPV-negative counterpart (64% among our included patients). In fact, HPV-positive OPSCC incidence in Italy has passed from 16% in 2000e2006 to 46% in 2013e2018, as reported by Del Mistro et al. [14].

HPV detection methods have been widely discussed in the literature. Although authors agree that the gold standard for diagnosing HPV driven carcinogenesis is E6 and E7 mRNA detection, most studies use different assays. For instance, we used p16 immunohistochemistry (IHC), which is the most employed diagnostic tool worldwide, although it is considered as a surrogate marker with relevant specificity issues. In fact, p16 IHC is linked to a non-negligible percentage of false positive cases. As p16-positive HPV-negative OPSCCs present the same prognosis as p16-negative cases, treatment de-escalation would probably result detrimental on prognosis in this group of patients. p16 IHC is considered an acceptable detection method according to current guidelines, that were followed in the treatment decision-making of the present study. However, any future de-intensification protocol for the management of HPV-positive OPSCC should pay attention to avoid detection methods with low-specificity [15].

In the last three decades, a metamorphosis in the choice of treatment was observed, despite the lack of a prospective randomised trial defining the best therapeutic option for OPSCC. Traditional and more invasive open surgical approaches have been gradually replaced by RT/CRT since the 90's. However, the emerging role of transoral robotic surgery (TORS) has completely reopened the debate, proposing surgery as an effective alternative in selected cases [16e18]. Although primary CRT and TORS are competing for similar oncologic results [19], CRT may result in significant functional complaints such as severe dysphagia and feeding tube dependence and, on the other hand, TORS might result in surgical

defects depending on the size of the resection and the anatomic location [9,20]. Nevertheless, TORS may better identify the locoregionally advanced population thanks to the pathologic examination of the specimen, which may have the potential of improving the oncologic outcomes [21]. However, it must be kept in mind that in a significant proportion of patients undergoing TORS and needing adjuvant treatments based on pathological results, combined treatment may intensify the morbidity as opposed to single modality RT or dual modality CRT without surgery [6]. With the aim of obtaining a complete and effective treatment with a single modality strategy, National Comprehensive Cancer Network (NCCN) guidelines recommend primary surgery as the preferred treatment strategy in T1-T2 N0eN1 with <3 cm maximal lymph node dimensions independently from the HPV status. In fact, lymph node dimensions >3 cm together with extranodal extension, positive/close margins, pT3 or pT4 primary or multiple positive nodes, nodal disease in levels IV or V, perineural/vascular/lymphatic invasion are considered negative prognostic factors advocating the use of adjuvant radiotherapy [22]. Furthermore, transoral surgery is recommended as part of the diagnostic workout for unknown primary tumours [23].

Our treatment policy is in line with the NCCN recommendations, since 90% of the patients were cT0-T2 and about 80% were cN0-N1. After surgery, 92% were staged as pT0-T2, and 71% were still classified as pN0-N1. In our study, a clinical N downstaging, due to micrometastases revealed only at pathological examination, was accompanied by a clinical T overstaging (only 2 of the 5 cT4 were confirmed as pT4). This could be explained considering the difficulties in clinically verifying the infiltration of extrinsic tongue muscles, and especially of the styloglossus muscle. The styloglossus is a thin muscle crossing the parapharynx and oropharynx between the inferior pole of the palatine tonsil and the base of tongue before merging with the posterior third tongue muscles [20]. Due to its proximity to the palatine tonsil and the base of tongue and to its thinness, it is very difficult to radiologically evaluate its infiltration.

Likewise, styloglossus proximity to different muscular structures such as the superior constrictor, stylopharyngeus and palatopharyngeus muscles makes its identification very difficult on pathologic specimens [9]. However, the real negative prognostic role of OPSCC infiltration of the styloglossus muscle should be better investigated in further studies, as the literature is currently lacking on this regard. Of importance, considering the 48 cases with primary tumours <4 cm discussed at our internal tumour boards in the last 12 months (data not published), in more than 80% a non-surgical treatment was indicated because of cT4 staging due to suspect styloglossus infiltration.

Furthermore, primary cT3 of the palatine tonsils are challenging to diagnose since a tumour > 4 cm in its maximal diameter usually involves nearby structures that upstage it to cT4, such as the extrinsic muscles of the tongue and the medial pterygoid.

In our study, 25.2% of patients underwent adjuvant RT and 30.9% postoperative CRT. Interestingly, these percentages reflect those found by De Almeda et al. [24] in their systematic review published in 2014, where they analyzed the role of TORS for early stage OPSCC, finding that up to 26% and 41% of patients needed postoperative RT and CRT, respectively.

Regarding unknown primary tumours, identification of the primary site in head and neck cancer is crucial, allowing for a more focused volume of treatment, reducing morbidity related to an extended radiation volume, and offering the opportunity for a definitive surgical management based on tumor location. In fact, evidence in the literature shows that despite a correct diagnostic workup including fibre optic examination with NBI, computed tomography (CT) scan or MRI with contrast medium and total body PET scan, the primary tumor remains undetected in 40% of patients [25]. The probability of tumor detection with complete removal of palatine and lingual tonsil, is higher in patients with HPV-positive diseases [25]. In our series, 19 patients were categorised as cTx, and in 14 out of 19 the primary tumour was identified either in the base of tongue or in the palatine tonsil. The resulting overall rate of

primary tumour finding was registered at 73.7%. This high detection rate may be justified by the high percentage of p16-positive unknown primaries in our casuistry (n ¼ 17/19, 89.5%). At our institutions, TORS is used as a diagnostic tool in the unknown primary workup both in p16-positive and p16-negative cases since the detection of the primary lesion permits a more target irradiation with healthy tissue sparing. Our data are consistent with what had already been reported in the literature confirming TORS as indispensable in the diagnostic workout of head-neck unknown primary [26,27]. Considering the high positive detection rate, further studies should be performed to establish the eventual neck dissection indication and its correct timing.

As previously stated, transoral surgery, in particular TORS, is currently recommended as a minimally invasive strategy especially for T1-T2 N0eN1 OPSCC, with the aim of providing an effective single modality treatment. Regarding oncological outcomes and survivals, our series showed results comparable to the recent published studies. In a recent meta-analysis [2], primary TORS obtained similar oncologic outcomes compared to primary RT, according to both OS (91.3% vs. 83.6%) and DFS (89.4% vs. 79.6%). The ORATOR trial [4] showed no differences between radiotherapy and surgery in terms of OS (RT, 88.2% vs. TORS, 85.3%), and progression-free survival (RT, 88.2% vs. TORS, 82.4%). Also, the systematic review performed by De Almeida et al. [24] in 2014 on early T-stage oropharynx cancer, showed a 2-year overall survival ranging from 82% to 94%. Similarly, Meulemans et al. [6] investigated the role of TORS in head and neck oncologic surgery, finding a 2-year overall survival and disease-specific survival of 90.5% and 95.6%, respectively. Interestingly, differently from our study and that by De Almeida et al. [24], in this study less patients underwent adjuvant CRT (only 16.95%).

Considering that we currently have at our disposal both minimally invasive surgical treatments and medical treatments with their own inherent toxicity, the possibility to combine the various treatments in a patient-tailored therapy could theoretically mini-

mise morbidity and mortality related to the treatment itself, especially in stage III and IV. Some indications are still present in the current literature. For example, Dabas et al. [16] published the largest cohort of locoregionally advanced HPV-negative OPSCC treated with TORS plus adjuvant (chemo) radiation, obtaining a 4-year OS of 91.5%, disease specific survival of 96.5% and recurrence free survival of 81.7%. On the other hand, Park et al. [17] demonstrated the effectiveness of induction chemotherapy combined with transoral robotic surgery in treating T3 or T4 oropharyngeal cancer. Furthermore, a recent U.S. cancer database study suggested there might be an advantage in III and IV stage cancer patients receiving triple-modality therapy (TORS with concomitant CRT) compared with patients who underwent TORS followed by only RT and those who received primary CRT, with a calculated 3-year OS of 90%, 85% and 82%, respectively [28]. Although it would be interesting to define if in such cases the survival benefit was more associated to a better local or regional control and if any differences in terms of distant failure exists between patients undergoing surgery followed by CRT versus primary CRT, such data was not reported in the study by Roden et al. [28]. In this setting, Kaczmar et al. [29] analyzed factors predicting locoregional and distant failure in HPV-positive patients undergoing TORS. They found that locoregional recurrence and development of distant metastases are uncommon in patients who are appropriately selected for surgical management of p16-positive OPSCC, even in the presence of negative prognostic feature. Further studies are needed to better clarify the patterns of failure between patients undergoing primary surgery followed by adjuvant treatment versus primary CRT. An additional advantage of upfront TORS is the ability to obtain a pathologic re-staging that often leads to downstaging and thus may avoid adjuvant chemotherapy and reduce total radiation doses [28]. Moreover, it is crucial to explore the effectiveness of immunotherapy in the neoadjuvant and adjuvant setting eventually in combination with standard chemotherapy regimens. In this context TORS could enlarge its applications by intercalating in more com-

plex and personalised treatment algorithms.

As mentioned earlier, various studies have investigated the role of TORS in p16-positive OPSCC, finding it to be a safe tool in the perspective of treatment deintensification. In particular, the AVOID trial [30] has studied the possibility of RT deintensification after TORS in patients with pT1-pT2 N1-3 p16-positive OPSCC, concluding that avoiding irradiation of the primary tumor site after TORS may be safe in selected patients. Also, the ECOG-ACRIN 3311 study [31] investigated adjuvant treatment deintensification in patients with intermediate risk p16-positive OPSCC, finding that transoral resection is safe and results in good oncologic outcomes, thus representing a promising deintensification approach. Conversely, the ORATOR2 trial [32] compared TORS to primary RT in early p16-positive OPSCC patients in terms of toxicity, reporting a higher mortality rate in the surgical arm. Of importance, this study highlights the relevance of critical interpretation of the published literature. In fact, this finding of the ORATOR 2 trial has been advocated to the low sample size consequent to the premature accrual completion, and thus to chance [33]. Currently, there are also many ongoing trials concerning the value of TORS in OPSCC. The Best Of study aims to evaluate the differences in terms of functional and oncological outcomes of TORS compared to RT in early stage OPSCC, both p16-positive and p16-negative. The PATHOS trial is another ongoing study aiming to evaluate the benefit of reducing the adjuvant RT dose in HPV-positive OPSCC undergoing transoral surgery in terms of post-treatment deglutition function. Also, the SIRS2.0 trial is currently recruiting patients to study whether treatment of HPV-related OPSCC in patients with undetectable postoperative HPV circulating tumor DNA, either with transoral robotic surgery (TORS) alone or combined with reduced doses of radiation and chemotherapy can result in cancer control and survival comparable to those previously reported with standard therapy. Finally, the ongoing trial DART-HPV aims to compare standard adjuvant RT doses to a less intense postoperative RT treatment in HPV-positive OPSCC in terms of oncological outcomes.

The relatively small number of included patients and the retrospective nature are the main limitations of this study. Indeed, data was not sufficient to perform additional comparisons between subgroups, and further retrospective or even prospective studies with larger cohorts of patients are needed.

The modern management of OPSCC should include TORS, although definitive CRT still remains a strategic milestone. In fact, TORS is useful in the management of selected cases of OPSCC, to limit the treatment at the sole surgical approach or to de-intensify adjuvant treatments. However, the choice of the therapeutic strategy for OPSCC requires an evaluation by a multidisciplinary team.

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CRediT authorship contribution statement

Armando De Virgilio: Conceptualization, Study concept, quality control of data and algorithms, Writing e review & editing. Raul Pellini: study design, quality control of data and algorithms, Writing e review & editing, corresponding author. Giovanni Cammaroto: Writing e review & editing, study design, manuscript editing, writing. Rossella Sgarzani: Formal analysis, data acquisition, data analysis and interpretations. Andrea De Vito: manuscript preparation and review. Manlio Gessaroli: Formal analysis, quality control of data and algorithms, data analysis and interpretation. Andrea Costantino: Formal analysis, sdata acquisition, data analysis and interpretation. Gerardo Petruzzi: quality control of data and algorithms, Formal analysis. Bianca Maria Festa: data acquisition, statistical analysis. Flaminia Campo: data acquisition, statistical analysis. Claudio Moretti: data acquisition, Formal analysis. Barbara Pichi: Formal analysis, study design, data analysis and interpretation. Giuseppe Mercante: manuscript, Writing e review & editing. Giuseppe Spriano: manuscript, Writing e review & editing. Claudio Vicini: manuscript review. Giuseppe Meccariello: study concepts and design, manuscript editing.

Declaration of competing interest

Claudio Vicini is consultant and proctor for Intuitive Surgical Inc.

Giuseppe Meccariello has nothing to declare.

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