



Research Article

Transoral Robotic Surgery for Squamous Cell Carcinoma of the Oropharynx. Outcomes of the First Multicentric Series in Spain

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Abstract

Background: Transoral Robotic Surgery (TORS) has become one of the mainstays of oropharyngeal cancer treatment in the last decade. However its introduction in Spain has been very limited. We present the first clinical case series study in our country.

The objective is to analyse the outcomes of this approach in our country in order to contribute to the definition of the role of this technique.

Methods: Retrospective analysis of prospectively collected data from patients receiving TORS for oropharyngeal cancer in three centers. Management protocols, including the reconstructive scheme after TORS, are reviewed.

Results: Eighty-three patients receiving TORS, 87.8% as a primary treatment and 12.2% as a salvage procedure, were included; 55.4% were advanced stages. Global complication rate was 13.4%, being bleeding the most frequent (9.8%). Reconstructive procedures were associated in 14.4% of cases. Normal swallowing was achieved in

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82.4% of patients at three months after surgery. Patients treated with TORS as a primary treatment did not need complementary treatment in 56.6% of cases.

Conclusion: We found TORS to be a safe and effective approach in the treatment of oropharyngeal cancer. In our experience the practical contribution would be the reduction of the need for chemoradiation which could explain the functional outcomes.

Keywords: Head and Neck Cancer; Oropharyngeal Neoplasms; Radiotherapy Dosage; Reconstructive Surgical Procedures; Robotic Surgical Procedures

Abbreviations

RT: Radiation therapy; CRT: Chemoradiotherapy; HPV: Human Papillomavirus; TORS: Trans Oral Robotic Surgery; RT 70Gy: Radiotherapy 66-70 Gy dose; RT 60Gy: Radiotherapy 54-63 Gy dose; FEES: Fiberoptic Endoscopic Evaluation of Swallowing; PCR: Polymerase chain reaction; IMRT: Intensity-Modulated Radiation Therapy.

Background

Due to the morbidity caused by surgical procedures in this area, non-surgical treatments have been widely used for head and neck cancer over the past 30 years. Although there are no randomised prospective comparative studies that show the superiority of Radiation Therapy (RT) over open surgery, the former was adopted as the most common standard treatment of these tumours [1]. During the early 2000s, after studies showing improved survival with the addition of chemotherapy, Chemoradiation (CRT) became the standard [2,3]. Nevertheless the morbidity profile related to these treatments resulted in an increase in acute and late toxicities. The meta-analysis of Machtay, et al., [4] showed that CRT as a primary treatment left severe toxicity in more than 43% of cases.

The incidence of squamous cell carcinoma of the larynx, oral cavity, and hypopharynx has decreased in recent years, whereas that of squamous cell carcinoma of the oropharynx has been steadily increasing [5]. This seems related to epidemiological changes due to Human Papillomavirus (HPV) infection [6]. The HPV has been confirmed as an etiologic agent for oropharyngeal carcinomas. Its incidence is very high in northern European countries, as well as in the USA [7,8,9,10,11]. In Spain, as in other Mediterranean countries, the incidence is possibly lower, although there is currently very little evidence in this regard [12,13].

The response to treatments of these HPV-related tumours has been found to be very different from squamous cell carcinomas mediated by classical etiological factors (related to toxic habits, particularly tobacco and alcohol) [14,15,16]. Clearly, HPV mediated carcinoma shows a better prognosis, even in those patients who also have toxic habits. This improvement in survival has been reported both in those patients undergoing surgical treatment [17,18,19] and primary treatment based on RT [20,21,22].

Since the development of laser microsurgery [23], transoral surgery has evolved with technological progress. Possibly the most important single factor in recent years has been the introduction of endoscopes that have supported new surgical techniques either with the use of laparoscopic tools [24] or with robotic platforms [25]. Oropharyngeal surgery has moved towards transoral approaches to reduce the morbidity of open approaches, which have been associated with a complication rate of 10 to 60%, including dysphagia, temporomandibular malocclusion, aesthetic deformity, and fistula [26,27]. The transoral choice carries a benefit in efficiency and functionality compared to alternative surgical approaches and other non-surgical treatment options [28,29]. In addition, these approaches reduce the need for reconstructive procedures [30], while maintaining the oncological results [31,32].

Currently there is a need to define the exact position of transoral approaches, and particularly of Transoral Robotic Surgery (TORS) in the treatment of head and neck cancer, especially in squamous carcinoma of the oropharynx. Unlike other countries, TORS has had a limited expansion in Spain. The objective of this paper is to present the first outcomes in our country and analyze its role through a multicentric series.

Methods

This study is based on a retrospective analysis of oncological data collected prospectively from patients undergoing TORS with the da Vinci robotic system (Intuitive Surgical Inc) for squamous cell carcinoma of the oropharynx, in three different centers that currently gather the majority of TORS cases in the country. Participating institutions include Hospital Universitario Rey Juan Carlos (Madrid), Hospital Universitari Son Espases (Mallorca), Hospital Universitari Germans Trias i Pujol (Badalona/Barcelona). The earliest TORS programme in the 3 centres was started in July 2013, and in year 2015 and 2017 respectively in the other two.

All the patients received clear and accurate information about the procedure they would be undergoing. Informed consent was obtained from all individual participants included in the study.

Inclusion criteria were patients undergoing TORS for oropharyngeal cancer in those centres until January 2018.

The treatment scheme for every patient was decided after consultation with a multidisciplinary tumour board on each institution. The treatment protocol for these patients is based on anatomoclinical features of the tumour and on patient's clinical conditions. Thus, patients with tumours classified as T1-T2-T3 [33] with a reasonable prospect to achieve free margins, and N0 or N+ without suspected extracapsular spread [34], are considered for TORS.

Adjuvant treatment is evaluated according to pathology. Adverse features like positive margin or extracapsular spread are treated with 66 to 70Gy Radiotherapy (RT 70Gy) associated or not with systemic therapy (CRT). Locally advanced tumours (T3-T4) with negative margins usually were treated with 54 to 63 Gy RT (RT 60Gy).

The alternative standard treatment for these patients would be radical RT (70Gy) or CRT. Surgical treatment was also proposed in those patients who have received prior RT in the head and neck area and cannot be reirradiated with radical doses, or in patients not suitable for CRT due to medical conditions. Some of them might not be candidates for a fully transoral approach due to tumour extension, but a

combined TORS and transcervical approach according to oncological extension was used to reduce surgical morbidity. Our reconstructive algorithm (Figure 1) is based on the local extension of the tumour, the depth of the surgical defect and whether prior therapy was received. We performed reconstruction on those patients with carotid exposure and oro cervical communication, and in some instances on pretreated patients in order to avoid bleeding complications.

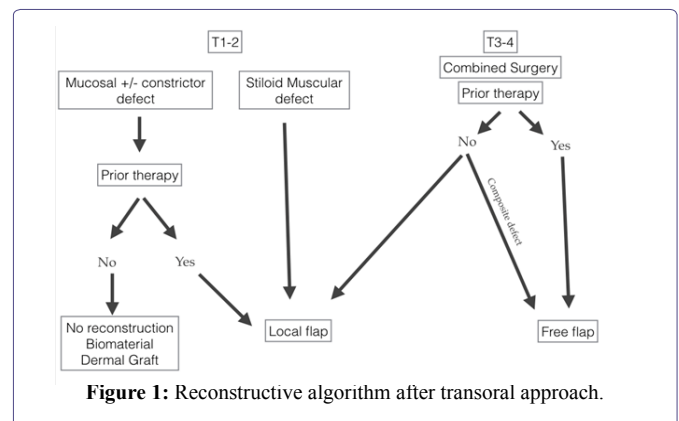


Figure 1: Reconstructive algorithm after transoral approach.

Perioperative management was fairly uniform between the centres. In general, prophylactic tracheostomy was not prescribed. Those patients who showed edema at the end of the surgery or doubts about their airway safety remained intubated (oro-traqueal or nasotraqueal) for 12h-24h; if the situation did not improve, a temporary tracheostomy was considered.

Prior to hospital discharge, a functional assessment of swallowing was performed by Fiberoptic Endoscopic Evaluation of Swallowing (FEES) and / or videofluoroscopy, and patients were assessed in the dysphagia unit of each centre.

The method to identify HPV varied with time. Polymerase Chain Reaction (PCR) analysis was preferably used, taking advantage of the previous lab circuit for the uterine cervix until 2016, and later and following current recommendations it is based on p16 immunohistochemistry and PCR combination detection [35].

We analysed tumour extension according to TNM staging, surgical margins, associated procedures, nasogastric and/or gastrostomy tube, hospital stay, complications, need for complementary treatment and swallowing function. The Chi-square test and the T test were used to compare qualitative and quantitative variables, respectively. Survival curves were estimated using the Kaplan-Meier actuarial method.

Results

A total of 86 patients receiving TORS for oropharyngeal carcinoma were included. The conversion rate was 3.5% due to 3 cases who had to be converted to open surgery due to anatomical conditions which made tumour exposure impossible with FK-WO (Olympus Corp) or Crowe-Davis mouth gag.

Those 3 patients were excluded of the subsequent TORS outcomes analysis.

Patients consisted of 67 men and 16 women, with a mean age of 62 years (SD: 8.95). HPV was detected in 29% of the cases (n=25), in

60% by PCR and p16 and in 40% by p16. Clinical staging is shown in table 1. The correlation between the primary site and local stage is shown in figure 2.

Seventy two (87.8%) patients were treated with TORS as a primary surgery. Eleven (12.2%) previously received RT or CRT and underwent TORS as a salvage procedure. Unilateral neck dissection was performed in 19.3% (n = 16) and bilateral neck dissection in 25.3% (n = 21) in the same surgical procedure. Reconstructive procedures were associated in 14.4% of the cases (n=12). When primary or salvage surgery was considered, reconstruction was performed in 9.7% of first line surgery cases (6 regional flaps and 1 free flap), and in 45% of salvage cases (3 free flaps and 2 regional flaps). Temporary tracheostomy was required in 7 cases (8.4%). Free resection margins were achieved on 85% of the cases (n=71), close margins appeared in 10% (n=8) and affected margins in 5% (n=4).

| | N2 | | | | | | Total |
|-------|----|----|-----|-----|-----|----|-------|
| | N0 | N1 | N2a | N2b | N2c | N3 | |
| T1 | 13 | 3 | 7 | 0 | 0 | 2 | 25 |
| T2 | 24 | 5 | 4 | 7 | 1 | 2 | 43 |
| T3 | 6 | 1 | 0 | 2 | 1 | 1 | 11 |
| T4 | 2 | 2 | 0 | 0 | 0 | 0 | 4 |
| Total | 45 | 11 | 11 | 9 | 2 | 5 | 83 |

Table 1: Clinical TNM staging of the included patients.

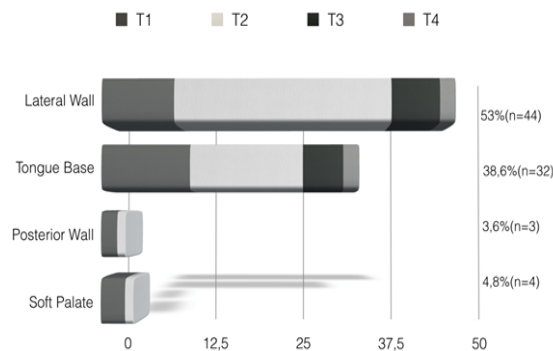


Figure 2: T stage according to Oropharyngeal location.

The complication rate was 13.4%. Bleeding was the most frequent complication (9.8%) and required revision hemostatic surgery in 91% of cases. 1.2% of the patients suffered postoperative dyspnea, 2.4% pharyngocutaneous fistula (managed conservatively, without surgery in all of the cases), and 1.2% death due to bleeding aspiration. Complications appeared to be associated with pT staging, although this did not reach statistical significance (p=0.084).

Mean hospital stay was 8.3 days (DE: 8.0) with a median of 7 days. The duration of the hospital stay was not associated either with salvage surgery, staging or T category, but a statistically significant association was found with the presence of postoperative complications (p=0.001).

At the time of hospital discharge, functional assessment of swallowing by FEES was normal in 48.8% of the patients. Up to 28.8%

received diet adaptation, 13.3% swallowing rehabilitation and 8.8% a nasogastric feeding tube. At 3 months, swallowing evaluation was normal in 82.4% of the patients, while 6.8% kept diet adaptation, 4% swallowing rehabilitation and 6.8% a feeding tube (gastrostomy). The mean duration of feeding tube postoperatively was 7,1 days.

Specific swallowing care was not associated with T stage, with primary or salvage surgery.

Among patients who received primary surgery, 56.6% did not need complementary treatment (“TORS alone” cases). RT 60Gy was given to 13.2%, CRT to 28.9% and RT 70Gy to 1.2%. We analysed the need for adjuvant treatment according to the initial staging (Figure 3).

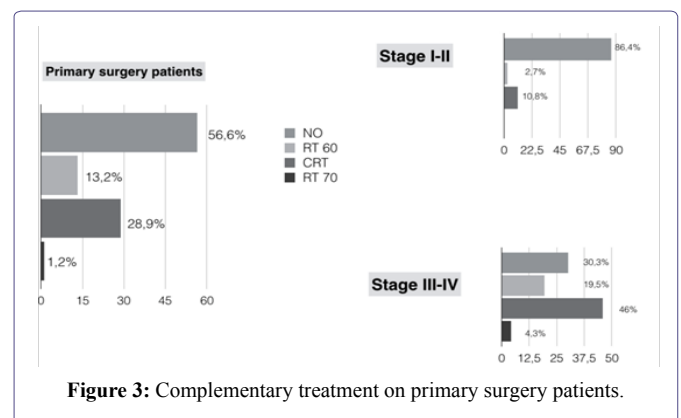


Figure 3: Complementary treatment on primary surgery patients.

For early stages (I,II, n=37) TORS alone cases were 86.4%, while for advanced stages (III,IV) were 30.3% of the cases. The need for complementary treatment was associated with the initial staging (p=0.001).

Mean follow-up was 17.7 months (DE: 14.4m). Overall 2 years survival was 88.8% and specific 2 years survival was 91.4%. Two years Survival for patients undergoing salvage surgery was 66,7 % while for primary surgery patients this was 91,5% (p=0.002) (Figure 4).

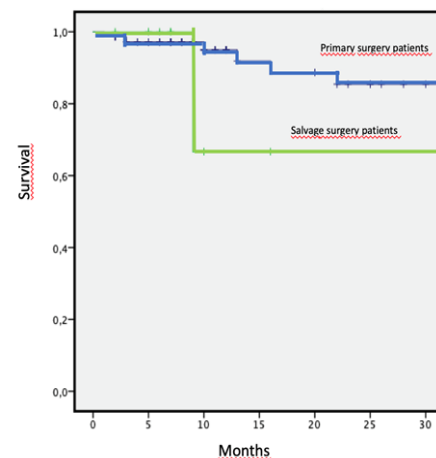


Figure 4: Overall 2 years survival for primary surgery and salvage surgery patients.

Discussion

Regardless of the surgical approach that is chosen for the treatment of squamous cell carcinoma of the oropharynx, the principles of complete resection with minimum free oncological safe margins should be respected; usually, when a minimally invasive approach is used, a satisfactory functional outcome is also expected. Complementary CRT should not be considered as a solution to insufficient surgery. Also, a significant reduction in the dose of adjuvant treatment should be obtained compared to primary treatment with CRT [36]. When TORS is considered, a careful assessment of the patient should be made, focusing on the examination of the mouth opening and dentition, the size of the base of the tongue and jaw, the cervical length and the atlanto-occipital extension [37]. Contraindications for TORS should be ruled out: Involvement of the base of the skull, the jaw or the carotid artery, or unresectable lymphadenopathies [38]. An appropriate access to these tumours requires that the tumour can be completely visualised with the endoscope so that a complete circumferential resection can be done, while controlling the cervical neurovascular structures in the deep limit of the resection.

When assessing the need for complementary treatment, neck status should be evaluated. Cases with pN0 staging would not need adjuvant treatment after neck dissection, while those N+ with capsular rupture, size greater than 6 cm or more than 4 positive nodes would be candidates for adjuvant CRT, decreasing the potential benefit of TORS as primary treatment.

Stages I-II should be offered a unimodal treatment. In this group of patients, the treatment options would be TORS versus radical RT (which should be Intensity-Modulated Radiation Therapy, IMRT as a standard). For patients in stages III and IV, treatment options would be TORS versus CRT. In general, multimodal treatment is considered for advanced stages. In this situation, the reason for starting with TORS would be to decrease the need for adjuvant treatment, which means reducing the dose of RT or avoiding the need for concurrent systemic therapy.

Stages I-II patients received TORS alone in 86.5% of cases. For advanced stages we could reduce or spare adjuvant treatment in 53.8% of patients.

Some studies analyse the need for adjuvant treatment after TORS. Lorincz, et al., [39] present 50 patients T1-2 N0 and N+ without suspected extra capsular spread 40% of the patients received "TORS alone" without adjuvant treatment and in 34% either the dose of RT was reduced or chemotherapy avoided. That means that in 74% of the patients the need of adjuvant treatment was decreased or avoided. Smith, et al., [36] prospectively analyse 44 patients stages I to IV. 52% required adjuvant treatment (21% RT and 31% CRT). This need for treatment was associated with T and N categories. Nevertheless, 18% of the patients were re-staged after surgery. Local control and survival in the surgery group were better, although without statistical significance. In our series T was changed in 9.6% and global stage in 14.5% (mostly because of discrepancies between radiologic and pathologic examination of the neck).

Our study cohort showed a 91.4% specific disease survival. One of the limitations of the study was the limited follow-up time (mean 17.7 months). Expected survival, according to published data is between 83% and 96% for T1 and between 54% and 92% for T2. TORS studies show better survival results, although follow-up is still shorter (with an average of 2 years) [40]

Although TORS is a minimally invasive surgical approach which functional outcomes overcome those of open surgery, it is also associated with potentially severe complications. Bleeding is a particular concern due to the site because it can be aspirated and end in death by asphyxia. The incidence of bleeding complications described in the literature ranges from 1.5% to 11% [41]. In patients with salvage surgery this can be as high as 19%. Another complication is the pharyngo-cutaneous fistula, particularly when neck dissection is done simultaneously.

Our complication rate was 13.4% and hemorrhagic complications were 9.8%. These did not present a statistical relationship with salvage surgery. In those patients undergoing salvage surgery, the decision threshold to go for a reconstructive procedure with the aim of reducing possible complications was reduced compared to those treated with TORS in the first line of treatment. While on first line surgery we performed reconstructive procedures in 9.7% of the cases, in salvage surgery it was 45%. We found a statistical trend in the relationship between complications and category T that denotes greater resection.

Favourable functional outcomes with normal swallowing in the long term vary between 70% and 100% [42]. Regarding feeding tube dependence Setton, et al., [43] presented a multicentric study with 2,300 patients treated with IMRT with an incidence between 3.7% and 4.4% depending on the stage, although numbers vary in a wide range from 2% to 20% one year after treatment. In TORS series the percentage is consistently between 0% and 9% at one year [44]. Furthermore there are several studies comparing quality of life for TORS patients (with or without RT) versus primary RT or CRT, and no differences were found except for dysphagia where there is a tendency to be subjectively better in patients treated with surgery [45,46,47].

This study is the largest reported oropharyngeal cancer TORS cohort in our country, and joins the learning curve and later experience of three centres. Probably it could be a weakness of our study because of the heterogeneity between centres. On the other hand, It could prove that TORS is a reproducible technique and with good oncological and functional results in selected cases.

We think this can support the shifting paradigm for oropharyngeal cancer from chemoradiotherapy to surgery. This concept is not broadly accepted yet in our nation.

Conclusion

TORS has an important and expanding role in the treatment of oropharyngeal squamous cell carcinoma. Good oncologic and functional outcomes are found across three centres in the earliest series in our country, both as a first line treatment and as a salvage surgery.

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