Oral Oncology 86 (2018) 165–170

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Oncological and functional outcomes of trans-oral robotic surgery for pyriform sinus carcinoma: A French GETTEC group study

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ARTICLE INFO

Keywords:
Transoral robotic surgery
Pyriform sinus cancer
Robotic hypopharyngectomy
Hypopharyngeal squamous cell carcinoma
Head and neck cancer
Organ preservation

ABSTRACT

Background: Pyriform sinus carcinomas (SCC) present specific functional and oncological issues. The recent advent of trans-oral robotic surgery (TORS), as a conservative procedure, has opened up new perspectives.
Objectives: To present the oncological and functional outcomes of TORS for pyriform sinus SCC.
Materials and methods: We included, retrospectively, all TORS procedures for pyriform sinus SCC performed between 2009 and 2017 in eight French tertiary referral centers. We excluded lesions involving the pyriform sinus that had developed from the oropharynx, larynx, or other anatomic sub-sites of the hypopharynx.
Results: We included 57 TORS procedures. Median hospital stay was 10 days. A preventive tracheotomy was performed in seven cases (12%), and all were successfully decannulated. Oral re-feeding was possible for 93%, after a median of 5 days. The main surgical complications were hemorrhages (three cases), all successfully handled, although 2 patients with heavy comorbidities died from blood loss in the days after. Adjuvant therapy was proposed in 31 cases (54%), including two cases of salvage surgery (total pharyngolaryngectomy). After a median follow-up of 23 months, overall and disease-free survival were, respectively, 84% and 74% at 24 months, and 66% and 50% at 48 months. At the end of follow-up, organ preservation rate was 96%. None of the surviving patients needed a tracheotomy and oral diet was possible for 96%.
Conclusion: The functional and oncological outcomes of TORS for pyriform sinus cancer are encouraging, and this procedure can be considered safe for selected early or moderately advanced cases as a conservative treatment.

Introduction

Hypopharyngeal squamous cell carcinomas (SCC) represent 20% of all upper aerodigestive-tract carcinomas, and have an associated poor prognosis. Overall survival at 5 years is estimated at between 15% and 45%; mostly because of the late diagnosis of these lesions, and the high potential for lymphatic dissemination in patients with numerous co-morbidities [1,2]. Among the tumors, those located in the pyriform sinus, which account for 70% of hypopharyngeal cancers, represent a challenge for oncologists and surgeons. Their close association with swallowing, breathing, and speaking functions make open surgery challenging. There is difficulty in restoring these functions with a partial pharyngectomy, or there is often the need for radical surgery, such as a total pharyngo-laryngectomy. These constraints have led to the development of organ-preservation protocols using radiotherapy or chemoradiotherapy. These are now the gold-standard treatment for early and moderately advanced hypopharyngeal SCC [3–5].

The recent advent of transoral robotic surgery (TORS), as a conservative procedure, has opened up new perspectives [6,7]. Well-described and validated for oropharynx and larynx surgery [8–10], it

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https://doi.org/10.1016/j.oraloncology.2018.09.014
Received 8 May 2018; Received in revised form 10 September 2018; Accepted 13 September 2018
Available online 25 September 2018
1368-8375/

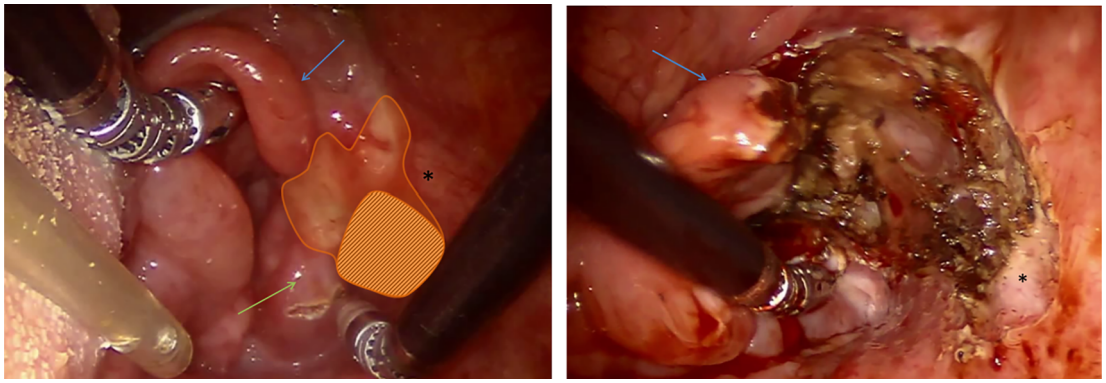


Fig. 1. Excision of a lesion centered on the anterior angle of the pyriform sinus (*orange hatching*), with extension to the 3-folds region, in salvage therapy for a tracheotomized patient, before (*left*) and after (*right*) excision. (*Note the ablation of the right arytenoid, part of the epiglottis and the entire pharyngolaryngeal wall*). *Green arrow: right arytenoid; blue arrow: epiglottis; asterisk: thyroid cartilage*. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

could be used in the therapeutic arsenal for pyriform sinus SCC. Some feasibility reports [11–15] and preliminary studies [16,17] show encouraging results using TORS for hypopharyngeal cancer. Park et al. recently reported on a long-term, prospective cohort that include 27 tumors located in the pyriform sinus: 100% of larynx were preserved with good oncologic results [18].

The objectives of this study were to present the functional and oncological outcomes of TORS on the pyriform sinus for SCC since 2009.

Materials and methods

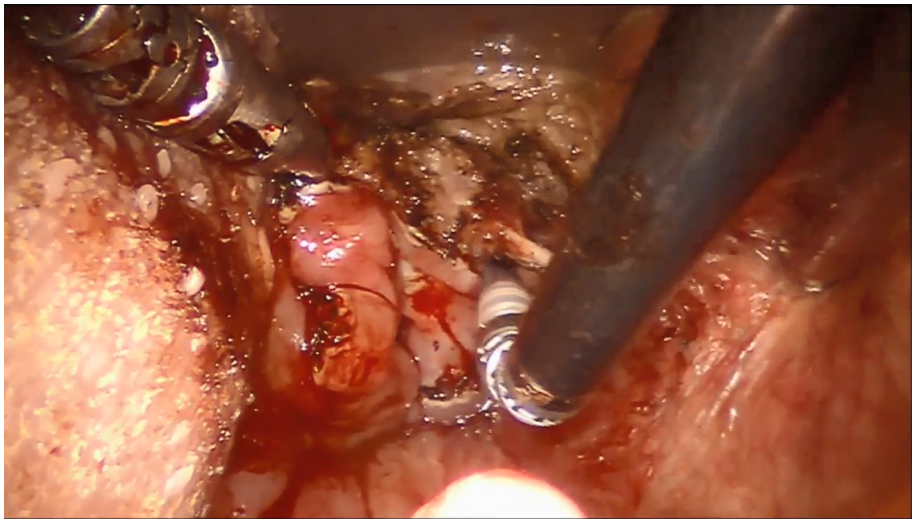
Design and protocol

We conducted a retrospective multicentric study between November 2009 and May 2017 in the French GETTEC group (Groupe d'Etude des Tumeurs de la Tête Et du Cou [Study Group for Head and Neck Tumors]). We included all TORS procedures for SCC located in the pyriform sinus during this period. We excluded lesions involving the pyriform sinus that had developed from the larynx, oropharynx, or other anatomic sub-sites of the hypopharynx (i.e. pharyngeal posterior wall and retrocricoid region).

Surgical procedure and operative technique

All surgical indications (TORS with or without neck dissection) were approved by a multidisciplinary board at each center after endoscopic and imaging assessment. During the initial endoscopy, it was systematically verified that the transoral exposure and accessibility to the tumor were sufficient for TORS with a specific mouth retractor for robotic surgery. Indications were small and superficial carcinomas (cT1, cT2 and selected cT3) located in the pyriform sinus. In addition, tumors involving the vertebrae, carotid artery or thyroid cartilage were anatomical and/or oncological contraindications (cT4).

The surgery was performed using the da Vinci® (Intuitive Surgical, Sunnyvale, CA, USA) robotic system and consisted of a full or partial resection of the pyriform sinus (Fig. 1; Video 1), as previously described [8,12]. The surgical field was focused on the three-folds region and anterior angle of the pyriform sinus. An 8.5-mm or 12-mm endoscope at 0° or 30° was used, with two 5-mm or 8-mm EndoWrist® (Intuitive Surgical, Sunnyvale, CA, USA) instruments: forceps (Maryland, De Bakey) and Bovie electrocautery spatula. Dissection was usually performed from top to bottom, including parts of the adjacent anatomical structures medially (epiglottis, arytenoid), if needed, to obtain macroscopic safe margins. Laterally, the inner thyroid perichondrium can be peeled off and is an easily dissected plane. Complementary resections with intraoperative margin analysis were performed in case of any doubt of insufficient margins. The need for a tracheotomy or feeding tube was considered by the surgeon during the procedure, depending on the estimated risk of bleeding or swelling. All the patients received clear, accurate, and comprehensive information regarding the procedure.



Video 1.

Adjuvant therapy

The need for adjuvant therapy was also decided upon by the board, with regard to the histological final results. Indications for adjuvant radiotherapy, with or without chemotherapy, were based on the usual criteria for a poor prognosis, comprising: positive margins on surgical sample, perineural or lymphovascular invasion, more than 1 lymph node involved, and extracapsular nodal spread.

Statistical analyses

Before the analyses, a verification of missing, aberrant, or inconsistent data was performed. After corrections, the database was locked. We first described the characteristics of patients using appropriate descriptive statistics according to the types of variables. Descriptive statistics included the number of observations, median with interquartile range (IQR) for continuous variables, the number of observations with frequencies (%) for categorical variables and Kaplan-Meier curves for survival endpoints. In an exploratory setting, we assessed factors associated with outcomes: categorical variables were compared between groups using the $\chi 2$-test (or Fisher's exact test when necessary). Anova or Student's *t*-test was used to compare the distribution of continuous data (the Kruskall-Walli's or Mann-Whitney's test was used when the distribution departed from normality or when homoscedasticity was rejected). Survival analysis was conducted using a Cox's model to obtain hazard ratios (HRs) and 95% confidence intervals (CI) for overall survival and disease-free survival.

All reported *p*-values were two-sided and the significance threshold was $p < 0.05$. Statistical analyses were performed using STATA software 14.1 (STATA Corp., College Station, TX, USA).

Results

Patients and procedures

Data from a total of 57 patients were analyzed from eight French tertiary referral centers, with a median follow-up of 23 months [IQR: 11–42]. The median age was 60 years [Range: 44–80], 91% were males, 95% were tobacco smokers, and 77% had excessive alcohol consumption. Twenty patients (35%) presented with prior upper aerodigestive-tract carcinoma: eleven (19%) underwent cervical radiotherapy, and ten (18%) had benefited from neck dissection. The TORS procedure was considered as a salvage or recurrent therapy for five patients (9%) (Table 1).

Fifty-six tumors (98%) were stage T1 or T2, but the disease was stage III or IV for 27 (47%) in relation to the nodal spread, according to the AJCC 7th edition classification (Table 2). The anatomic distribution of lesions was equitable, with 20 (35%) located on the medial wall of the pyriform sinus, 20 (35%) on the lateral wall, and 17 (30%) in the anterior angle. Resection was extended to the epiglottis or arytenoid in 13 cases (23%). Systematic intraoperative margin analysis was performed in 40 cases (70%). We noted no case of abortive procedure due to exposure problem.

A neck dissection was performed in 41 patients (72%), all during the same procedure. All surgical fields were handled by secondary intention healing, without closure or reconstruction. No case of external conversion was needed.

Adjuvant therapy was proposed for 31 patients (54%), including two cases (3.5%) of salvage surgery with a total pharyngo-laryngectomy, because their histopathology showed massive margins involvement. For others, radiotherapy alone was proposed in 12 cases (21%), and concurrent chemoradiotherapy in 17 cases (30%) (Table 3). For the 29 patients (51%) who received radiotherapy (with or without chemotherapy), the indications for adjuvant treatment were in relation to: pejorative tumoral histopathology result (limited or positive margins, perineural or lymphovascular invasion) for seven (13%), lymphatic involvement (more than one lymph node involved and/or extracapsular spread) for eleven (19%) and both of the aforementioned for eleven (19%). All cases of concurrent chemotherapy presented multiple lymph node invasion and/or extracapsular nodal spread, and 7 of them limited or positive margins.

Postoperative outcomes (Table 4)

Median hospital stay was 10 days [IQR: 6–17]. We noted three cases (5%) of tumor-site hemorrhage, which were all successfully handled (one with radiological arterial embolization, two with trans-oral

Table 1
Patient characteristics (N = 57).

Characteristics	No (%) or median [IQR]
Sex	
Male	52 (91)
Female	5 (9)
Age, years	60 [56–62]
Use history	
Tabaco	54 (95)
Alcohol	44 (77)
Prior aerodigestive tract carcinoma	20 (35)
Prior pharyngolaryngeal surgery	8 (14)
Prior cervical radiotherapy	7 (12)
Prior pharyngolaryngeal surgery AND radiotherapy	4 (7)
Prior neck dissection	10 (18)
Context	
Upfront treatment	52 (91)
Salvage or recurrence therapy	5 (9)

Table 2
cTNM classification (AJCC 7th edition).

	N0	N1	N2a	N2b	N2c	N3	Total
T1	18	3	–	8	–	–	29 (*51%*)
T2	12	5	1	9	–	–	27 (*47%*)
T3	1	–	–	–	–	–	1 (*2%*)
T4	–	–	–	–	–	–	–
Total	31 (*54%*)	8 (*14%*)	1 (*2%*)	17 (*30%*)	–	–	57

Stage I: N = 18 (32%); Stage II: N = 12 (21%); Stage III: N = 9 (16%); Stage IV: N = 18 (31%)

Table 3
Therapeutic procedure (N = 57).

Characteristics	No (%)
Tumor location	
Anterior angle	17 (30)
Medial wall	20 (35)
Lateral wall	20 (35)
Excision extension	13 (23)
To arytenoid	8 (14)
To epiglottis	8 (14)
To base of tongue	1 (2)
External conversion	0 (0)
Concurrent neck dissection	41 (72)
Selective unilateral	33 (58)
Radical unilateral	5 (9)
Selective bilateral	3 (5)
Radical bilateral	0 (0)
Adjuvant therapy	31 (54)
Surgery (total pharyngolaryngectomy)	2 (4)
Radiotherapy alone [average radiation dose on T/N]	12 (21) [57,2 Gy/ 49 Gy]
Concurrent chemoradiotherapy [average radiation dose on T/N]	17 (30) [62,8 Gy/ 61,6 Gy]

T: tumor site; N: lateral neck compartments.

cauterization procedures). Two of the three patients died days later: both presented with advanced cirrhosis. One died from multi-organ failure and the other after recurrent biologic blood loss without exteriorization, without being able to determine the origin of the bleeding (from the tumor site or from another cause in this patient who presented severe esophageal varices). Of the 41 patients that benefited from a concurrent neck dissection, one developed a cervical hematoma, and one a pharyngeal fistula, which was spontaneously regressive.

A perioperative preventive tracheotomy was realized in seven cases (12%): all were removed after a median period of 8 days [IQR: 7–15]. There were no cases of immediate postoperative dyspnea, but two secondary therapeutic tracheotomies were needed during radiotherapy, because of pharyngolaryngeal edema: both were also successfully removed.

Regarding nutrition, we excluded one patient from the analysis because he had already undergone enteral feeding via a gastric tube, plus the two patients that died during the postoperative period. Full oral feeding was possible for 50 patients (93%) after a median of 5 days [IQR: 3–7]. Sixteen patients (30%) showed initial laryngeal aspiration, two of which developed pneumopathy, but both were successfully treated. Fifteen (28%) patients needed specific rehabilitation after leaving the unit. Four patients (7%) had initial severe swallowing troubles and needed enteral alimentation via a gastric tube.

In our exploratory analysis, TNM staging, tumor location, concurrent neck dissection, adjuvant therapy, or prior treatment (head-and-neck surgery and/or radiotherapy) were not significantly associated with postoperative complications (dyspnea, bleeding, hematoma, infection, death), tracheotomy (and decannulation), or nutritional status (swallowing disorders, pneumopathy, gastric tube).

Oncological outcomes

Regarding the pathology, the final status of the margins was considered safe in 40 patients (70.2%). Perioperative re-excisions were performed in 40 cases (70.2%), and tended to be associated with a lower rate of positive or limited margin status (47.1% positive or limited margins without re-excision vs 22.5% with re-excisions, $p = 0.0637$). On the contrary, tumors located in the anterior angle of the pyriform sinus were significantly associated with a higher rate of positive or limited margins (5% of final positive or limited margins in the medial wall, 35% in the lateral wall, and 53% in the anterior angle, $p = 0.0052$).

Within a median follow-up of 23 months [IQR: 11–42], seven patients (12%) developed a recurrence, with a median of 11 months (Fig. 2). Twelve patients died during follow-up, including the two that died postoperatively (Fig. 3). Using the Kaplan-Meier method, the overall survival and disease-free survival rates were, respectively, 84% and 74% at 24 months, and 66% and 50% at 48 months (Fig. 4).

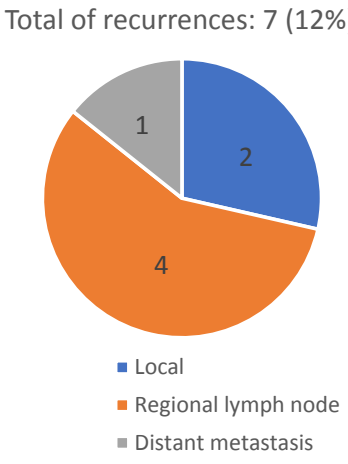


Fig. 2. Sites of recurrence.

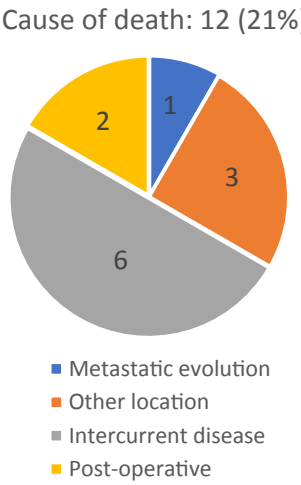


Fig. 3. Causes of death during follow-up.

We noted 96% of larynx preservation at the end of follow-up. At the time of the latest news (or at time of death or recurrence diagnosis when occurred), and excluding the two patients that died postoperatively and the two that benefited from a salvage pharyngolaryngectomy (N = 53), none needed a tracheotomy, and oral feeding was possible for 51 patients (96%) (Table 5).

In our exploratory analysis, patient age, TNM staging, prior treatment (head-and-neck surgery and/or radiotherapy), tumor location, margins status, or adjuvant therapy were not significantly associated with long-term functional (organ preservation rate, nutritional and respiratory functions) and oncological outcomes (recurrence, overall and disease-free survival).

Discussion

TORS for the pyriform sinus is one of the most difficult robot-assisted procedures. Since its first technical descriptions and feasibility reports [11,13–15], only a few studies have reported oncological outcomes for hypopharyngeal SCC. Among them, Lorincz et al., Wang et al., and Park et al. included respectively 5, 10 and 27 cases of pyriform sinus tumor resection [12,17,18]. Our study, while retrospective and having a short follow-up, is the first one focusing on pyriform sinus lesions, with a substantial population (N = 57), including all TORS procedures for pyriform sinus SCC in the eight French tertiary referral centers.

Moreover, all the authors are members of the French GETTEC Robotic Surgery group, created in 2009, ensuring a relative homogenization of the procedures in our series. They recently reported guidelines for robotic surgery with the ENT French Society, including hypopharyngeal carcinomas, where a strict selection of the patients and the tumors is recommended [19]. Indeed, the pyriform sinus is the most difficult location to expose and to reach in trans-oral surgery [20]. In our opinion, the best indications are small and superficial tumors (T1-T2), located in the upper part of the pyriform sinus, where the range of instrument movement is usually sufficient and allows en bloc resection. Nevertheless, the pyriform sinus is narrow and its anterior angle and deepest part are very difficult to expose. Surgeons also have to deal with other anatomical limits laterally, represented by the thyroid cartilage anteriorly and the common carotid artery posteriorly. For these reasons, endoscopic and imaging assessments are key points of the procedure, and the opinion of a trained senior surgeon is highly recommended to confirm the TORS indication [21], which must be reserved for the last stage of the surgeon's learning curve. In the future, next-gen flexible robotic systems, with specific instrumentation, could

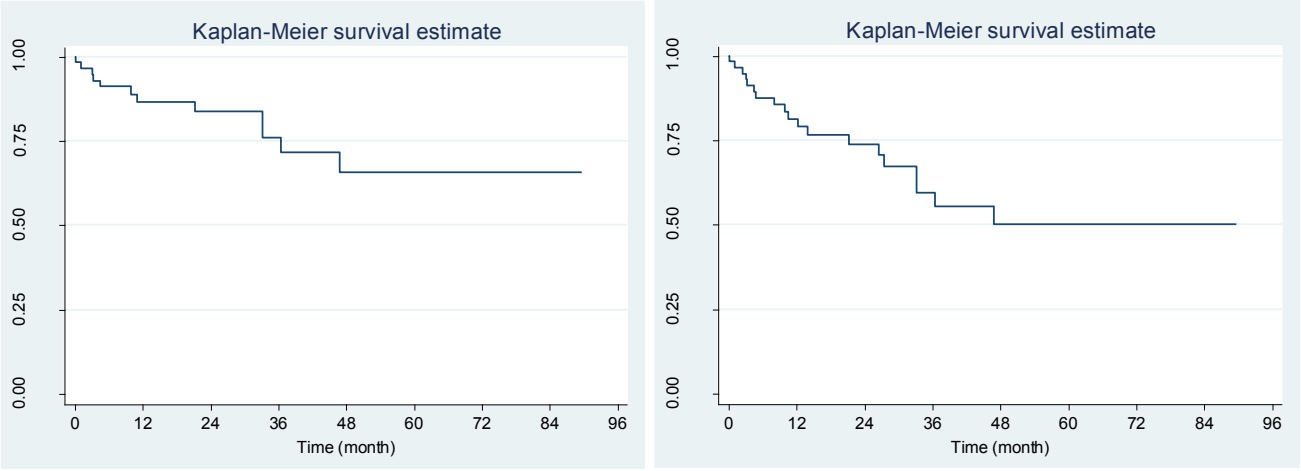


Fig. 4. Kaplan-Meir survival curves for overall survival (left) and disease-free survival (right).

Table 4
Postoperative functional outcomes (N = 57).

Measure	No (%)
Median hospital stay, in days [range]	10 [3–41]
Feeding (*3 patients excluded*)	
Peroperative feeding tube	39 (72)
Return to oral diet/Gastric tube	50 (93)/4 (7)
Days to oral diet, in days [range]	5 [2–34]
Initial laryngeal aspiration	16 (30)
Pneumopathy	2 (4)
Need of external swallowing reeducation	15 (28)
Tracheotomy	
Concurrent preventive	7 (12)
Secondary therapeutic (during postoperative time)	0 (0)
Decannulation	7 (1 0 0)
Days to decannulation, in days [range]	8 [6–166]
Surgery-related complications	
Death	2 (4)
Bleeding	3 (5)
Dyspnea	0 (0)
Cervical hematoma	1 (2)
Pharyngostoma	1 (2)

Table 5
Distant functional outcomes, at time of latest news if free-disease survival patient, or at time of death or recurrence diagnosis.

Measure	No (%)
Organ preserved (N = 57)	55 (96)
Nutritional status (N = 53*)	
Oral diet with no restriction	43 (81)
Oral diet with restrictions	6 (11)
Enteral diet	2 (4)
Mixed oral and enteral diet	2 (4)
Respiratory status (N = 53*)	
No tracheotomy and no dyspnea	50 (94)
No tracheotomy with dyspnea	3 (6)
Tracheotomy	0

* Four patients excluded: 2 benefited from a salvage total pharyngolaryngectomy, 2 died postoperatively.

help improve and democratize the procedure [22,23].

Regarding perioperative airway management, we have noticed a decreasing trend in tracheotomy since the first TORS descriptions, for all procedures [24]. Park et al. performed a systematic perioperative tracheotomy, with 92% of patients decannulated, whereas we performed only 12% perioperative tracheotomy procedures with 100% of patients successfully decannulated and no postoperative dyspnea. Wang et al. didn't perform perioperative tracheostomy, but 60% stayed intubated for more than one day, according to the endoscopic exam at the end of the procedure. Although they noted no cases of post extubation dyspnea or bleeding, there is no evidence in the literature favoring one of these two strategies, and both can be discussed.

TORS-related complications were dominated by hemorrhages (5%). In our study, incidence was lower than estimated in the literature, which was reported between 6.5% and 16%, but it was associated with high morbidity, with 2 patient deaths [25–27]. Arterial ligation during TORS procedure is controversial, and for those 3 patients, no arterial ligation was done. Kubik et al. and Gleysteen et al. suggest that ligation of the external carotid artery or branches has no consequence on the incidence of hemorrhages, but reduces the severity of the bleed [28,29]. As such, we consider ligation of the superior laryngeal artery necessary during the procedure, and even more so when no tracheotomy is performed. It can be performed via an external approach during neck dissection or via a trans-oral approach during the dissection of the pharyngo-epiglottic fold.

Concerning oncological outcomes, we noticed a good local control rate, with only 2 cases of local recurrence. This contrasts with the pathology results, where almost 30% of cases of margin status were interpreted as limited or positive. Although no data is available in the literature, this rate may be increased and overestimated by the burns and tractions exerted on the piece during excision in this exiguous space. It could lead to difficulties in margins interpretation for pathologists. Nevertheless, pyriform sinus tumor removal is challenging and, in our study, tumors located in the anterior angle of the pyriform sinus were significantly associated with a higher rate of positive or limited margins. Park et al. also reported a high positive margin rate of 21% (for all hypopharyngeal cases), but evenly associated with a good local control rate, with only one local recurrence. Moreover, we found no statistical difference in survival rates and local control rates regarding the excision quality. Some surgeons propose performing systematic re-excisions to prove negative margin status. In our study, it allowed reclassifying the margin status from positive to negative in eleven cases (19%). Wang et al. performed systematic re-excisions with immediate histopathology examination, which allowed to extend the excision margin if necessary; this resulted in no case of positive margins in the final histopathology examination. Finally, some preliminary studies suggest that TORS associated with magnifying endoscopy with Narrow Band Imaging could improve the extent of the resection and ensure safe margins the first time [30].

Today, there is no level one evidence in the literature for the treatment of pyriform sinus SCC between surgery and radiotherapy

protocols. The place of trans-oral surgery also remains uncertain. The first data published about the safety of the procedure and the long-term oncological results seem to be encouraging: disease-free survival rate is estimated at 45% at 5 years by Park et al. In our series, we describe higher survival rates, with a shorter follow-up, but a larger cohort. In contrast, trans-oral laser surgery seems to be less effective, according to Martin et al. and Weiss et al., with disease-free survival rate estimated, respectively, at 38% at 60 months and 37% at 45 months [31,32]. In our study, head and neck radiotherapy or surgery history does not influence the oncological and functional outcomes. It should not represent a contra-indication for trans-oral surgery when the lesion is accessible, such as suggested by Meulemans et al. [33].

Conclusion

TORS can be considered as a conservative and safe procedure for small lesions in the pyriform sinus, in first or salvage therapy. It has acceptable oncological and excellent functional outcomes. However, it is one of the most complex types of robot-assisted surgery, and strict selection of cases is needed, in particular for lesions that involve the anterior angle, where exposure is difficult and safe margin excision is hard to achieve.

Conflict of interest

None declared.

Acknowledgements

The authors express their sincere gratitude to the CHU de Toulouse - Direction de la Recherche, du Développement et de l'Innovation, in particular for their translation support.

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