Chapter 7
Pros and Cons of Endoscopic Surgery

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Introduction

Transoral laser microsurgery (TLM), transoral robotic surgery (TORS), and transnasal endoscopic surgery (TES) can be considered three of the most innovative techniques introduced during the last decades in head and neck surgical oncology. The aim of these technologies is to provide patients with treatments associated with the same outcome in terms of local control compared to traditional surgical techniques or radiation/chemoradiation (RT/CRT), but with less morbidity and decreased hospitalization time. The value of TLM, TORS, and TES in the management of early-stage lesions is widely recognized, while the debate is still ongoing on their role in the treatment of selected intermediate/advanced tumors.

If we specifically look at laryngeal/hypopharyngeal and oropharyngeal intermediate/advanced cancers, treatment options more commonly include surgery via an external approach (with or without the need for reconstruction) or CRT. Meta-analysis data have demonstrated a significant rate of treatment-related toxicities, particularly acute mucositis, xerostomia, and long-term swallowing dysfunction, in case of nonsurgical organ preservation protocols [1–4]. The rate of gastrostomy tube (GT) dependence for patients treated with CRT has been reported as typically between 9 and 39 % [5, 6]. CRT does not avoid the need for temporary/permanent tracheotomy [6] and does not guarantee functional preservation. In fact, Hanna et al. observed no significant difference between total laryngectomy and primary CRT in speech and swallowing–related quality of life scores [7]. In case of locally advanced laryngeal cancer, there is still debate about the oncological comparability of organ

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preservation protocol and surgery in real-world clinical settings [8–13]. On the other hand, when considering the therapeutic strategy for locally-advanced hypopharyngeal squamous cell carcinoma (SCC) (surgery vs. organ preservation protocols), there are no significant differences between the two groups in relation to survival outcomes. In the advanced stage setting, concurrent CRT is frequently proposed for patients with low to moderate volume disease in which functional status has not been irreversibly compromised. Otherwise, a primary surgical approach followed by postoperative RT is typically adopted [14–16]. In this scenario, TLM and TORS may be considered good options in well selected cases of locally intermediate/advanced cancer, where, in view of the extent and location of the lesion, tumor resection within free margins may be expected with less morbidity compared to external approaches.

Transoral Laser Microsurgery

Laryngeal Cancer

In the last 25 years, several experiences have demonstrated the oncological reliability of TLM for early laryngeal tumors (Tis, T1, and T2), comparable to more traditional approaches. The excellent results reported led to a gradual expansion of the indications to include locally advanced tumors (T3–T4a), traditionally managed by open-neck surgery (either partial or total laryngectomies), and nonsurgical organ preservation protocols [17–31]. The main advantage of TLM is the ability to perform individualized surgery according to the size and location of each tumor, thus preserving the maximal amount of healthy tissue [32]. From a technical point of view, tumor resection in a single piece ("excisional biopsy" generally applicable for Tis-T1 and most T2) is not always possible for advanced or bulky lesions. In this scenario, the tumor must be divided into multiple blocks ("multibloc technique"), with the great advantage of visualizing the deep and inferior extent of the tumor (Figs. 7.1 and 7.2) [33–35]. General absolute contraindications to TLM are the impossibility to adequately expose the larynx, involvement of the posterior commissure, cricoid cartilage invasion, extensive subglottic involvement, and massive extralaryngeal tumor extension [33, 36–39]. Furthermore, suboptimal exposure, anterior commissure involvement in the cranio-caudal plane, thyroid cartilage erosion, arytenoid fixation, and massive infiltration of the preepiglottic and paraglottic spaces represent the most controversial scenarios for management of glottic and supraglottic tumors by TLM [38]. If all laryngeal subsites are not appropriately visualized, misdiagnosis, incomplete resection, or unnecessary need for adjuvant therapy can be encountered [36, 38, 39]. Tumors affecting the anterior commissure represent a controversy for TLM because of a reduced local control compared to external partial techniques, even in case of negative margins [40–44]. It is extremely important to differentiate between tumors affecting the anterior commissure in the horizontal plane (T1b) from those that grow along a cranio-caudal direction,

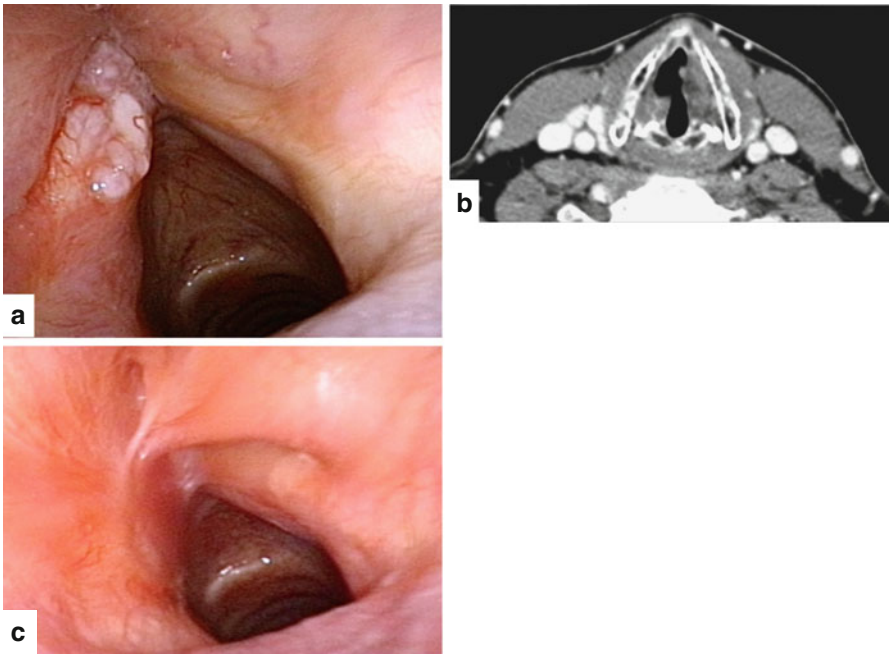

Fig. 7.1 (**a**) Endoscopic view of a squamous cell carcinoma (SCC) of the left vocal fold. (**b**) Preoperative CT scan of the same lesion showing the invasion of the left anterior paraglottic space. (**c**) Endoscopic view 3 years after TLM

affecting the supra- and/or subglottis (T2–T3 transcommissural lesions), in which endoscopic dissection may be more troublesome [45–50].

For some authors [39], radical control of disease by a transoral approach cannot be achieved when the lesion involves the laryngeal framework and/or tends to grow outside the laryngeal box. The efficiency of CT or MRI to preoperatively diagnose minimal cartilaginous involvement is around 60–80 %; [44, 51] therefore, cartilage infiltration is often an intraoperative finding, accompanied by the impossibility to obtain frozen sections on cartilaginous tissue. The removal of a cartilage window or extensive vaporization of the involved thyroid laminae recommended by some authors [32–34] is not a guarantee of good oncologic results [38, 39, 52, 53].

Vocal cord mobility is another crucial issue: vocal fold fixation (associated or not with arytenoid fixation, [33, 38]) represents an independent risk factor for local recurrence in patients treated by TLM, with 5-year local control ranging between 50 and 70 % [54]. As proposed by Holsinger et al., tumors with complete fixation of the arytenoid and vocal cord should be classified as T3b, while tumors with scarce mobility or cord fixation, but with a functional cricoarytenoid joint, should be categorized as T3a. Only the latter are amenable to partial or subtotal removal of the arytenoid [55]. Although it is technically possible to perform total arytenoidectomy, this extreme endoscopic procedure has functional limitations, with frequent secondary aspirations.

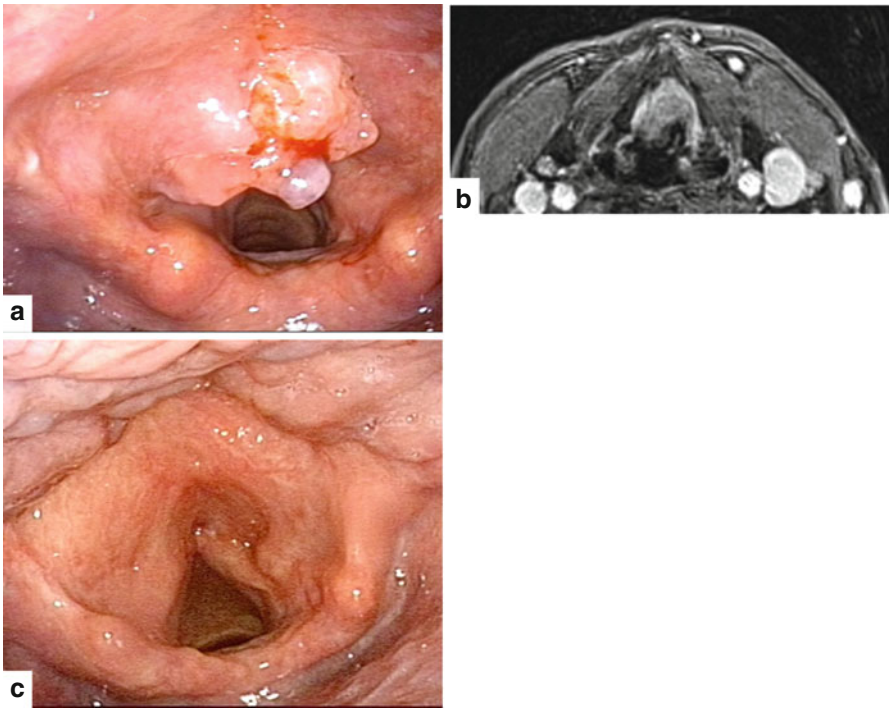

Fig. 7.2 (**a**) Endoscopic view of an SCC invading the infrahyoid portion of the epiglottis. (**b**) Preoperative MRI showing partial involvement of the preepiglottic space without infiltration of the thyroid cartilage. (**c**) Endoscopic view 2 years after TLM

Moderate infiltration of the paraglottic and preepiglottic space can be managed by TLM: however, the narrow space of work in the posterior crico-thyro-arytenoid corner, in comparison with the relatively wider view allowed at the supraglottic level, may be crucial in determining a higher failure rate [39].

Another matter of debate is the decision of skipping neck dissection in cases of a clinically and radiologically negative neck (cN0). During conventional open surgery, neck dissection is generally performed at the same time as the primary resection. Many authors recommend to perform neck dissection 2 weeks after TLM as a second-stage procedure, thus decreasing the risk of laryngeal edema (and, consequently, tracheotomy) and fistula, and allowing reevaluation of the surgical field in view of the definitive histopathology [29, 37, 56]. In case of a wait-and-see policy, strict clinical examination every 2–3 months in the first 2 years, with periodic ultrasound examinations of the neck, is mandatory to identify positive nodes at an early stage in order to perform delayed neck dissection without compromising survival. Oncologic outcomes of TLM in locally-advanced glottic and supraglottic tumors are summarized in Tables 7.1 and 7.2, respectively.

From a functional point of view, the possibility to tailor the TLM resection allows various structures to be maintained. Preservation of the laryngeal framework,

Table 7.1 Review of published data on oncologic results of TLM for advanced glottic cancer

Author(s)	Number of patients	pT	Treatment	LC with TLM (follow-up)	Final LC (follow-up)	DSS (follow-up)	OS (follow-up)
Ambrosch et al. (2001) [57]	167	T3	TLM	68 % (5 y)	87 % (5 y)	62 % (5 y)	–
Motta et al. (2005) [58]	51	T3	TLM	65 % (5 y)	–	72 % (5 y)	64 % (5 y)
Grant et al. (2007) [30]	10	T3–4	TLM ± RT	45 % (4 y)	–	–	62 % (4 y)
Peretti et al. (2010) [24]	11	T3	TLM	71.6 % (5 y)	–	100 % (5 y)	–
Vilaseca et al. (2010) [54]	51	T3	TLM	47.1 % (5 y)	88.2 % (5 y)	86.3 % (5 y)	73.1 % (5 y)
Blanch et al. (2011) [44]	26	T3 (AC+)	TLM	–	80.4 % (5 y)	–	–
Peretti et al. (2013) [59]	30	T3	TLM ± RT/CRT	55 % (5 y)	–	–	–
Canis et al. (2014) [60]	122	T3	TLM ± adjuvant RT/CRT	71.5 % (5 y)	83 % OP (5 y)	84.1 % (5 y)	58.6 % (5 y)
Pantazis et al. (2015) [13]	19	T3	TLM ± adjuvant RT/CRT	52.6 % (5 y)	73.7 % (5 y)	63.2 % (5 y)	63.2 % (5 y)

AC anterior commissure, *CRT* chemoradiation, *DSS* disease specific survival, *LC* local control, *OP* organ preservation, *OS* overall survival, *RT* radiotherapy, *TLM* transoral laser microsurgery, *y* years

Table 7.2 Review of published data on oncologic results of TLM for advanced supraglottic cancer

Author(s)	Number of patients	pT	Treatment (follow-up)	LC with TLM (follow-up)	Final LC (follow-up)	DSS (follow-up)	OS (follow-up)
Iro et al. (1998) [27]	48	3–4a	TLM ± ND ± RT	83.3 % (5 y)	–	–	–
Rudert et al. (1999) [29]	17	3–4a	TLM ± ND ± RT	–	–	–	47 % (5 y)
Ambrosch et al. (2001) [57]	50	3–4a	TLM ± ND ± RT	86 % (5 y)	91 % (5 y)	71 % (5 y)	–
Motta et al. (2004) [61]	18	3	TLM	77 % (5 y)	–	81 % (5 y)	81 % (5 y)
Grant et al. (2007) [62]	10	3–4a	TLM ± ND ± RT	T3 100 % (3 y) T4 80 % (4 y)	–	–	T3 67 % (3 y) T4 75 % (4 y)
Cabanillas et al. (2008) [63]	15	3	TLM ± ND ± RT	70 % (5 y)	–	80 % (5 y)	–
Peretti et al. (2010) [24]	20	3	TLM ± ND ± RT/CRT	83 % (5 y)	–	–	–
Vilaseca et al. (2010) [54]	96	3	TLM ± ND ± RT	69.8 % (5 y)	91.7 % (5 y)	61.8 % (5 y)	45.8 % (5 y)
Canis et al. (2013) [35]	104	3	TLM ± ND ± RT/CRT	77.3 % (5 y)	92 % OP (5 y)	84.2 % (5 y)	66.5 % (5 y)
Pantazis et al. 2015 [13]	24	3	TLM ± ND ± RT/CRT	87.5 % (5 y)	91.7 % OP (5 y)	91.7 % (5 y)	87.5 % (5 y)

CRT chemoradiation, *DSS* disease specific survival, *LC* local control, *ND* neck dissection, *OP* organ preservation, *OS* overall survival, *RT* radiotherapy, *TLM* transoral laser microsurgery, *y* years

infrahyoid musculature, superior laryngeal nerves, pharyngeal constrictor muscles, and hyoid bone limits the consequences on postoperative swallowing mechanisms [59, 64–69]. This leads to a reduced need for tracheotomy or feeding tube, faster rehabilitation, and reduction of more than 50 % in hospital stay compared with open-neck procedures [59, 60, 68–70].

In studies including advanced cancers, complications have been significantly correlated with tumor size, surgeon experience, and tumor location [71]. The most significant complications reported are postoperative bleeding, aspiration pneumonia, cervical emphysema, dyspnea, local infection, and cervical fistula. Postoperative hemorrhage is the most common and feared complication due to the vital risk for patients generally without tracheotomies [33], with a similar incidence to open approaches (3–14 %) [71]. The second most frequent complication, especially in case of supraglottic laryngectomy, is aspiration pneumonia: temporary aspiration rate favorably compares with data reported after open partial approaches (32–89 %) and CRT organ preservation protocols (up to 84 %) [72–74]. In the study by Vilaseca et al., the reported rate of aspiration pneumonia in a cohort of patients with T3–4a supraglottic carcinomas treated by TLM was 6.5 % (only 1.3 % of patients had repeated pneumonia) [34].

Peretti et al., in a cohort of glottic pT2 and selected pT3, reported that postoperative subjective satisfactory swallowing was significantly better (95.7 %) compared to data reported in the literature after supracricoid partial laryngectomy (59.8 %) and CRT (61.9 %). The same trend was confirmed by objective evaluation of swallowing, with the majority of patients presenting normal function after TLM. Hospitalization time was significantly shorter compared to RT protocols (8.3 vs. 20–24 days). Moreover, reduction in perioperative morbidity following TLM seems to fit better with the overall general frail conditions of elderly patients and those with poor pulmonary function (both at higher risk of aspiration pneumonia) [59, 71].

Oropharyngeal Cancer

The majority of studies investigating the role of TLM in the treatment of oropharyngeal cancer have recruited a limited number of patients with a short follow-up [75–77]. However, a multicenter study by Haughey et al. [78] analyzed a series of 204 patients undergoing TLM for high-stage oropharyngeal cancer, 34 % with T3–T4 tumors. After resection, 117 (58 %) patients received adjuvant RT alone, whereas 33 (16 %) received adjuvant CRT. The authors documented a statistically significant difference in survival in T1–T2 vs. T3–T4 tumors ($p=0.025$), with a risk of death that was twofold greater (HR 2.0–2.3) in higher T categories. Furthermore, the group with negative margins had fewer T3–T4 cases than the positive margins group (34 vs. 50 %), but the difference did not reach statistical significance. In this series, the 3-year overall survival was 86 %, locoregional control 93 %, and the long-term GT rate approximately 4 %. Similar results have been reported for a cohort of 71 patients, including 32 % of T3–T4 lesions,

Table 7.3 Summary of survival outcomes in recent series on TLM and TORS for advanced oropharyngeal cancer

Author(s)	Number of patients	Stage	Survival (follow-up)	Local control (follow-up)
TLM				
Haughey et al. (2011) [78]	204	III–IV	*Stage III+IV* (*3 y*) OS: 86 % RFS: 88 %	LC 97 %
Canis et al. (2013) [80]	102	I–IV	*Stage III+IV* (*5 y*) OS: 56 % RFS: 60 %	*T3–T4a* (*5 y*) LC 75 %
TORS				
Weinstein et al. (2010) [81]	47	III–IV	*Stage III–IV* (*2 y*) DSS: 90 %	*Stage III–IV* (*2 y*) LC 98 %

DSS disease specific survival, *LC* local control, *OS* overall survival, *RFS* recurrence free survival, *TLM* transoral laser microsurgery, *TORS* transoral robotic surgery

who underwent CRT [79]. Three-year overall survival was 83 %, locoregional control rate 90 % (including salvage surgery), but a GT rate of 35 % was observed. A similar study by Canis et al. [80] confirmed the efficacy of TLM, demonstrating 75 % 5-year locoregional control and 56 % 5-year overall survival for tonsillar pT3 and pT4a. Only 3 % of patients needed a permanent GT after surgery and adjuvant treatment. In this view, while maintaining comparable oncologic results (Table 7.3), TLM offered better functional outcomes than CRT.

Hypopharyngeal Cancer

Approximately 70–85 % of patients affected by hypopharyngeal SCC reported in large series have stage III–IV disease at presentation, and the 5-year overall survival rate is reported to range from 15 to 45 %. In such a scenario, nonsurgical organ preservation protocols have been largely incorporated [6], but minimally invasive organ and function preserving surgery such as TLM has been investigated in the attempt to reduce CRT-related morbidities [82, 83]. However, in locally advanced tumors (T3–T4), experience with TLM is still limited and only a few institutions have treated a reasonably large cohort of patients [82, 84, 85]. Generally, TLM in hypopharyngeal SCC is the least established transoral laser procedure, even though in selected cases it has progressively replaced open partial pharyngectomies, especially in view of the better results achieved in chronic aspiration and pneumonia (Fig. 7.3) [86]. Furthermore, TLM has no age limit and tracheotomy is usually not required [87]. Tumors of the lateral pharyngeal wall are generally accessed with ease, while in tumors involving the retrocricoid area, an endoscopic approach is only suitable for lesions without cartilage or arytenoid joint involvement. In tumors of the medial wall and the apex of the piriform sinus, the absence of anatomical

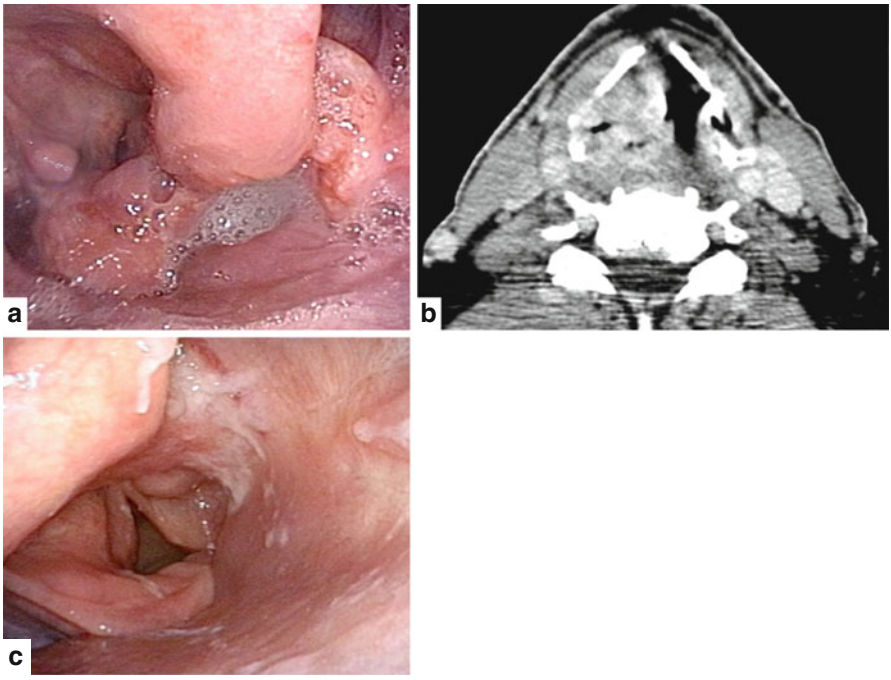

Fig. 7.3 (**a**) Endoscopic view of a T4a hypopharyngeal SCC of the right pyriform sinus and supraglottis. (**b**) Preoperative CT scan showing infiltration of the thyroid cartilage and adjacent tissues. (**c**) Endoscopic view 4 years after TLM and adjuvant CRT

barriers to the supraglottic larynx and paraglottic space allows rapid invasion of these areas. In addition, the ipsilateral supraglottis and paraglottic space lateral to the vestibular fold should be included in the resection. A contraindication to TLM for hypopharyngeal cancer is invasion of the paraglottic space lateral to the true vocal cord [86].

Most patients affected by stage III-IV disease receive adjuvant RT/CRT and local control rates are better than those obtained with nonsurgical treatment alone [88]. In such a scenario, the question is whether the intensity of adjuvant treatment should be reduced after TLM, thus making the surgery worthwhile or, on the contrary, will only increase side-effects. On one hand, surgery gives the possibility to have objective pathologic data about the true tumor extension and neck involvement. On the other, the risk of distant disease supports the use of CRT regimens as adjuvant treatment. In any case, these treatments are expensive, may increase toxicity, and reduce the possibility of its use in the not uncommon event of a second primary which may then not be treated by TLM [87]. In summary, the oncologic results of TLM in hypopharyngeal cancer appear comparable with open approaches, with a 5-year overall survival (OS) of about 40–50 % in stage III and IV, and 5-year disease specific survival (DSS) around 60 %. Higher rates of laryngeal preservation in these selected cases are also reported (Table 7.4).

Table 7.4 Oncologic results of TLM for advanced hypopharyngeal cancer

Author(s)	Number of patients	Stage	Survival (follow-up)	Local control
Steiner et al. (2001) [84]	129	III–IV	*Stage III+IV* (*5 y*) OS: 47 % RFS: 69 %	–
Vilaseca et al. (2004) [85]	28	II–IV	*Stage II+IV* (*4 y*) OS: 43 %	LC T3 56.2 % (*n*=49) LC T4 100 % (*n*=1) OP 79 %
Martin et al. (2008) [82]	172	III–IV	*Stage III* (*5 y*) OS: 64 % DSS: 86 % *Stage IV* (*5 y*) OS: 41 % DSS: 57 %	LC T3 75 % (*n*=75) (82 % plus adjuvant RT vs. 66 % without) LC T4 57 % (*n*=28)

DSS disease specific survival, *LC* local control, *OP* organ preservation, *OS* overall survival, *RT* radiotherapy, *RFS* recurrence free survival

Transoral Robotic Surgery

Laryngeal Cancer

The current size and rigidity of instruments commonly used in TORS can render a transoral robotic approach to the larynx and hypopharynx cumbersome; [89–91] furthermore, tracheotomy is often required [92]. New instruments and surgical systems that are not limited by "a straight line approach" (the Flex System, the Robo-ELF, and the MicroRALP system) [93, 94], can potentially overcome these challenges, but applicability in surgical procedures of the larynx has not yet been shown in a clinical setting [95–97].

TORS has mainly found three applications in cancer of the larynx: supraglottic laryngectomy [98, 99], total laryngectomy [100], and cordectomy [101]. When glottic cancer is considered, there are no reports on treatment of locally advanced tumors by TORS. Even for early lesions there is a lack of data on long term oncologic outcomes, while functional results (in terms of tracheotomy rate and nasogastric feeding tube) tend to be suboptimal compared to TLM [102–105].

Similarly, series on TORS supraglottic laryngectomy predominantly include early tumors (T1–T2), even though T3 lesions, based on preepiglottic space extension, are also amenable to this technique. Up to now, the overall small number of patients reported does not allow realistic comparison with other types of treatment, also considering the wide range of tracheotomy and GT rates in the different series [106–110]. Furthermore, Mendelsohn et al. described tumor stage as an important predictor of functional recovery, with low-T categories (pT1–pT2) having significant earlier return to swallowing, than more advanced ones (pT3) [111].

The rationale behind robotic total laryngectomy, although technically demanding and more costly, is to decrease postoperative morbidity and reduce recovery times [112], with a smaller pharyngotomy and maximally mucosa-sparing incisions, which minimize lateral dissection and preserve fascial barriers between the neopharynx and carotid sheaths. The indications for the procedure are yet to be well-defined and its main advantage seems to be experienced in salvage laryngectomy for functional reasons after CRT. However, to date, there are no data showing better results than open total laryngectomy [113–115].

Oropharyngeal Cancer

Before considering the potential applications of TORS for the treatment of advanced oropharyngeal squamous cell carcinomas (OPSCCs), it is essential to mention that the current staging system has relevant limitations in regard to stage grouping. For example, stage IV groups together patients with totally different disease, such as T1N2a and T4N2c. Therefore, it appears more reasonable to stratify indications for treatment based on T and N categories.

Especially in advanced tumors, the first-line approach has typically been CRT, in view of the good response and nonnegligible morbidity, even in the best hands, of conventional surgery. However, data published in the last decade have emphasized the remarkable late effects of CRT. At the same time, the striking increase of human papillomavirus (HPV)-related OPSCCs, which typically affect young patients not exposed to traditional risk factors such as smoking and alcohol, and associated with a better prognosis, have fostered the search for treatments that minimize functional sequelae without jeopardizing the disease control.

TORS have emerged in this context, showing promising potential especially for treatment of early OPSCC, but with less evidence in advanced tumors (Fig. 7.4). In this view, optimal treatment should find a balance between oncologic outcomes and functional results: on one hand, undertreatment can increase the risk of recurrence; while on the other, overtreatment can lead to worse functional results without improving survival. In high-stage OPSCC, the right balance is generally a dual-modality treatment (i.e., CRT or surgery + RT) or, in selected cases, a single-modality treatment (i.e., RT alone, or surgery alone). In some situations, TORS exposes the patient to a risk of overtreatment (i.e., triple-modality treatment: surgery + CRT) in case of positive margins or extracapsular extension at final histopathology. For this reason, in patients in whom preoperative staging reveals in advance the postoperative need for adjuvant CRT, TORS may not be the ideal choice of treatment. On the other hand, TORS provides both a therapeutic and diagnostic step that allows for assessment of pathologic findings and de-intensification of adjuvant treatment, thus avoiding chemotherapy in approximately 40 % of patients, with 10 % requiring no RT/CRT or allowing for utilization of standard postoperative RT dosages.

Taking into consideration recent data concerning the treatment of OPSCC, Lorincz et al. [116] developed a decisional algorithm including TORS, conventional

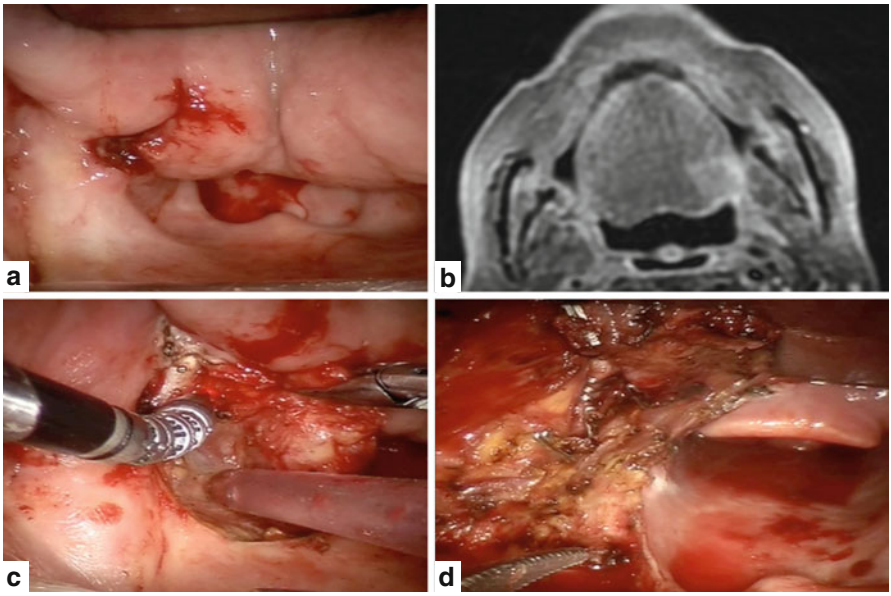

Fig. 7.4 (**a**, **b**) Intraoperative view and preoperative MRI of a T4a SCC of the left base of tongue and glossotonsillar sulcus. Deep infiltration of the tongue into the extrinsic muscles is depicted by MRI. (**c**, **d**) Intraoperative view during TORS and after tumor resection

surgery, RT, and CRT. In their evaluation, TORS + neck dissection is considered as a valuable choice in tumors with low T categories (T1 or T2) and without radiologic signs of lymph-node extracapsular extension, reserving surgery + postoperative RT (60 Gy) in N2 and N3 patients. In fact, while different authors have reported optimal outcomes even in tumors with high T classification, there is no evidence of the reproducibility of such results outside these very selected series.

To date, there is limited data on oncologic outcomes of locally advanced tumors treated by TORS, since most series prevalently include T1–T2 neoplasms, with T3–T4 approximately accounting for only 20 % of cases [101, 117–119]. In a single series, compared directly to open approaches, TORS for T1–T3 tonsillar cancer was seen to have a higher rate of negative margins and more rapid functional recovery [120], showing its potential even in moderately advanced tumors. In a study by Weinstein et al. [81], excellent disease-free survival at 1 (96 %) and 2 years (79 %) was reported in 47 patients with stage III or IV OPSCC treated by TORS (Table 7.3). Regarding the need for adjuvant therapy, 39 % each required RT or CRT. However, comparison with CRT is difficult because of the heterogeneity of the different series, with TORS patients being generally characterized by lower stage and higher prevalence of HPV positive tumors. Furthermore, morbidity is often overestimated in the nonsurgical group used for comparison. In fact, in an "all stages" MSKCC cohort treated mainly (88 %) with concurrent CRT, the authors reported GT dependency in 7 % of patients at 1 year, which compares favorably with the significantly higher

rates of functional complications after CRT reported in other studies [121–123]. Moreover, in this light, data from MSKCC are similar to those on chronic GT dependence after TORS, which in a systematic review by Hutcheson et al. [124] ranged from 0 to 7 % (mean follow-up, 11–26 months).

Transnasal Endoscopic Surgery

TES was introduced in the 1980s for treatment of inflammatory diseases of the nose and paranasal sinuses. The indications rapidly expanded to include first the management of benign tumors and subsequently the resection of malignant lesions of the sinonasal tract and nasopharynx.

The first experiences in the treatment of naso-ethmoidal malignancies were limited to lesions of different histology not encroaching the anterior skull base [125, 126]. However, with the refinement of duraplasty techniques, endoscopic surgeons started to approach even tumors eroding the skull base, invading the dura, or with limited extension to the brain (T3–T4a-b) [127–130]. The indications for TES in nasopharyngeal carcinoma vary in relation to histology. Based on the WHO classification [131], TES can be considered an alternative to re-irradiation in residual/recurrent T1, T2, and very selected T3 nasopharyngeal carcinomas or a reasonable primary treatment option in the more rarely observed salivary gland-type carcinomas or papillary adenocarcinoma.

Malignant Lesions of the Sinonasal Tract

Malignancies of the sinonasal tract are rare, accounting for 3 % of all cancers of the head and neck. Their major peculiarity is the extreme histological variability, which is frequently associated with variable natural history and response to different treatments. For a long time, surgery followed by RT or CRT has been invariably considered the standard of care for management of advanced lesions. The major advancement in surgery was the introduction in the 1960s of anterior craniofacial resection (ACR), a technique providing a reasonably good local control even to lesions encroaching on the anterior skull base. A multicenter collaborative study analyzing 1307 patients (with a reasonable number of patients in each histology group), who underwent ACR followed in most cases by radiotherapy, provided an excellent dataset on survival and morbidity outcomes to be used as a benchmark for future comparisons with alternative treatments [132, 133].

When TES was proposed for treatment of selected malignancies of the naso-ethmoidal complex, it was considered heresy, mainly for the impossibility in most cases to perform the resection according to an “en bloc” principle. However, from the beginning the philosophy guiding endoscopic surgery was to obtain radical resection of the tumor in free margins similar to external procedures. In view of the

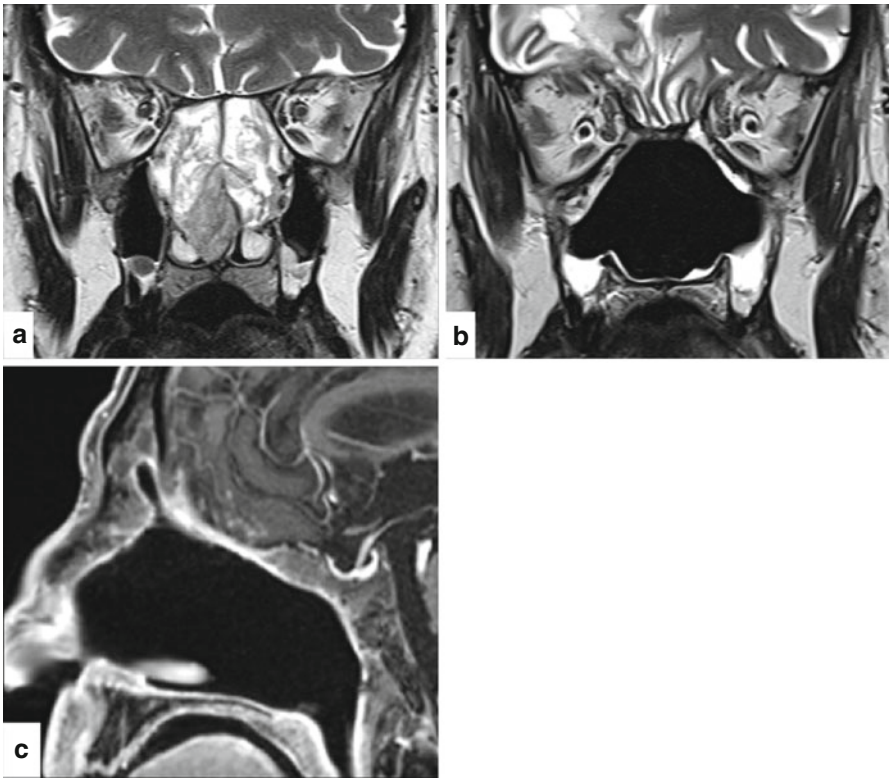

Fig. 7.5 Sinonasal adenoid cystic carcinoma in a 55-year-old man. (**a**) Coronal T2 weighted MRI sequence showing the lesion, which involves both nasal cavities with no evidence of orbital or transdural spread. Endoscopic resection with transnasal craniectomy and three-layer skull base reconstruction with iliotibial tract was performed. Histologic examination of the surgical specimen demonstrated microscopic infiltration of periobit and dura (pT4bN0M0G2). The patient underwent adjuvant RT. (**b**) Coronal T2 weighted and (**c**) contrast-enhanced sagittal T1 weighted MRI sequences show no evidence of disease and perfect healing of skull base reconstruction at 4 years after treatment

narrow access through the nostril(s), a new principle of resection ("tumor disassembling"), starting from the endonasal portion of the tumor and progressively removing in a centrifugal fashion different layers of tissue (mucoperiosteum of the naso-ethmoidal cavity on the most involved side; septum, if required; mucoperiosteum of the contralateral side; periorbit and/or dura, in relation to tumor extent), was introduced [127]. When dura of the anterior cranial fossa is resected, duraplasty is performed preferably with autologous material, with a multilayer technique [134] (Figs. 7.5, 7.6 and 7.7).

There are still "anatomic" contraindications for the use of TES in malignant tumors of the sinonasal complex. Basically, this technique is not suitable for lesions of the maxillary sinus, apart the very rare cases limited to its medial wall, and finds its main playground in naso-ethmoidal tumors. Contraindications within this group

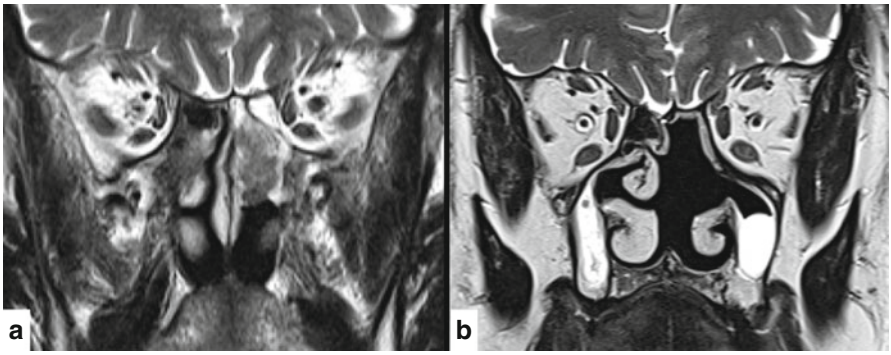

Fig. 7.6 Sinonasal intestinal-type adenocarcinoma in a 64-year-old male woodworker. (**a**) Coronal T2 weighted MRI sequence shows the lesion localized in the posterior ethmoid and confined to the left nasal cavity. Endoscopic resection with unilateral transnasal craniectomy and two-layer skull base reconstruction was performed. Histologic examination of the surgical specimen was consistent with intestinal-type adenocarcinoma pT2N0M0G2. No adjuvant radiotherapy was added. (**b**) Coronal T2 weighted MRI sequence shows no evidence of disease and regular healing of the surgical cavity 2 years after treatment

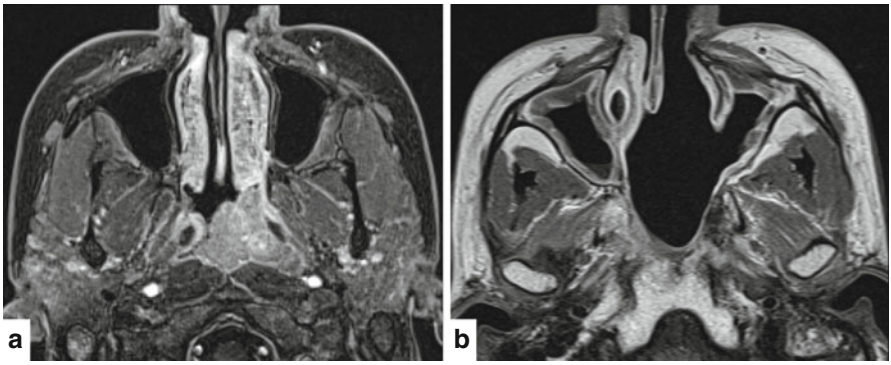

Fig. 7.7 Nasopharyngeal adenoid cystic carcinoma in a 32-year-old woman. (**a**) Contrast-enhanced axial T1 weighted MRI sequence shows the lesion centered in the left nasopharynx with contralateral extension along the posterior wall. Bilateral type III nasopharyngeal endoscopic resection was performed as primary treatment. Histologic examination of the surgical specimen confirmed the histologic diagnosis and showed the presence of perineural spread. The patient underwent adjuvant RT. (**b**) Axial T2 weighted MRI sequence shows no evidence of disease at 7 years after treatment

include infiltration of nasal bones and palate, massive involvement of the frontal sinus, gross invasion of the lacrimal pathway, extension into the infratemporal fossa, involvement of the orbital content, extension of dura involvement beyond the meridian of the orbit, and massive invasion of brain parenchyma. These situations require a combination of endoscopic and external approaches.

Other than the extent of tumor to critical areas, which limits the indications for TES, there are biologic features of the tumor itself, which in general suggest

adopting a nonsurgical treatment strategy, such as concomitant CRT, or use of neoadjuvant chemotherapy to select the next step (CRT or surgery followed by CRT). This approach seems applicable in high-grade tumors (i.e., poorly differentiated SCC, sinonasal undifferentiated carcinoma, neuroendocrine carcinoma, NUT midline carcinoma) [135, 136], which are associated with a high risk of distant metastasis and are frequently diagnosed at an advanced local stage requiring extensive and mutilating surgery.

Twenty-five years after TES was proposed as an alternative to ACR, it is time to try to compare the two techniques with regards to survival and morbidity outcomes. However, there are factors which include the rarity of the disease, histologic heterogeneity, and the length of follow-up in relation to the propensity of some tumors to recur many years later, which made it difficult to accrue large series with sufficient follow-up to make statistically robust comparisons [130]. The three major series (Table 7.5), collected at two Italian Tertiary referral centers, at the M.D. Anderson Cancer Center in Houston, and at the Royal National Throat Nose & Ear Hospital in London, respectively, include a number of patients ranging from 120 [128] to 184 [127]. In spite of the different distribution by histology, with a prevalence of olfactory neuroblastoma in the series from the USA [128] and UK [130], and adenocarcinoma in the Italian study, the results in terms of oncologic outcomes are similar, with 5-year OS varying from 76 to 84 %, and DSS from 82 to 87 %. When morbidity is considered, it is noteworthy that complications occurred in 9–11 % of patients, and no death in the postoperative period was observed. Although the comparison with the results of the collaborative study on ACR is hindered by the different distribution of patients by stage, with a higher rate of advanced tumors in the ACR group, the reported 5-year OS and DSS of 54 % and 60 %, respectively [132], a 36.3 % complication rate, and 4.7 % mortality rate [133] suggest that ETS may favorably compete with ACR in specific indications.

This assumption was confirmed by the results of a very recent paper, which compared the outcomes of endoscopic and open surgery in 82 and 42 patients, respectively, by using a propensity score matching analysis to normalize the differences in comorbidities for the comparison [137].

In the attempt to overcome the limitations related to histologic diversity, several studies have concentrated on the results of ETS in specific histotypes. At the same time, some speculations on the indications for adjuvant therapy have been offered.

Olfactory neuroblastoma is most likely the tumor with the highest number of specific reports [138–142]. A recent systematic review and meta-analysis of 36 studies on 609 patients comparing the results of open surgery vs. ETS concluded that the two techniques have comparable results in relation to long-term survival and oncologic outcomes [143]. However, the rate of intracranial and overall complications was significantly higher in the external surgery group, 20.1 % vs. 7.5 % and 52.9 % vs. 28.1 %, respectively [143]. Following the first extensive review on treatment results of olfactory neuroblastoma [144], the recommended treatment is surgery followed by RT. Since that time, the situation is relatively unchanged, even in view of the nonnegligible tendency of the tumor to metastasize to lymph nodes [145], with the need to include the first echelons in the irradiation plan. Notwithstanding,

Table 7.5 Characteristics of the three largest sinonasal malignant tumors endoscopic resection series to date

	Nicolai et al. (2008) [127]	Hanna et al. (2009) [128]	Lund et al. (2015) [130]
Number of cases, *n*	184	120	140
Reporting period	1996–2006	1992–2007	1996–2014
Mean age, years	59	53	63
Male sex, *n* (%)	117 (64)	65 (54)	68 (49)
Surgical approach, *n* (%)			
Endoscopic	134 (73)	93 (77)	140 (100)
Cranioendoscopic	50 (27)	27 (23)	–
Prior treatment, *n* (%)	52 (28)	70 (58)	25 (22)
T stage, *n* (%)			
1	52 (28)	30 (25)	57 (41)
2	26 (14)	30 (25)	27 (19)
3	32 (17)	25 (21)	41 (29)
4	52 (41)	35 (29)	17 (11)
Histology, %			
Esthesioneuroblastoma	22 (12)	20 (17)	36 (26)
Adenocarcinoma	68 (37)	17 (14)	19 (14)
Squamous cell carcinoma	25 (14)	16 (13)	9 (6)
Mucosal melanoma	17 (9)	17 (14)	33 (24)
Adenoid cystic carcinoma	13 (7)	8 (7)	1 (1)
Others	39 (19)	42 (29)	42 (29)
Adjuvant treatment, *n* (%)	86 (47)	60 (50)	95 (68)
Complications, *n* (%)	16 (9)	13 (11)	14 (10)
CSF leak	8 (4)	4 (3)	3 (2)
Mean follow-up, months	34	37	60
Survival results, %			
5 year	82 (DSS)	87 (DSS) 76 (OS)	−84 (OS)
10 year	– –	80 (DSS) 50 (OS)	−69 (OS)
Site of recurrence, *n* (%)			
Local	28 (15)	18 (15)	14 (11)
Regional	2 (1)	7 (6)	10 (7)
Distant	13 (7)	6 (5)	12 (9)

DSS disease specific survival, *OS* overall survival

future studies should address if adjuvant RT is actually indicated in early cases, Hyams grade I–II, treated with aggressive surgery (unilateral resection of the anterior skull base and olfactory bulb), negative margins, and no intracranial extension at definitive pathologic examination.

Adenocarcinoma has been extensively studied in Europe where the large majority of cases are intestinal-type adenocarcinomas (ITAC) [146–148], a disease typically

affecting wood and leather workers. Based on the analysis of the results of three studies which included treatment outcomes in 451 patients [146–148], Nicolai et al. [148] concluded that there is evidence-based support for the use of ETS, when planned according to precise indications and contraindications, as the surgical treatment of choice for ITAC. The missing link in the comparison between the efficacy of external and endoscopic approaches was provided by a recent single institution, retrospective, comparative study [149]. By analyzing two groups of patients with ITAC that were homogeneous in terms of stage, histologic findings, and adjuvant therapy, treated with an external ($n=31$) or endoscopic ($n=43$) approach, Grosjean et al. [149] observed a 3-year OS of 61.3 % and 76.7 %, respectively. Similarly to the majority of the other histologies, adjuvant RT has been always recommended in adenocarcinoma. However, a recent retrospective case-control study comparing results in two cohorts of patients with T1–T2 adenocarcinoma receiving ETS, with or without adjuvant RT, suggests that RT can be spared in patients with low-grade tumors resected in free margins [150].

Malignant mucosal melanoma is the second or third most prevalent malignancy in the major series of tumors treated by ETS (Table 7.5). Specific studies on this very aggressive tumor are rare [151–155], and all group together patients treated with different surgical approaches. In spite of the many limitations which affect comparison of the results, at least in three studies [152–154] the conclusion is that ETS is not associated with an increased risk of death. Five-year OS is in the range of 28–38 % [152, 154]. Although the role of adjuvant RT is controversial, some data suggest benefits in local control of disease, without, however, any benefit on OS [155].

Malignant Lesions of the Nasopharynx

Surgery has always played a limited role in management of nasopharyngeal malignancies in view of the difficulty in accessing an area located in the center of the skull and the otherwise good response, in particular of NPC, to RT and CRT. External approaches, such as the infratemporal [156] and maxillary swing [157], which have been proposed for the treatment of selected residual/recurrent lesions, have gained limited popularity because of related sequelae and potential complications. The first report on the use of ETS to treat nasopharyngeal carcinoma was by Yoshizaki et al. [158]. As expected in relation to the epidemiological distribution of the tumor, which is endemic in southeast China and Hong Kong, most studies are from this geographic area [159–161] and only a few from Europe [162] and USA [163]. There is general agreement that endoscopic resection is one of the treatment options together with re-irradiation and external surgery in residual/recurrent nasopharyngeal carcinomas (NPC) (T1–T2 and selected T3 with minimal bone erosion involving the floor of the sphenoid sinus). Additional indications include primary treatment of papillary adenocarcinoma or salivary gland-type carcinomas, which are well known to be less radiosensitive than NPC. Absolute contraindications for ETS are

Table 7.6 Characteristics of the four largest nasopharyngeal malignant tumors endoscopic resection series to date

	Chen et al. (2009) [159]		Ko et al. (2009) [165]		Castelnuovo et al. (2013) [162]		You et al. (2015) [160]	
Number of cases, *n*	37		28		36		72	
Reporting period	2004–2008		2004–2007		1997–2011		2001–2009	
Stage of primary tumors, *n*	–	–	–	–	9	5 T1 1 T2 2 T3 1 T4	–	–
Stage of recurrent tumors, *n*	37	17 rT1 18 rT2 2 rT3	28	12 rT1 16 rT2	27	12 rT1 1 rT2 13 rT3 1 rT4	72	32 rT1 27 rT2 13 rT3
Histology, *n* (%)								
NPC	37 (100)		28 (100)		23 (64)		72 (100)	
Adenoid cystic carcinoma	–		–		4 (11)		–	
Adenocarcinoma	–		–		4 (11)		–	
Others	–		–		5 (14)		–	
Positive margins, *n* (%)	13 (5)		3 (10)		3 (8)		–	
Median follow-up, months	24		13		33		49	
Survival results	2-y OS 84 % 2-y DFS 86 %		2-y OS 59 % 2-y DFS 58 %		5-y OS 75 % 5-y OS 58 %		5-y OS 77 % 5-y DFS 67 %	

DFS disease free survival, *m* months, *NPC* nasopharyngeal carcinoma, *OS* overall survival, *y* years

extensive erosion of the skull base, intracranial involvement, invasion of the orbital tissues, and intimate contact of the tumor with the internal carotid artery.

There are basically three different types of nasopharyngeal endoscopic resection (NER) [162, 164]. In Type 1 NER, the resection is limited to the posterosuperior nasopharyngeal wall, reaching the bony floor of the sphenoid sinus superiorly and the pharyngobasilar/prevertebral fascia posteriorly. Type 2 NER superiorly extends to include the anterior wall and the floor of the sphenoid sinus, as well as the rostrum. Type 3 NER is the most complex resection and requires a transmaxillary-transpterygoid approach to expose and remove the cartilaginous portion of the Eustachian tube and soft palate muscles (tensor and levator veli palatini). It is suitable for lesions laterally extending to the torus tubarius and the Rosenmuller fossa.

No prospective studies comparing survival outcomes of different surgical techniques or ETS and re-irradiation in recurrent NPC have been reported to date, and thus the present recommendations for treatment are based on studies with a low level of evidence (Table 7.6). A meta-analysis on 17 retrospective studies including 779 patients treated with surgery (open or ETS) for recurrent NPC reported that more than half of patients treated were salvaged by surgery. Interestingly, the overwhelming majority (83 %) were T1–T2 lesions. The 5-year OS and local

recurrence-free survival rates for the entire cohort were 51.2 % and 63.4 %, respectively. Multivariate analysis revealed that ETS offers better outcomes than open surgery for T3–T4 tumors in selected patients, and adjuvant re-irradiation provides an additional survival advantage over surgery alone [166].

Two recent Chinese studies from Sun Yat-sen University Cancer Center in Guangzhou have shed light on the role of ETS and its advantages compared with RT [160, 161]. The first is a retrospective analysis of 410 patients treated for recurrent NPC with IMRT, ETS, or 2D conventional RT [161]. Despite the authors' recognition that the distribution by T category was not homogeneous in the three treatment groups, with a significantly higher number of recurrent T1–T2 in the ETS group, subgroup analysis of T1–T2 showed that ETS was associated with better 5-year OS than IMRT and 2D conventional RT. In the subgroup of patients with recurrent T3–T4 NPC, although ETS still presented higher OS than IMRT and 2D conventional RT, all patients who received ETS were recurrent T3 and highly selected, with disease confined in the floor of the sphenoid sinus [161].

The second study went deeper further analyzed the results between ETS and IMRT in selected T1–T3 recurrent NPC by performing a retrospective case-matched analysis on 144 patients [160], 72 in each arm, which were well balanced in relation to prognostic factors based on propensity scores. Compared with IMRT, ETS was associated with significantly better 5-year OS (77.1 vs. 55.5 %, $P = .003$), quality of life conservation (mean global health status score 57.6 vs. 29.8 %; $P < .001$), significant decrease in posttreatment complications (12.5 vs. 65.3 %; $P < .001$) and, specifically, in complication-related deaths (5.6 vs. 34.7 %; $P < 0.001$). Medical costs of ETS were also significantly lower. Even though the conclusions are extremely important, the study suffers some limitations: neoadjuvant chemotherapy was delivered more frequently in the IMRT than in the ERS group; frozen sections were obtained in only some patients in the surgical group; and there is no mention of surgical margin status.

The possibility to use TORS to perform salvage nasopharyngectomy has also been described [167]. However, to increase the limited exposure enabled by the standard equipment via a transoral route, a longitudinal split of the soft palate has been recommended, which indeed increases the potential for complications related to the intervention. Another limitation of present technology is the impossibility to use drills or rongeurs to remove bony structures, which can be overcome by combining the use of ETS with TORS [168]. However, an important question arises: why two different tools, with an increase in costs, should be used in the nasopharynx if ETS at present shows better performance?

Conclusions

Technology is rapidly evolving and provides surgeons with new tools that arouse our curiosity, but which need to be judiciously tested in a preclinical setting and, subsequently, in clinical practice. The main goal is to offer patients treatments that can compete with standard nonsurgical and surgical methods considering survival

and morbidity. Appropriate evaluation of numerous outcomes pertaining to disease control, complications, quality of life possibly in the context of clinical trials together with analysis of costs is mandatory to provide evidence of the efficacy and efficiency of any "new method."

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