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HEAD AND NECK

Supratracheal laryngectomy: current indications and contraindications

Laringectomia sopratracheale: indicazioni e controindicazioni

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SUMMARY

Cancer of the larynx in the intermediate/advanced stage still presents a major challenge in terms of controlling the disease and preserving the organ. Supratracheal partial laryngectomy (STPL) has been described as a function-sparing surgical procedure for laryngeal cancer with sub-glottic extension. The aim of the present multi-institutional study was to focus on the indications and contraindications, both local and general, for this type of surgery based on the long-term oncological and functional results. We analysed the clinical outcomes of 142 patients with laryngeal cancer staged pT2-pT4a who underwent STPL. Five-year overall survival (OS), disease-specific survival (DSS), disease-free survival (DFS) and loco-regional control (LRC) rates were: glottic pT2 [71.4%, 95.2%, 76.0%, 76.0%], glottic-transglottic pT3 [85.3%, 91.1%, 86.4%, 88.7%], and pT4a [73.2%, 88.1%, 52.7%, 60.7%], respectively. DFS and LRC prevalences at 5 years were greatly affected by pT4a staging. Five-year laryngeal function preservation (LFP) and laryngectomy free survival (LFS) were: glottic pT2 [90.9%, 95.2%], glottic-transglottic pT3 [84.4%, 93.1%], and pT4a [63.7%, 75.5%], respectively, being affected by pT staging and age 65 ≥ years (LFP 54.1%). As a result of Type III open horizontal partial laryngectomies (OPHLs) (supratracheal laryngectomies), the typical subsites of local failure inside the larynx were the mucosa at the passage between the remnant larynx and trachea, the mucosa at the level of the posterior commissure and the contralateral cricoarytenoid unit as well as outside the larynx at the level of the outer surface of the remnant larynx. For patients with glottic or transglottic tumours and with sub-glottic extension, the choice of STPL can be considered to be effective, not only in prognostic terms, but also in terms of functional results.

KEY WORDS: Laryngectomy • Laryngeal cancer • Contraindications

RIASSUNTO

Il cancro della laringe in fase intermedio / avanzata rappresenta ancora una grande sfida in termini di controllo della malattia e di preservazione d'organo. La laringectomia parziale sopratracheale (STPL) è stata descritta come procedura chirurgica di function-sparing per il cancro della laringe con estensione sub-glottica. Lo scopo del presente studio multi-istituzionale è di concentrarsi sulle indicazioni e controindicazioni, sia locali che generali, per questo tipo di chirurgia sulla base dei risultati oncologici e funzionali a lungo termine. Abbiamo analizzato i risultati clinici di 142 pazienti con cancro della laringe in stadio pT2-pT4a sottoposti a STPL. A cinque anni i tassi di sopravvivenza globale (OS), di sopravvivenza malattia specifica (DSS), di sopravvivenza libera da malattia (DFS) e di controllo loco-regionale (LRC) sono risultati rispettivamente: pT2 glottici [71,4%, 95,2%, 76,0%, 76,0%], pT3 glottici-transglottici [85,3%, 91,1%, 86,4%, 88,7%], e pT4a [73,2%, 88,1%, 52,7%, 60,7%]. La DFS ed il LRC a 5 anni sono risultati fortemente influenzati dallo stadio pT4a. A cinque anni i tassi di conservazione della funzione laringea (LFP) e la sopravvivenza libera da laringectomia (LFS) sono risultati: pT2 glottici [90,9%, 95,2%], pT3 glottici-transglottici [84,4%, 93,1%] e pT4a [63,7%, 75,5%], risultando negativamente influenzati dal pT staging e dall'età di 65 ≥ anni (LFP 54,1%). A seguito di laringectomia parziale sopratracheale le sedi tipiche di recidiva sono risultate all'interno della laringe la mucosa al passaggio fra laringe residua e trachea, la mucosa a livello della commissura posteriore, l'unità cricoaritenoidica controlaterale e all'esterno la superficie esterna della laringe residua. Per i casi di tumore glottico con estensione subglottica o di tumore con importante estensione transglottica, la scelta di una STPL può essere considerata efficace, non solo in termini prognostici, ma anche in termini di risultati funzionali.

PAROLE CHIAVE: Laringectomia parziale • Cancro della laringe • Indicazioni • Controindicazioni

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Introduction

The subglottic extent of a glottic or transglottic tumour is often difficult to detect preoperatively, has a large propensity for extralaryngeal spread and poor prognosis, espe-

cially when adopting conservative therapeutic protocols such as chemoradiotherapy, transoral laser surgery or open partial laryngectomy¹⁻³.

In 1972, Italo Serafini⁴ reported a new type of open partial laryngectomy called tracheohyoidoepiglottopexy aimed at

managing laryngeal cancer with subglottic extension: this procedure entailed the preservation of the suprahyoid epiglottis as well as the pexy of the hyoid bone and the residual epiglottis to the first tracheal ring. Because of removal of both arytenoids, the resulting functional outcomes were poor and Serafini abandoned this technique in the early 1980s.

In the 1990s, Laccourreye et al.⁵ applied a modification of conventional supracricoid partial laryngectomy (SCPL), removing the cricoid ring in the case of glottic tumours with anterior sub-glottic extension: this has opened the way for “functional” supratracheal partial laryngectomies (STPL), whose current version was described in 2006 by Rizzotto et al.⁶

Nowadays, STPL involves resection of the entire glottic and subglottic sites along the thyroid cartilage, sparing both or at least one functioning cricoarytenoid unit (i.e. half of the posterior cricoid plate, with the corresponding arytenoid and the intact inferior laryngeal nerve on the same side). Inferiorly, the limit of resection encompasses the cricoid reaching the first tracheal ring.

Recently, the European Laryngological Society proposed a classification of the more commonly adopted procedures according to the extent of resection⁷, including three types of OPHL: Type I – supraglottic, Type II – supracricoid, and Type III – supratracheal.

In our practice, OPHL Type III expands the indications suggested by the National Comprehensive Cancer Network (NCCN) and the Italian Head and Neck Society (IHNS) guidelines for the treatment of laryngeal cancer with conservative surgery (T1–T2, N0 or selected T3): some problematic glottic cT3 (i.e. sub-glottic extension and cricoarytenoid joint invasion) and some large glottic-transglottic cT3 now became manageable by OPHL, showing promising oncological and functional results^{8,9}. With great caution, the same practice can be considered to be an upfront option in a very limited number of cT4a cases, with minimal anterior extralaryngeal extension, when it is reasonable to expect an exclusive treatment.

The aim of the present study is to focus on the indications and contraindications, both local and general, for this type of surgery. A multicentric retrospective outcome analysis of 142 patients, suffering from glottic/transglottic laryngeal squamous cell carcinoma (SCC) with subglottic extension in intermediate/advanced stage, was carried out over a 10-year period during which organ-preservation protocols with chemoradiotherapy or total laryngectomy were applied as conventional therapeutic options for these types of locally advanced tumours.

Materials and methods

Patients

All patients were from the Hospital of Vittorio Veneto, Treviso, the Martini Hospital of Turin, the San Raffaele Hospital of Milan, and the Policlinico Hospital of Modena. Selection

was based on clinical and radiologic evaluation performed within 3 weeks of surgery, to evaluate the superficial and depth extent of the tumour, as previously described¹⁰.

Inclusion criteria were histological diagnosis of intermediate/advanced stage glottic or transglottic laryngeal SCC⁸, laryngeal chondrosarcoma¹¹ or other rare tumours, and a Karnofsky index¹² higher than 80.

The tumours were glottic in 113 patients and transglottic in 29 patients. Vocal fold mobility was: 31 cases with normal or impaired vocal cord mobility (22 glottic pT2, 9 supraglottic pT4a), 52 cases with fixed vocal cord and mobile cricoarytenoid joint (10 transglottic pT3, 3 supraglottic pT4a, 16 glottic-subglottic pT3, and 23 glottic pT4a) and 59 cases with fixed vocal cord and cricoarytenoid joint (7 transglottic pT3, 31 glottic-subglottic pT3, and 21 glottic pT4a).

Exclusion criteria were severe diabetes mellitus, severe bronchopulmonary chronic obstructive disease, neurological problems impairing the ability to expectorate and/or swallow, or severe cardiac disease. Advanced age, an important cut-off for relative surgical indication¹³, was not considered, in itself, an exclusion criterion.

Surgery

After informed consent had been obtained, 142 patients were selected to undergo Type III OPHL between August 29, 2002 and December 28, 2012.

Despite the fact that most of these cases had already been included elsewhere⁹, the preoperative and intraoperative records, and pathological reports were reviewed to allow proper reclassification of these cases according to the 2002 TNM classification system¹⁴.

Forty-eight patients (33.8%) included in the present analysis had been treated previously for laryngeal carcinoma by CO₂ transoral laser surgery (27 of 142; 19.0%), (chemo)-radiation therapy (12 of 142; 8.5%), open partial laryngectomy (4 of 142; 2.8%), or cordectomy (5 of 142; 3.5%).

Accordingly to the European Laryngological Society Classification⁷, only Type III OPHLs were performed, where “+CAU” represents the removal of one cricoarytenoid unit: Type IIIa (supratracheal partial laryngectomy/tracheo-hyoido-epiglottopexy) = 13 (9.2%), Type IIIa + CAU = 108 (76.1%), Type IIIb (supratracheal partial laryngectomy/tracheo-hyoido-pexy) = 7 (4.9%), Type IIIb + CAU = 14 (9.9%). In all patients, resection margins were examined intraoperatively with frozen sections: when positive, the resection was expanded until margins were negative. The margins of the surgical specimen were always checked again upon definitive pathology.

Neck dissection (ND), graded according to the American Academy of Otolaryngology-Head and Neck Surgery Foundation classification¹⁵, was performed in 101 patients (71.1%) and was monolateral in 56 (55.4%) and bilateral in 45 (44.6%) cases. ND was elective (ND levels II–IV) in 90 cN0 patients (63.4%), and curative (ND levels II–V

+ internal jugular vein in one case) in 11 cN > 0 patients (7.7%). In 67 patients, whole level VI or unilateral paratracheal lymph node clearance was added. No ND was performed in an additional 41 patients (28.9%) (elderly and/or cN0 disease or in previously treated neck).

Postoperative care and adjuvant treatments

All patients were monitored for early complications (local and general) and late sequelae. Apart from those with serious early complications, patients underwent the same rehabilitation protocol, which included: (1) insertion of an uncuffed tracheal cannula and beginning of phonation (days 1 to 4); (2) intermittent occlusion of the tracheostomy with saline-soaked gauze and starting of feeding without the tracheal cannula in position (days 4 to 6); (3) nasogastric (NG) tube removal as soon as a good level of swallowing of both solids and liquids had been achieved (day 6 onwards)¹². Postoperative aspiration was graded in accordance with Pearson's scale¹⁶ (0 = none; I = occasional cough but no clinical problems; II = constant cough worsening with meal or swallowing; III = pulmonary complications).

Adjuvant treatments

On the basis of pathological findings (pN+ and/or extracapsular spread (ECS), large extralaryngeal extent), 41 patients (28.9%) were subjected to adjuvant radiotherapy. The indications for adjuvant therapy were: 13 N+ (8 level VI N+ and 5 pN2) and 28 cases with extralaryngeal extent (9 supraglottic pT4a and 19 glottic pT4a).

A large volume encompassing the primary site and all draining lymph nodes was irradiated with a dose of up to 54 Gy/2 Gy. Regions at higher risk for malignant dissemination received a 12-Gy boost (total 66 Gy/2 Gy – range 62–68 Gy). Six of 41 patients (level VI- Delphian node pN+ and pN2 with ECS, and pT4a showing close margins toward pre-laryngeal tissues) also received 100 mg/m² cisplatin on days 1, 22 and 43 of the course of radiotherapy¹⁷.

Statistical methods

Overall survival (OS), disease-specific survival (DSS), disease-free survival (DFS), loco-regional control (LRC), local control (LC), laryngectomy-free survival (LFS) and laryngeal function preservation (LFP) were assessed by Kaplan–Meier curves. Log-rank and Gehan-Breslow-Wilcoxon tests (for early events) were used to compare Kaplan–Meier estimates between groups (staging, clinical history of previous treatment, and age). The corresponding incidences were evaluated by chi-squared tests. The endpoints considered were obtained as the length of time from the date of diagnosis to: OS – the date of death; DSS – the date of death from the disease; DFS – the date of the first recurrence; LRC – the date of the first loco-regional recurrence; LC – the date of the first local recurrence; LFS – the date of total laryngectomy; LFP – the date of total laryngectomy or presence of tracheostomy,

NG tube, gastrostomy feeding, or non-intelligible voice. All analyses were performed with GraphPad Prism version 6.0c (GraphPad Software, San Diego CA, USA), with $p < 0.05$ as the statistically significant cut-off.

Results

Patients

In total, 148 patients undergoing STPLs were initially included in this study. After excluding those treated for non-SCC, a cohort of 142 patients undergoing Type III OPHLs was considered. Current or former smokers made up 92% of the cohort. Patients were followed for a mean period of 3.29 years.

Pathology

All patients suffered from a biopsy-proven glottic or transglottic laryngeal SCC, which was classified as pT2, pT3 or pT4a, according to the 2002 TNM classification system¹⁴. Furthermore, pathology reports indicated close margins (< 2 mm) in 13 cases (9.1%), and positive margins were not found in any case at definitive histopathologic examination. One hundred and thirty-one patients (92.3%) had been staged as cN0 by palpation and neck CT scan or MRI. Overall, lymph node metastases were detected in 13/142 patients (9.1%), of whom 5 (3.5%) had multiple metastases.

Survival and disease control

The 5-year OS, DSS, DFS, LRC, and LC were 78.7%, 90.4%, 69.1%, 73.8% and 80.6%, respectively (Fig. 1). At last follow-up, a total of 24 patients had died, of whom 12 had died from the cancer under study.

Chart data stratification

Locally intermediate/advanced laryngeal carcinomas differ greatly in surgical indications and prognosis. The analyses were hence conducted on the basis of pathological staging to obtain homogeneous prognostic data. By stratifying the chart data, we evaluated whether pT, previous treatment, or age could affect the DSS, DFS, or LRC end points in terms of prevalence (Fig. 2).

We found that none of the factors affected DSS at 5 years. Indeed, the 5-year DSS of pT2 tumours was 95.2%, while those of pT3 and pT4a SCC were 91.1 and 88.1%, respectively. Similarly, the 5-year DSS of previously-treated patients was very comparable to that of untreated patients (91.2 and 90.5%, respectively). Finally, slight differences in DSS outcome, although not statistically significant, were found between older and younger patients (88.2 and 91.2%, respectively).

DFS and LRC prevalence at 5 years were greatly affected by local staging. Despite pT2 and pT3 carcinomas displaying comparable DFS prevalence (76.0 and 86.4%, respectively), the 5-year DFS of pT4a tumours was on-

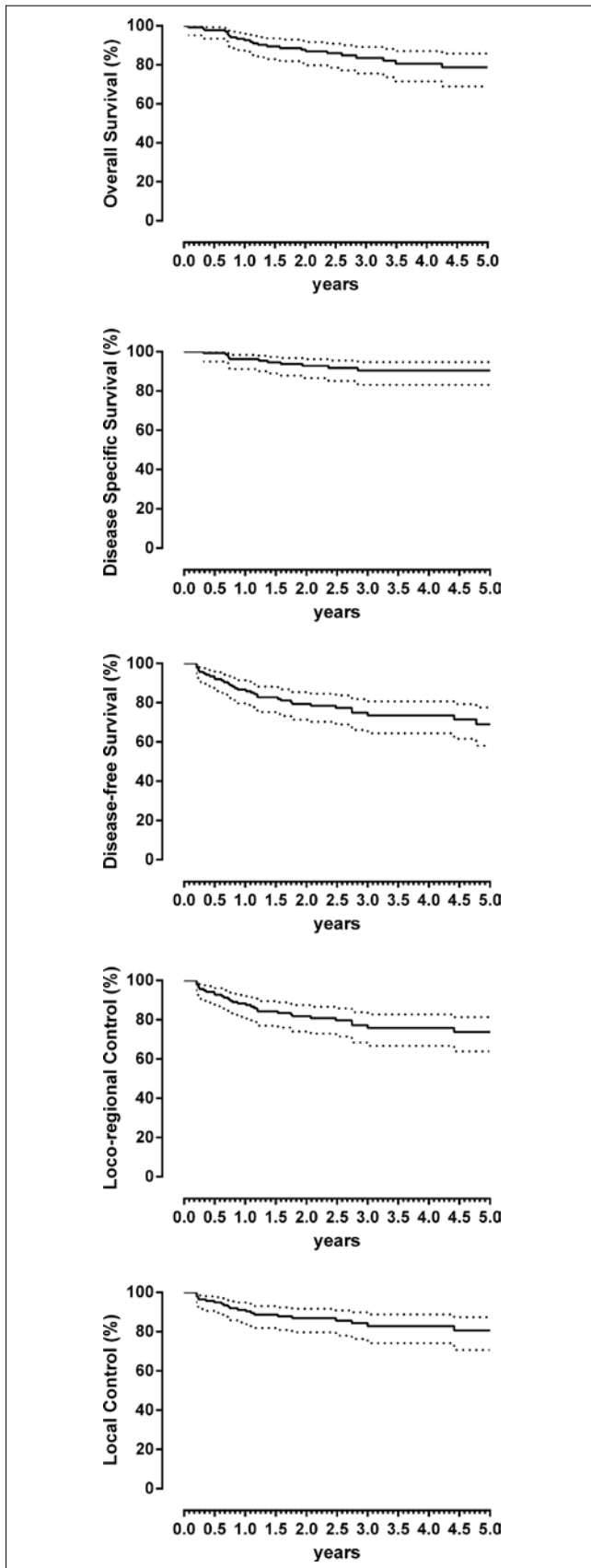


Fig. 1. Overall survival, disease-specific survival, disease-free survival, loco-regional control and local control over a 5-year period in 142 patients with laryngeal cancer staged pT2–pT4a who underwent supratracheal partial laryngectomy.

ly 52.7% ($p < 0.05$); the same pattern was also evident for the LRC endpoint: 76.0% in pT2, 88.7% in pT3, but 64.8% in pT4a patients. Otherwise, the clinical history of previous treatment or age did not affect the 5-year rates of DFS and LRC. In fact, DFS and LRC were 61.0% and 73.2% in pre-treated patients, whereas they were 71.3 and 74.5%, respectively, in patients undergoing OPHL Type III as primary surgery. Similarly, age did not correlate with DFS and LRC: older patients had a prevalence of 67.3% for DFS and 72.3% for LRC, while younger ones had a prevalence of 70.6 and 74.7%, respectively. Finally, in terms of incidence, the overall analyses of the endpoints considered are reported in Table I.

Patterns of failure

Loco-regional recurrences affected 30 patients within 5 years from surgery. According to the site of pathology, they were sub-grouped as 21 local (70.0%) and 9 regional (30.0%) recurrences. Local recurrences were observed in 13 (13.8%) untreated and 8 (16.7%) pre-treated patients. Among these, 3 had subglottic extension and inclusion of a cricoarytenoid joint, 1 had surface extension as far as the inferior edge of the cricoid ring, 14 had extralaryngeal extension (9 anterior, 5 posterior) and 3 showed surface extension toward the posterior commissure. Inside the larynx, the typical subsites of local failure were the mucosa at the passage between the remnant larynx and trachea, the mucosa at the level of the posterior commissure and the contralateral CAU as well as outside the larynx at the level of the outer surface of the remnant larynx (probably one of these options: in transit metastasis, lymph node metastasis at the level of Berry's ligament, direct invasion of the thyroid gland). The most frequent site of close margins was the posterior commissure mucosa. In all patients with local recurrence, salvage therapy included total laryngectomy and adjuvant radiation therapy and/or chemotherapy in 17 patients, and laser surgery in four cases. One patient was lost to follow-up, seven patients died of laryngeal cancer from progression of disease

Table I. Incidence of disease-specific survival (DSS), disease-free survival (DFS) and loco-regional control (LRC) in terms of local staging, previous treatment and age.

	Patients	DSS	DFS	LRC
pT				
pT2	22/142	21/22 (95.5%)	17/22 (77.3%)	17/22 (77.3%)
pT3	58/142	54/58 (93.1%)	51/58 (87.9%)	52/58 (89.7%)
pT4a	62/142	56/62 (90.3%)	40/62 (64.5%)*	43/62 (69.4%)*
Previous treatment				
Untreated	94/142	87/94 (92.6%)	72/94 (76.6%)	75/94 (79.8%)
Treated	48/142	44/48 (91.7%)	36/48 (75.0%)	37/48 (77.1%)
Age (years)				
< 65	97/142	90/97 (92.8%)	76/97 (78.4%)	78/97 (80.4%)
≥ 65	45/142	41/45 (91.1%)	32/45 (71.1%)	34/45 (75.6%)

χ^2 -test; * $p < 0.05$.

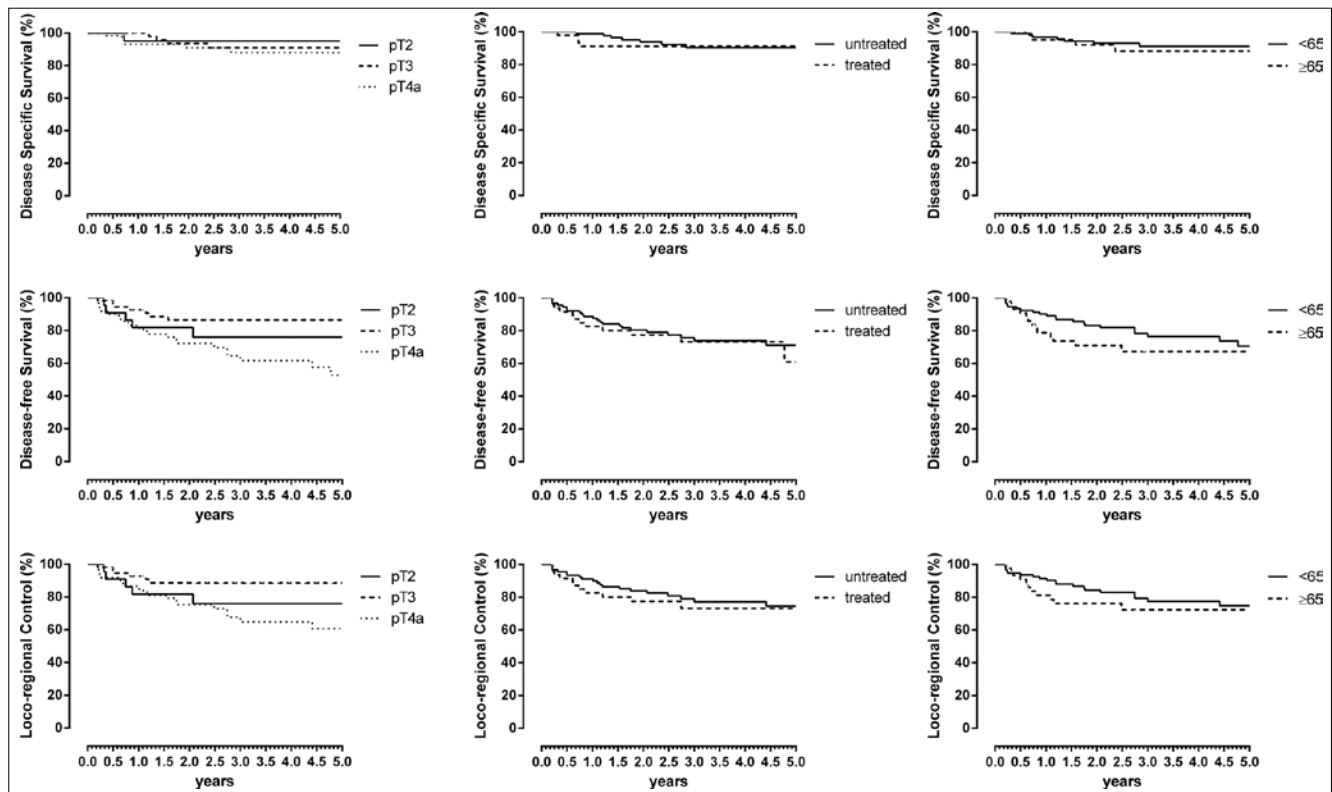


Fig. 2. Disease-specific survival, disease-free survival and loco-regional control in terms of local staging, previous treatment and age over a 5-year period in 142 patients with laryngeal cancer staged pT2–pT4a who underwent supratracheal partial laryngectomy.

(average 14.0 months, range 7.4–34.1 months) and three patients died of other disease, while at the last follow-up, three patients were alive with disease and seven patients were alive and disease-free; overall local control after salvage therapy was achieved in 7 of 21 patients (33.3%), and at 3 years the local control rate was 66.6%.

Recurrence in the neck was observed in nine cases, five of whom were previously classified as cN0 and four as cN > 0 patients. At the time of primary resection, five of these nine received bilateral neck dissection, and six of nine recurrences were observed at level VI. Five recurrences in the neck were treated with surgery and adjuvant radiation therapy and/or chemotherapy, four recurrences with chemotherapy, one of whom also received radiation therapy; three patients died due to regional recurrences (range 3.8–21.0 months, mean 13.7 months) while at the last follow-up, one patient was alive with disease and five patients were alive and disease-free.

Postoperative course and morbidity

Overall, acute complications during hospitalisation occurred in 10 of 142 patients (7.0%) (Table II) and there were no perioperative deaths. The mean hospitalisation time for patients with acute complications was 37 ± 6 days, which was significantly longer than that for patients without acute complications (25 ± 5 days; p < 0.001). Late sequelae following discharge were observed in 40 of 142

cases (28.2%) (Table II). Of these, 37 were successfully treated with transoral CO₂ laser surgery (33/37, 89.2%), injective laryngoplasty using Vox-implants, which successfully treated dysphagia (3/37, 8.1%), or total laryngectomy (1/37, 2.7%).

Laryngeal function preservation

In our patient cohort, the 5-year LFS and LFP were 85.4% and 75.0%, respectively. Furthermore, we evaluated whether LFP could be affected by local staging, presence of previous treatment, or age ≥ 65 years (Fig. 3). Patients affected by advanced pT stage or characterised by older age were more prone to lose laryngeal function than those with intermediate pT stage or younger patients (p < 0.05

Table II. Acute postoperative complications and late sequelae.

	Patients (%)
Acute complications	
Cervical bleeding	1/142 (0.7%)
Wound infection	2/142 (1.4%)
Aspiration pneumonia	5/142 (3.5%)
Other	2/142 (1.4%)
Late sequelae	
Laryngeal soft tissue stenosis	25/142 (17.6%)
Dyspnoea	3/142 (2.1%)
Aspiration pneumonia	12/142 (8.5%)

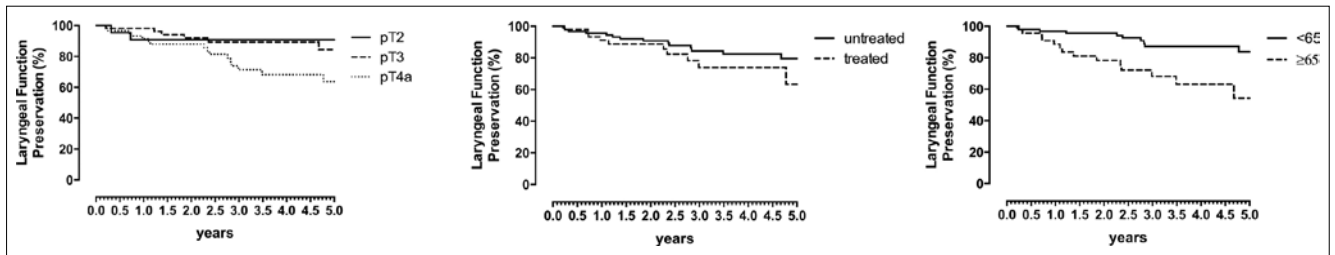


Fig. 3. Laryngeal function preservation in terms of local staging, previous treatment and age over a 5-year period in 142 patients with laryngeal cancer staged pT2–pT4a who underwent supratracheal partial laryngectomy.

and $p < 0.01$, respectively). In fact, functionality was maintained in 90.9% of pT2 and in 84.4% of pT3 patients, but in only 63.7% of pT4a patients. Similarly, laryngeal function was maintained in 83.8% of younger patients compared to 54.2% of the elderly, a difference that can be considered to be an early event, which was also significant with the Gehan Breslow Wilcoxon test ($p < 0.01$). Finally, LFP was not biased by previous treatments (not shown).

Overall, aspiration pneumonia (AP) was observed in 14/142 patients (9.9%), five cases during hospitalisation and 12 cases during follow-up (Table II). Due to intense dysphagia and AP episodes, a temporary gastrostomy was required in 10 patients (7.0%); for six of these, it was removed within the first postoperative year. The gastrostomy was maintained in only four cases due to repeated episodes of AP and severe dysphagia for liquids. In two cases, total laryngectomy was proposed for persistent aspiration: one patient accepted this treatment while the second refused, preferring to keep the gastrostomy and maintain voice. The other two patients were subjected to the endoscopic procedure of injective laryngoplasty using a Vox implant, which successfully resolved the dysphagia, allowing gastrostomy removal.

Discussion

The basic goal of a partial intervention on the larynx is to obtain loco-regional control of the disease, sparing laryngeal functions^{18–20}. To this end, surgery offers either transoral excision of the neoplasm, usually by carbon dioxide laser²¹, or open neck partial, “functional” laryngectomies^{22,23}, the greater part of which, especially in Europe, is represented by open horizontal partial laryngectomies (OPHL). Literature addressing this topic is rich, and a number of surgical procedures have been described to cope with the different patterns of endolaryngeal tumour site and spread^{8,22–25}. Schematically, among the currently available surgical options, total laryngectomy (TL)²⁶ and OPHL Type II²⁷ are the more established solutions for intermediate-advanced stage laryngeal tumours affecting the glottis. However, in an attempt to tailor therapeutic choice to a number of variables related to the tumour and the patient, a significant number of lesions are not amena-

ble to be treated safely by OPHL Type II: (i) glottic/transglottic tumours with subglottic extension when the lesion reaches the cricoid (anteriorly, the cricoid ring is about 15 mm from the glottis while posteriorly, the cricoid plate is about 5–8 mm from the vocal folds); (ii) glottic/transglottic T4a because of extralaryngeal progression through the caudal end of the thyroid cartilage and/or through the cricothyroid membrane.

In this study, we considered 142 patients affected by II–IV staged laryngeal SCC undergoing OPHL Type III, which allows safer resection of subglottic extended lesions^{8,9}. Because of their superficial involvement of the cricoid, glottic-subglottic pT2 are characterised by normal or impaired vocal cord mobility. The latter can be advantageously treated by a CO₂ laser resection²¹, or by OPHL Type II²³, by removing the mucosa from the cricoid cartilage. In both cases, the deep margin could be close, but is often safe. Conversely, despite the fact that OPHL Type III might seem an overtreatment due to the resection of the corresponding part of the cricoid, we must remember that posterior subglottic lesions are difficult to manage with any surgical solution. In the absence of cartilage involvement, non-surgical treatment should always be taken into serious consideration^{28,29}.

The glottic/transglottic pT3 category with subglottic extension represents the actual core group for OPHL Type III. The clinical feature most often characterising these tumours is vocal cord and arytenoid fixation with cricoarytenoid joint and cricothyroid space involvement, combined with arytenoid and/or cricoid sclerosis. The choice of an OPHL Type II procedure would result in a greater risk of positive margins. The introduction of OPHL Type III has opened a useful window into function sparing surgical protocols. In fact, open neck partial surgery can now be conducted using the principles of a modular approach. This states that the resection is always prepared in standard mode and the larynx is opened from the side less affected by disease. Sub-sites involved are removed and the resection can be easily enlarged as follows: OPHL Type II +ARY → OPHL Type III +CAU, OPHL Type IIIa/b → OPHL Type IIIa/b +CAU, OPHL Type III/a → OPHL Type III/b. Resection margins must be examined with frozen sections: if positive, the resection can be ex-

panded until free margins are achieved. The systematic application of whole organ sections represents the quality control for both the surgical procedure and imaging accuracy. It demonstrates that the more extirpative OPHL Type III is mandatory for cancers affecting the cricothyroid space and reaching the upper limit of the cricoid. In these cases, an OPHL Type II would almost certainly result in a positive margin along the upper border of the cricoid. In the present study for pT3, the 5-year OS and DSS were 85.3 and 91.1%, respectively, which are better than what was previously reported for both concomitant chemoradiotherapy or induction chemotherapy and radiotherapy (~60%)^{26,29}.

More advanced pT4a tumours require a series of considerations: first, it must be noted that, in all of the cases in the present cohort, the extralaryngeal extent was minimal. The second is the widespread agreement that total laryngectomy would be the elective intervention for a tumour with extralaryngeal spread, which occurs almost always through invasion of the laryngeal framework. OPHL Type III results have demonstrated that a careful selection can make a good number of patients eligible, even in a few very well selected “extreme cases”. Treating anterior cT4a tumours (full-thickness involvement of the thyroid lamina and/or minimal extralaryngeal extension) by OPHL requires an absolutely comparable radicality to that resulting from total laryngectomy. At the end of the work-up, the surgeon must be able, as much as possible, to ensure safe margins thus avoiding an upfront total laryngectomy. As the elective indication in these cases is extirpative surgery, patients should be driven by a strong desire to avoid total laryngectomy and must be informed in advance. Adopting these selection criteria in pT4a cases, OPHL Type III displayed 5-year OS and DSS of 73.2 and 88.1%, respectively, which are in line with those achievable with total laryngectomy. However, the DFS for pT4a cancer (52.7%) was significantly lower than that for pT3 cases (86.4%), but higher in comparison to what was obtained by radiotherapy and/or chemoradiotherapy management (26 to 38%)^{26,29}. On the other hand, the absence of major comorbidities and the ability to undergo a rigorous post-operative rehabilitation represent general prerequisites for all partial laryngectomies.

More attention should be given to local contraindications related to disease extension. OPHL Type III is not able to give a sufficient radicality in: (i) lesions arising from the epilarynx (junction zone between the supraglottic larynx and the other regions); (ii) lesions with major invasion of the preepiglottic space involving the hyoid bone, the interarytenoid space, the posterior commissure and both arytenoid cartilages; (iii) large extralaryngeal spread of cancer; and (iv) lesions reaching the first tracheal ring.

Larynx function preservation has substantial advantages in tailoring surgery to the actual extent of the tumour. Its maintenance was more critical in patients affected by pT4a

cancer (63.7%) and in those older than 65 years (54.2%). Persistent slight dysphagia and aspiration pneumonia still represent major complications in patients undergoing OPHLs^{20,25,30-31}, while voice was significantly deteriorated, and generally quite hoarse and breathy⁹. Fortunately, these phenomena are infrequent, tend to be easily controlled and are well tolerated by patients.

In cases indicated for a more extreme OPHL Type III, ethical considerations can arise. In fact, these cases are considered “amenable with total laryngectomy” and therefore, upfront directed to non-surgical treatment to spare the larynx. The patient must be clearly informed that if the resection margins are positive from frozen sections, the intervention will be converted to a total laryngectomy, thus “jumping” the option of concomitant chemoradiotherapy (recommendation IA in the current guidelines). For these reasons, both the severity of the intervention and the necessity for adjuvant radiotherapy demand that extreme caution must be taken in considering the indications.

In conclusion, we summarise the precise indications and contraindications for OPHL Type III (see OPHL Handbook in the Appendix 1). Furthermore, we demonstrate that the choice of a modular OPHL Type III approach can be considered viable in comparison to chemoradiation protocols for some well-studied glottic and/or transglottic tumours with sub-glottic extension. Advantages can be obtained in terms of prognosis (better identification of upstaging and reduction in prevalence of recurrence) and functional results such as a reduction in the number of total laryngectomies, even at the expense of voice quality and occurrences of sequelae (aspiration pneumonia).

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Appendix 1

Type III OPHL Handbook

Local indications

As definitions for the Type III (a+b) OPHLs have only recently been introduced, the precise T classification related indications and contraindications are separately reported:

- *Glottic T2 with subglottic extension*

The OPHL Type III option has been considered for tumours with anterior or lateral subglottic extension, spreading above the conus elasticus and reaching the cricoid. In all these cases, vocal cord mobility has been normal or impaired, while arytenoid mobility has always been normal. As a rule, the lesion has shown a superficial subglottic extension, more than 10 mm anteriorly and about 5–8 mm posteriorly.

The CT scan shows a glottic lesion extending downward, apparently without involvement of the cricothyroid space and/or extension through the cricothyroid membrane, and which reaches the cricoid plate posteriorly and/or the cricoid ring anteriorly. There is no evidence of direct involvement of the laryngeal framework although it is possible to highlight sclerosis of the arytenoid or the cricoid cartilage, indirect signs of the lesion reaching the cartilage perichondrium (Fig. S1 a-c).

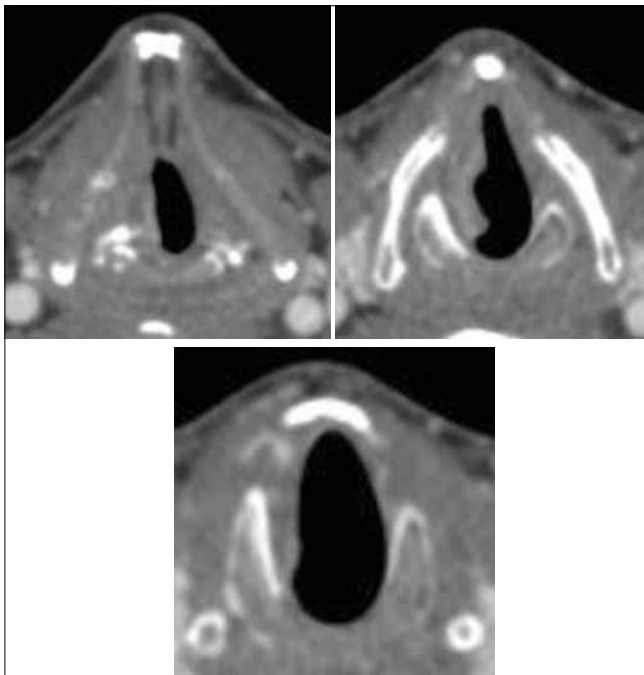


Fig. S1. a-b) CT scan in axial view of right recurrent glottic T2 with impaired mobility of the vocal cord, extending superficially to the subglottic site along the elastic cone toward the cricoid cartilage. c) The tumour reaches the cricoid plate and ring.

- *Glottic/transglottic T3 with subglottic extension*

This category is extremely heterogeneous and the majority of lesions are manageable with an OPHL Type II (supracricoid laryngectomy). In these cases, the most evident clinical feature is the fixed vocal cord with mobile arytenoid, a sign of no invasion of the cricoarytenoid joint.

OPHL type III was essentially adopted in two situations:

A. glottic-subglottic T3 tumours spreading within the paraglottic space and controlled by the conus elasticus medially and the perichondrium of the thyroid cartilage laterally (Fig. S2 a-d) (tumour growth is directed downward and laterally; sometimes it can infiltrate the inferior edge of the thyroid cartilage or exit the larynx between the thyroid and cricoid cartilages through the cricoarytenoid membrane: the so-called early glottic pT4a) (Fig. S3 a-c). Surface extension toward the posterior commissure can be observed. Typical clinical features are the fixed vocal cord, fixed arytenoid and subglottic swelling.

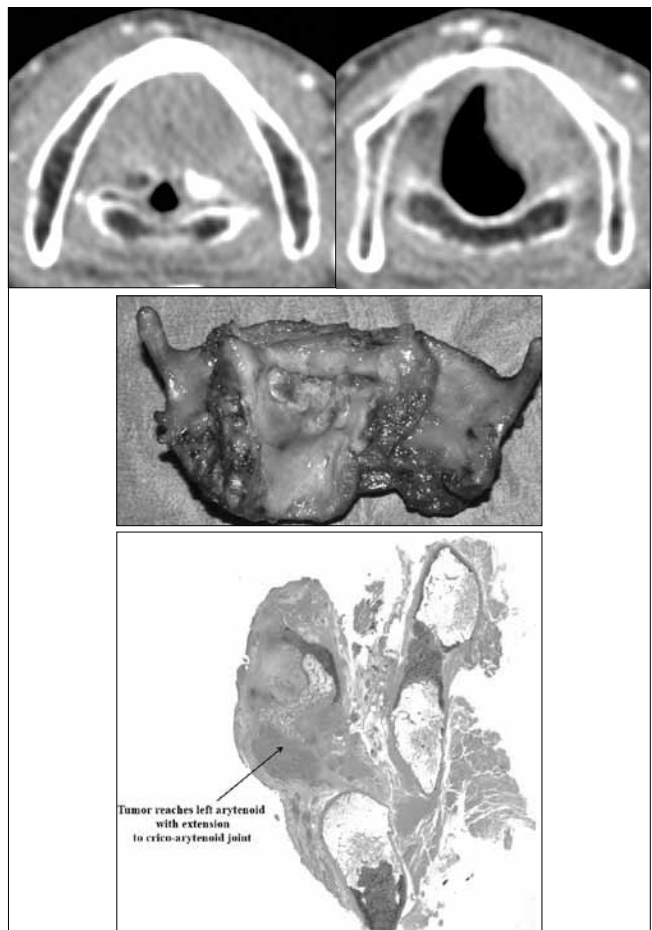


Fig. S2. a-b) CT scan in axial view of left glottic T3 with fixed vocal cord and hypomobile arytenoid, extending downward and laterally within inferior paraglottic space. Note the intense sclerosis of the arytenoid without evidence of direct invasion of the cricoid. c) The specimen of OPHL type III + left CAU. d) Macrosection of the same specimen: the lesion reaches the crico-arytenoid joint (arrow).

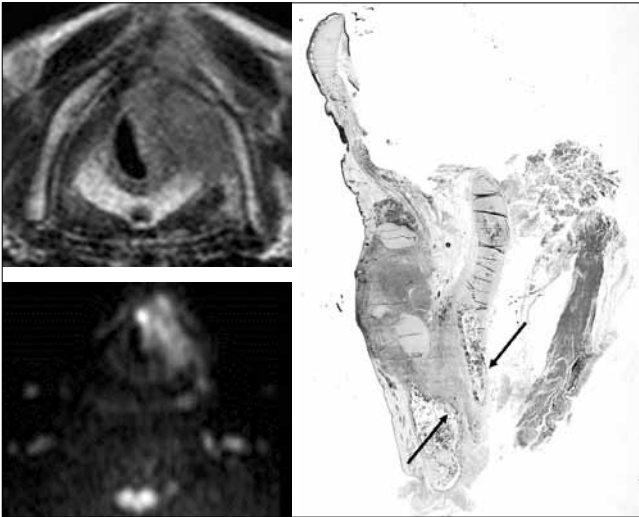


Fig. S3. a-b) MRI in axial view of left glottic T3 with fixed vocal cord and arytenoid, extending downward and laterally reaching the crico-thyroid space. Note the intense sclerosis of the cricoid with suspect involvement of thyroid cartilage. c) Macro-section on the specimen of OPHL type III + left CAU: the lesion involves the cricothyroid space, the inferior edge of the thyroid cartilage and superior edge of the cricoid (arrows).



Fig. S4. CT scan in coronal view of right transglottic T3 with fixed vocal cord and arytenoid. The tumour clearly invades the superior and inferior paraglottic space with transglottic extension toward the cricoid cartilage.

B. transglottic T3 tumours spreading superiorly into the deep tissue of the ventricular band under the quadrangular membrane and progressing into the subglottic area, where they reach the internal lamina and the inferior edge of the thyroid cartilage or the superior edge of the cricoid (Fig. S4). Also in these cases, both the vocal cord and arytenoid can be fixed.

- *T4a with limited anterior or lateral extralaryngeal extension*

Gross extralaryngeal spread of cancer represents a clear contraindication to any type of partial laryngectomy. However, OPHL type III has been advantageously adopted in

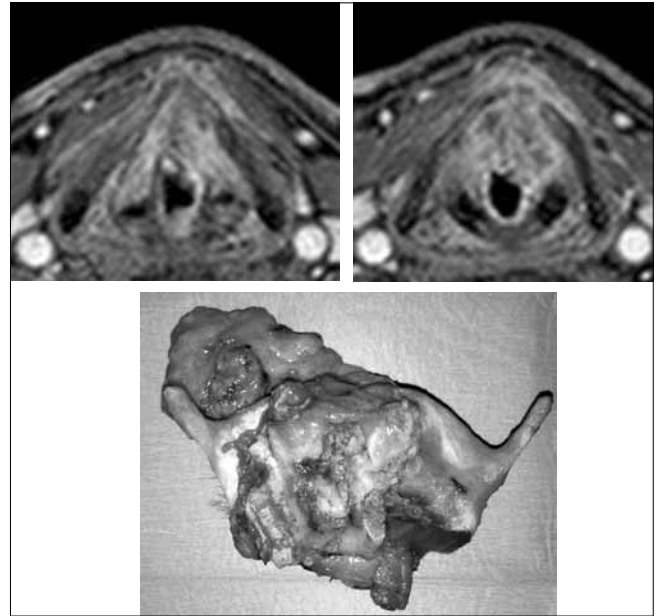


Fig. S5. a) MRI in axial view of left glottic T4a with fixed vocal cord and arytenoid, extending downward and laterally within inferior paraglottic space. Note the involvement of the arytenoid and the crico-arytenoid joint without evidence of direct invasion of the cricoid. b) Anterior extralaryngeal spread through the thyroid cartilage. c) The specimen of OPHL type III + left CAU.

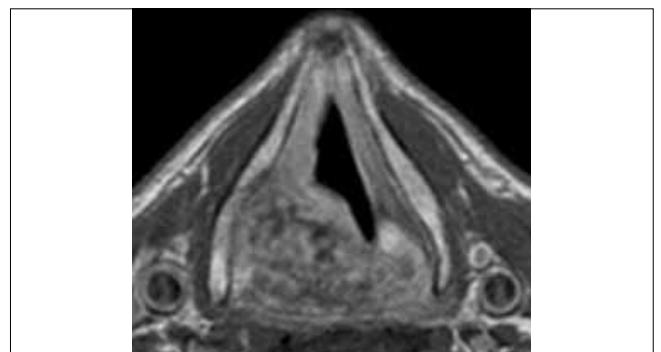


Fig. S6. MRI in axial view of right intermediated grade larynx chondrosarcomas without involvement of the whole cricoid plate.

clinically T3 tumours but strongly suspected of having an initial extralaryngeal extension through the laryngeal framework or cricothyroid space/membrane (Fig. S5 a-c). In these cases, because of the suspicion of extralaryngeal extension, the radicality provided would be comparable to that of total laryngectomy.

Other indications

OPHL Type III was also successfully adopted for radical resection of low-intermediate grade laryngeal chondrosarcomas without involvement of the whole cricoid plate¹¹ (Fig. S6) and in a case of recurrent papillary thyroid carcinoma with thyroid cartilage involvement and intralaryngeal spread (Fig. S7 a-b).

Contraindications

With respect to the local extent of the tumour, our absolute contraindications were as follows:

- supraglottic T4a tumours reaching the base of the tongue or invading the hyoid bone (Fig. S8 a-b);
- glottic-subglottic T3 tumours with massive invasion of the paraglottic space reaching the posterior cricoarytenoid muscle and the pyriform sinus submucosa (Fig. S9);
- gross glottic-subglottic T4a with massive cricoid invasion (Fig. S10) or reaching the first tracheal ring (Fig. S11);
- lymph nodes staged N3.

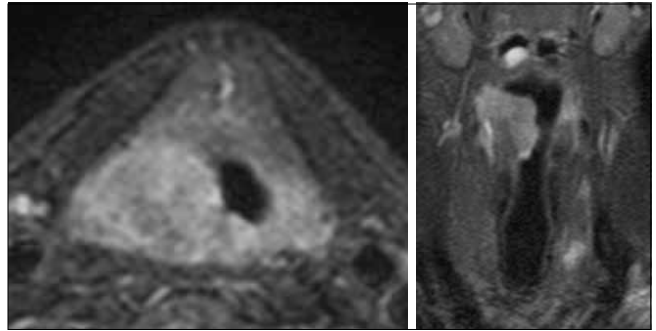


Fig. S9. a-b) MRI in axial and coronal view of right glottic T3 with fixed vocal cord and arytenoid, extending posteriorly to the pyriform sinus submucosa and reaching the posterior commissure and posterior crico-arytenoid muscles.

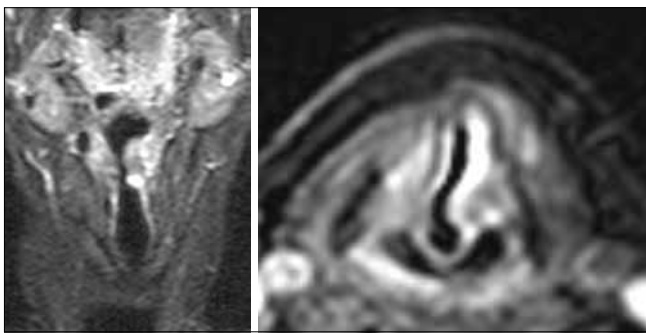


Fig. S7. a-b) MRI in coronal and axial view of recurrent papillary thyroid carcinoma with thyroid cartilage involvement and intralaryngeal spread.

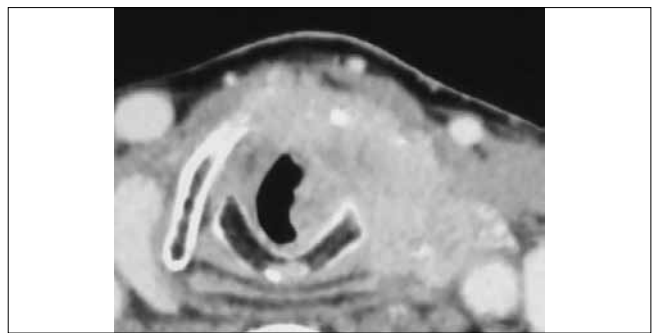


Fig. S10. CT scan of large glottic-subglottic T4a with massive cricoid invasion and extralaryngeal spread.

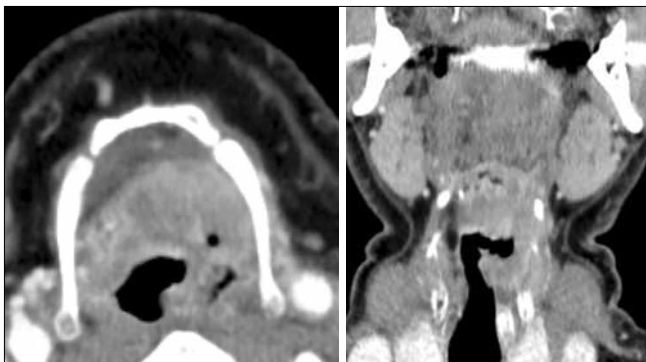


Fig. S8. a-b) CT scan of supraglottic T4a tumors reaching the base of the tongue and involving the hyoid bone. a) Axial view. b) Coronal view.



Fig. S11. CT scan of glottic-subglottic T4a reaching the first tracheal ring and with extralaryngeal spread.