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# CANCER OF THE LARYNX: WHEN A SIMPLE AND PRECISE WORK-UP MEANS A BETTER CHOICE OF THE THERAPEUTIC OPTION

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*Le cose migliori si ottengono solo con il massimo della passione*

*GOETHE*

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# INTRODUCTION

Laryngeal cancer (LC) is among the most common cancers of the head and neck, with about 110.000 to 130.000 new cases diagnosed worldwide annually, representing the 2% of the malignant neoplasms and the 60% of cervico-cephalic tumors[1]. In Italy every year around 5200 new cases of laryngeal cancer are diagnosed. Of these, 55-60% are early cancers (defined by the American Joint Committee on Cancer as cT1 or cT2 tumors without nodal involvement or distant metastases), while the remaining are classified as locally advanced (cT3 - cT4, without nodal involvement), loco-regionally advanced (any T with nodal metastases) and disseminated (any T, any N with distant metastases).

Survival rates of LC patients range from 73-92% for the early stage disease (I - II) to 50-64% for the advanced stage disease (III - IV)[2]. The latter is associated with a high rate of loco-regional relapse and cancer-related death. The overall survival (OS) of advanced stage LC is negatively affected by T status and the N status, which have been recognized as independent prognostic factors in the literature[3].

The LC treatment relies on many available therapeutic approaches: the overarching goal of all of them is to maximize survival and, whenever possible, preserve voice and swallowing function.

The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology[4] indicate the follows:

1. patients suffering from T1, T2 and selected T3 LC should be initially treated with the aim to preserve the larynx, using transoral laser microsurgery (TLM), partial laryngectomy (OPHL) or radiotherapy (RT)
2. patients suffering from T3 LC amenable to total laryngectomy (TL) can of course be treated with up-front surgery but better should be addressed to organ sparing protocol by concurrent chemoradiotherapy (CCRT) or induction chemotherapy followed by radiotherapy (IC-RT) in order to preserve the larynx and its functions.
3. TNM classification system of LC (VIII edition)[5] divided T4 into two categories: T4a, moderately advanced local disease, defined as tumors invading through the thyroid cartilage and/or invading tissues beyond the larynx (e.g. trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid or esophagus) and T4b, very advanced local disease, not eligible for surgery.

Patients suffering from T4a LC should be treated with up-front TL in the majority of cases, leaving the organ sparing options to selected patients who decline surgery.

For a century until the 1980s, up-front total laryngectomy (TL) was considered the only therapy for patients with locally advanced LC[6]. Although this strategy can provide a good disease loco-regional control (LRC), it is associated with a negative impact on patients' quality of life (permanent tracheostomy and loss of natural voice)[7]. For this reason, organ-sparing protocols, including non-surgical options, as chemo-radiotherapy, and surgical options, as transoral laser microsurgery (TLM) or open partial horizontal laryngectomies (OPHL), have begun to be considered as reliable alternatives to TL.

Starting from 1991, several clinical studies (Table 1) had analyzed organ-sparing potentialities in the non-surgical management of advanced LC, with confident results; consequently, the therapeutic trend for the treatment of advanced laryngeal cancer had progressively shifted from primary TL toward non-surgical organ preservation approaches. The era of chemo-radiation therapy in laryngeal oncology had taken off.

In 1991, the first pivotal study was conducted by the Laryngeal Cancer Study Group of the Department of Veterans Affair (VA). They investigated in good responder patients with locally-advanced LC whether IC-RT could represent a better approach respect to TL followed by post-operative radiotherapy (TL-PORT) in terms of OS and organ sparing. This study showed a new role for chemotherapy in patients with advanced disease, demonstrating that a treatment strategy involving IC-RT could be effective in preserving the larynx in a high percentage of patients, without compromising overall survival[8].

The Radiation Therapy Oncology Group (RTOG 91-11) confirmed the feasibility and the effectiveness of a chemo-radiation approach. In a large trial published in 2003, in fact, RTOG compared the outcomes obtained with cisplatin plus fluorouracil IC-RT, CCRT and RT alone, detecting a higher laryngeal preservation and locoregional control after the treatment with CCRT[9].

The efforts to improve patient quality of life without affecting the OS clearly altered the perception about treatment modalities. Clinical trials, and consequently guidelines that derived from, demonstrated that TL-PORT had better results in terms of OS on T4a tumors with evident progression through cartilage [10,11,4]. Notwithstanding, many countries and institutions perceived the organ preservation protocols as a TL replacement in the treatment of locally advanced LC. Thus, during the last 20 years, TL was increasingly considered just as a salvage surgery after the failure of organ preservation treatments[12]. Countries extensively adopting organ sparing protocols have seen a sharp increase in LC mortality rates, but they have persisted stable or reduced, where TL continued to be the standard treatment for advanced LC[13].

Starting from these considerations, controversies concerning the correct treatments of T4a LC, and the role of TL as up-front treatment are arguments nowadays deeply felt.
The most recent literature explored these critical issues, bringing arguments in favor of the return to more traditional surgical approaches in the treatment of locally advanced laryngeal cancer. Meanwhile, it was highlighted the therapeutic possibility to undergo partial laryngeal surgery for cT3 - cT4a tumors after a rigorous selection of patients.

The larynx loss due to surgical treatment brings several functional morbidities. Thus, it was one of the first cancer sites in the head and neck district to be considered for preservation by the employment on non-surgical therapeutic approaches. This scenario was also spurred by a greater potential of salvage surgery if compared with other cancer sites[14].

In the last five years, several studies (Table 2) compared survival and functional outcomes of patients affected by advanced stage LC (cT3 - cT4a) and treated distinctly by total laryngectomy and post-operative radiotherapy (TL-PORT), open partial laryngectomy (OPHL), concurrent radio-chemotherapy (CCRT) or RT alone. The main analyzed end-point taken into accounts were overall survival (OS), disease-free survival (DFS), disease specific survival (DSS), locoregional control (LRC), and different functional outcomes (e.g. laryngectomy free survival - LxFS, laryngoesophageal dysfunction free survival - LED, actuarial freedom from laryngectomy - FFL, actuarial freedom from laryngoesophageal dysfunction-free survival - FFLED).
The majority of them detected significant improvements in terms of oncological outcomes (OS, DFS, DSS, and LCR) only for patients affected by cT4a LC undergoing TL-PORT, if compared to those treated by CCRT or RT alone. This is in agreement with the Larynx preservation Consensus Panel recommendations for clinical trial[10] that consider patients with cT4a disease as ineligible for laryngeal preservation protocols, and with the recent National

Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology[4], American Society of Clinical Oncology (ASCO) guidelines[12] and Italian Association of Medical Oncology (AIOM) guidelines[11], which recommend up-front TL-PORT in cT4a glottic and supraglottic LC and listed CCRT and IC as options only if TL is declined.

Nevertheless, some Authors concluded that disappointing results regarding OS of patients with locally intermediated - advanced stage LC after non-surgical treatment could be due to an etiological shift, leading to a progressive reallocation of cases between the different sites of the larynx[15]. However, these studies were based on long-term analyses of patient cohorts from countries in which employment rate of TL was substantially unchanged and chemo-radiotherapy was used in a minority of cases. This situation made them unable to verify the improved survival associated with the TL.

Nowadays, the most recent literature recommends caution in indicating non-operative chemo-radiotherapy to treat patients not only suffering from cT4a LC but also by cT3 LC. Furthermore, when pursued, this challenging option requires both a multidisciplinary case evaluation and a frank discussion about options and expectations with the patient. Critical is, indeed, not only the tumor extent or the laryngeal function prior the treatment, but also the expected tolerance to treatment on the basis of recorded performance and nutritional status, as well as the presence of comorbidities, particularly cardiopulmonary chronic disease that is common in this population[8,16].

Beyond oncologic end-points, some Authors noticed many other disadvantages. First of all, suffering from numerous comorbidities (e.g. low renal and hepatic functions, poor performance status and insufficient compliance) old and very old patients could not tolerate chemo-radiotherapy approaches. Furthermore, in case of locally advanced LC with deranged laryngeal function prior the treatment or large cartilage destruction, any attempt to preserve the larynx by means of RT or CCRT protocols is hazardous. In fact, it should be always provided enough residual laryngeal cartilage to afford a high likelihood of mechanical stability and / or post-therapy regeneration[13,17-19]. This finding, according to some Authors, associates laryngeal preservation in cT4a LC with a high incidence of acute toxicity and disruption in laryngeal function, in term of significant pharyngeal and esophageal edema, fibrosis and stenosis, xerostomia with diminished perception of swallowing functions and aspiration, acute mucositis and dysphagia. Table 3 reported acute and late toxicities observed in the same studies previously mentioned encouraging organ-sparing protocols.

On the other hand, patients undergone TL develop some irrefutable sequelaes: loss of normal voice, swallowing problems, loss of nasal function, altered smell and taste, poor cough, lung function changes, tracheostomal complications, and lifelong functional and psychological consequences[20]. However, the preservation of the larynx alone does not guarantee its function. A patient with an intact but functionless larynx may be unable to swallow, with consequently respiratory complications. The quality of life of an individual with complications after a chemo-radiation protocols may be worse than that of a patient who has undergone a successful TL, who is able to eat and to breathe normally and who can talk with the aid of tracheo-esophageal puncture or by esophageal voice[21].

Voice rehabilitation in laryngectomy patients has been achieved in the past with surgical shunts, esophageal speech, electrolarynx devices, and others. Each of these methods has its advantages and disadvantages. However, since the introduction of voice prosthesis, tracheo-esophageal speech with voice prosthesis (T-E speech) is the accepted standard of care in voice rehabilitation after laryngectomy. In fact, it provides a lung-powered speech and, hence, a physiologically better voice quality[22].

Based on these considerations and focusing the attention only on cT4a LC, the up-front surgery with post-operative radiotherapy is the best treatment choice.

As indicated by the most adopted worldwide guidelines, TL remains the standard of care, even with the cost of laryngeal organ loss; chemo-radiation protocols are treatment options for the minority of highly selected patients with smaller-volume cancers, intact airway protection and swallowing function, good performance status and inadequate compliance to a surgical option as well as for patients who firmly reject the radical surgery.

**Emerging role for partial laryngeal surgery in selected T4 laryngeal cancer**

The same overarching goals of non-surgical organ preservation, meaning to spare the function without compromising the oncological outcome, have always spurred surgeons to look for technical solutions, which brought to a renaissance of conservative laryngeal surgery. Born from the brilliant intuitions of true Pioneers[23-27], this type of surgery has been acknowledged in recent years of multiple published studies (sometimes from large multi-centric series), which gave a significant boost in the understanding of its benefits and drawbacks. In fact, these procedures had proven to be viable options for the management of early-stage LC, but showed reasonable limits especially with advanced-stage cases.

The main clinical difficulty in facing advanced-stage tumors lies in preoperative diagnosis, since the efficiency of imaging techniques (CT-scan and MRI) in detecting infiltration of the thyroid cartilage does not achieve a total diagnostic accuracy[28]. Radical control of disease by a transoral approach (TLM and TORS) cannot be achieved when the lesion involves the laryngeal framework and/or when it tends to grow outside the laryngeal box[29,30]. In fact, anterior involvement of the thyroid cartilage, crico-thyroid or thyro-hyoid membranes makes the tumor at risk of persistence after TLM even when removals of a cartilage fragment or its extensive vaporization is carried out. Therefore, Peretti and colleagues stated that involvement of the posterior paraglottic space with encroachment of the crico-arytenoid joint and infiltration of the laryngeal framework negatively influence both oncological and functional results, thus limiting the role of TLM to anecdotal cases[31]. Supracricoid laryngectomy and the more recent supratracheal laryngectomy emerged as options for these advanced cancers inasmuch as they still achieve acceptable levels of locoregional control rate and contextually allow the maintenance of a functional larynx.

The factors that must be taken into account before offering the OPHL option to a patient suffering from locally advanced LC are diagnosis of a tumor belonging to favorable T-related disease subsets, performance and functional status of the patient, presence of comorbidities, compliance to a sometimes demanding rehabilitation protocol, plausible need of adjuvant RT.

A multidisciplinary team evaluation, in a high-experienced Center, as well as an accurate diagnostic work-up resulting from the strong collaboration with Radiologists, are the key to achieve good functional outcomes and minimize the risk of recurrence development and the consequent need of salvage laryngectomy, albeit in a limited number of LC in stage cT4a[32].

Despite many T4a cases had been successfully treated with OPHL and had been reported on single institution series (Table 4), the current evidence-based guidelines do not suggest their employment for the management advanced LC cases, even when the patient refuses the radical surgery.

Recently, Succo et al. carefully analyzed results achieved in different subcategories of cT3 and cT4a LC treated with OPHL, which were conducted using the principle of a modular approach. The Authors stated that glottic or supraglottic cT4a tumors with full-thickness involvement of the thyroid lamina and/or minimal extralaryngeal extension, but not interesting the posterior paraglottic space and not affecting the mobility of the arytenoid, are those amenable to be treated by OPHL, showing the greater probability of success[33]. The principle underlying the modular approach means that the resection is always prepared in standard mode and the larynx is opened from the side less affected by disease. At this point, under visual control, the sub-sites involved are removed and the radicality checked by the frozen sections.

In the clinical practice, such cases are the same that current guidelines consider as amenable to non-surgical organ sparing protocol, if the patient refuses the TL. The choice of OPHL with a modular approach instead of CCRT in favorable disease subsets could be considered to be viable not only in prognostic terms, but also as functional results, e.g. a reduction in the number of total laryngectomies.

Furthermore, Authors stated also that the radicality is the same achievable with more demolitive interventions, but the selection of patients must be made very carefully. Indeed, at the end of the work-up, the surgeon must be able to ensure safe margins with sufficient certainty, thus avoiding an up-front TL.

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**Table 1 Studies analyzing organ sparing protocols**

| Author - year publication | N° of patients | Cancer site and staging | Treatment modalities | LP | OS |
|---|---|---|---|---|---|
| VALCSG, 1991 [8] | 332 pz | Larynx, III-IV | PF -> RT vs<br>S -> RT | 64% | 68%/2 ys |
| EORTC 24891 [42] | 202 pz, | Hypo pharynx,<br>II-IV | PF -> RT vs<br>S -> RT | 22%/5 ys | - PF -> RT 38% / 5 ys<br>- S -> RT 33%/5 ys |
| GETTEC [43] | 68 pz | Larynx, II-IV | PF -> RT vs<br>S -> RT | 42% | - PF -> RT 69% / 2 ys<br>- S -> RT 84%/2 ys |
| RTOG 91,11 [9] | 547 pz | Larynx, III-IV | PF -> RT vs<br>CRT vs<br>RT | - PF -> RT 71%/5 ys<br>- CRT 84%/5 ys<br>- RT 66%/5ys | - PF -> RT 59%/5 ys<br>- CRT 55%/5 ys<br>- RT 54%/5ys |
| GORTEC 2000-01 [44] | 213 pz | Larynx,<br>Hypo pharynx, III-IV | PF -> RT vs<br>TPF -> RT | - PF -> RT 57% /3 ys<br>- TPF -> RT 70%/3 ys | - PF -> RT 60% /3 ys<br>- TPF -> RT 60%/3 ys |
| EORTC 24954-22950 [45] | 450 pz | Larynx,<br>Hypo pharynx, III-IV | PF -> RT vs<br>aPF -> RT (6w) | - PF -> RT 48%/5ys<br>- aPF -> RT (6w) 52%/5ys | - PF -> RT 53%/5ys<br>- aPF -> RT (6w) 60%/5ys |
| POSNER [46] | 166 pz | Larynx,<br>Hypo pharynx, III-IV | PF -> CRT vs<br>TPF -> CRT | - PF -> CRT 32% LFS / 3ys<br>- TPF -> CRT 52% LFS/3 ys | - PF -> CRT 40% / 3 ys<br>- TPF -> CRT 57% /3 ys |
| TREMPLIN [47] | 153 pz | Larynx,<br>Hypo pharynx, III-IV | TPF -> CRT vs<br>TPF -> Cet+RT | - TPF -> CRT 93% 3 months<br>- TPF -> Cet+RT 93% 3 months | - TPF -> CRT 85% 1,5 ys<br>- TPF -> Cet+RT 86% 1,5 ys |
| PRADES [48] | 71 pz | Pyriform sinus, III-IV | PF -> S or RT vs<br>P-RT | - PF -> S 68%%2 ys<br>- RT vs P-RT 92% / 2 ys | - PF -> S DFS36%%2 ys<br>- RT vs P-RT DFS41% / 2 ys |

YS= years, S= surgery, LP= larynx preservation, OS= overall survival, DFS= disease free survival, LFS= laryngectomy free-survival, CRT= chemo radiation, PF=platinum-fluorouracil, T= Taxotere, Cet= Cetuximab

**Table 2** **Studies analyzing total laryngectomy and organ-sparing protocols for cT3 - cT4a laryngeal cancer**

| Author year | Type of study | N | Cancer staging | Treatment | OS | DSS e DFS | LRC | LP , LEDFS | Conclusions |
|---|---|---|---|---|---|---|---|---|---|
| Bussu, 2013 [49] | Retrospective cohort study | 166 | T3-T4a | TL, OPHL, CRT | T4a 3 ys - TL 78%<br>- OPHL 68%<br>- CRT 54% | DSS<br>87%/2ys | | T3+T4a:<br>CRT 45%<br>OPHL 77% | In whole series no stat sign in the 3 arms for OS and DSS. |
| Francis, 2014 [20] | Retrospective cohort study and review | 108<br>24 studies | T4a | TL, RT, CRT | 81%/2 ys<br>60%/5 ys<br>Review:<br>/ 2aa:<br>- LT 30-100%<br>- RT 12-21%<br>- CRT 30-65% | | | | Primary TL provides a high survival rate for T4a.<br>High rate of laryngeal dysfunction after CRT. |
| Dziegielewski , 2012 [50] | Longitudinal cohort study | 258 | T3,T4 | TL-PORT/CT, RT, CRT | 2ys -5ys T3:<br>- TL- PORT /CT 2 ys 89%<br>5 ys 70%<br>- RT 2 ys 48%<br>5 ys 18%<br>- CRT 2 ys 66%<br>5 ys 52%<br>OS / 2 e /5 aa T4a:<br>- TL-PORT/CT 2 ys 60%<br>5 ys 49%<br>- RT 2 ys 12%<br>5 ys 5%<br>- CRT 2 ys 32%<br>5 ys 16% | DFS / 2ys T3:<br>- TL-PORT/CT<br>94% LRC - 0% LP<br>- RT<br>66% LRC - 28% LP<br>- CRT<br>LRC 53% LCR - 48% LP<br>DFS/ 2ys T4a:<br>- TL-PORT/CT<br>67% LRC - 0% LP<br>- RT<br>30% LRC - 3% LP<br>- CRT<br>54% LRC - 29% LP | | | TL-R/CT provides superior survival for T3 and T4a LC versus RT or CRT. |
| Grover, 2015 [51] | Retrospective cohort study | 969 | T4a | TL-PORT and LP-CRT | Median OS:<br>- TL-PORT 61 months<br>- LP-CRT 39 months | | | | Patients with T4a LC receiving LP-CRT had more advanced nodal disease and worse OS. Previous studies of (non-T4a) locally advanced LC showing no difference in OS between LP-CRT and TL may not apply to T4a disease. |
| Timmermans, 2015 [19] | Retrospective cohort study | 182 | T3 and T4 | TL-PORT (91% T4), RT, CRT | OS / 5 ys T3:<br>- TL-PORT 49%<br>- RT 47%<br>- CRT 45% | | T3+T4a:<br>- TL-PORT 87% | | No differences in survival.<br>T3 : > CRT<br>T4: > TL-PORT |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | OS / 5 ys T4a:<br>- TL-PORT 48%<br>- RT 34%<br>- CRT 42% | | - RT 65%<br>- CRT 76% | | |
| Timmermans, 2016 [52] | Population based study | 2072 T3 and 1722 T4 | T3-T4 | TL-PORT/CT, RT and CRT | OS / 5 ys T3:<br>- TL-PORT/CT 49%<br>- RT 47%<br>- CRT 45%<br>OS / 5 ys T4a:<br>- TL-PORT/CT 48%<br>- RT 34%<br>- CRT 42% | | | LFI T3:<br>- RT 81%<br>- CRT 77%<br>LFI T4a:<br>- RT 81%<br>- CRT 87% | For T4 disease, TL-PORT showed the best survival |
| Timme, 2015 [53] | Retrospective cohort study | 71 | T3 - T4 | TL or PL, CRT | /5 ys T3:<br>- TL or PL 41%<br>- CRT 40%<br>/5 ys T4a:<br>- TL or PL 54%<br>- CRT 53% | | | LP total CRT 79%<br>LEDFS 40% T3, 33% T4a | CRT : high rate of laryngeal and oesophageal dysfunction. |
| Rosenthal, 2015 [14] | Retrospective cohort study | 221 pz | T4a | TL-PORT and LP-CRT | median OS<br>- TL-PORT 47-48 months<br>- LP 38 months | DSS/5 ys<br>- TL-PORT 60%<br>- LP 48,5% | ys :<br>- TL-PORT 84%<br>- RT 63% | | TL-PORT can produce substantial long-term cancer control and survival rates for patients with T4 larynx cancer. |
| Luo, 2015 [54] | Meta-analysis and review | 2013 pz | T3-T4a | TL-PORT, IC-RT, CRT, RT alone | OS:<br>- TL-PORT 66%<br>- IC-RT 60,8%<br>- CRT 61%<br>- RT alone 71,6% | DFS:<br>- TL-PORT 56,6%<br>- IC-RT 41%<br>- CRT 44,9%<br>- RT alone 57,8%<br>DSS 55-70%/5ys | | | RT alone better OS, DFS, and LFS in patients with locally advanced LC. TL >DFS, but OS were similar across the different larynx-preserving treatments and TL. |
| Rodrigo, 2015 [55] | | 80 pz | T3-T4a | TL | OS/5 ys 55% | DSS / 5 ys 72% | | | TL is an effective treatment for the management of patients with locally advanced LC |
| Gorphe, 2016 [56] | Retrospective cohort study | 100 pz | T4a | TL-PORT | OS/ 2 ys 65%<br>OS/ 5 ys 52,4%<br>OS/ 10 ys 33,3% | DFS/ 2 ys 55%<br>DFS/ 5 ys 42,6%<br>DFS/ 10 ys 31,8% | LCR/ 2 ys 77%<br>LCR/ 5 ys 74%<br>LCR/10 ys65,9 | | Surgery for T4a larynx cancer remains a standard of care |
| Fu, 2016 [1] | Meta-analysis | | T3 and T4a | TL-PORT and LP-CRT | OS/2 ys<br>- TL-PORT 78,8%<br>- LP-CRT 52,9%<br>OS/5 ys<br>stat sign only T4a | | LC/2 ys<br>- TL-PORT 76%<br>- LP-CRT 54,6%<br>LC/5 ys | | TL-PORT significant advantage in OS and LCR T4a laryngeal cancer |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Not stat sign | | |
| Sanabria 2016 [57] | Review | | T3 and T4a | TL, CRT | 26% | | | | Evidence supports total laryngectomy for patients with T4 cancers. T3 possible CRT |
| Al-Gilani, 2016 [58] | Retrospective cohort study | 487 pz | T3 | Surgery vs LP-CRT | OS 5/ ys<br>- surgery 41%<br>- CRT 36% | | | | OS > in pz with T3 glottic SCC who underwent surgery compared with a nonsurgical treatment. Furthermore, adjuvant and nonsurgical treatment result in a dysfunctional larynx |
| Succo, 2016 [34] | Retrospective cohort study | 555 | pT3-pT4a | OPHL | 84,6% / 5 ys<br>pT3 87,8%<br>pT4a 71,2% | DFS 84,2%<br>pT3 87,9%<br>pT4a 68,1% | LRC 86,3%<br>pT3 89,7%<br>pT4a 71,7% | LFP 91,2%<br>pT4a 78,0%<br>LFS 93,3% | Evidence supports open partial laryngectomy for selected patients with T4a cancers with anterior extension |

YS= years, PZ= patients, OS= overall survival, DFS= disease free-survival, DSS= disease specific survival, LP= larynx preservation, LFI = laryngectomy free interval, LEDFS = laryngoesophageal dysfunction-free survival

## Table 3 Acute and delayed toxicities

| Author - year publication | Treatment modalities | Acute toxicity | Late toxicity |
|---|---|---|---|
| VALCSG, 199 [8] | PF -> RT<br><br>S -> RT | TD 3; mucositis 38%<br><br>TD 5 ; mucositis 24% | |
| EORTC 24891 [42] | PF -> RT vs<br><br>S -> RT | 7 toxic effects, 1 TD<br><br>1 vascular disease, 1 depressive illness | |
| GETTEC [43] | PF -> RT vs<br><br>S -> RT | Digestive 3%, hematological 1%<br><br>Digestive 0%, hematological 0% | |
| RTOG 91,11 [9] | PF -> RT vs<br><br>CRT vs<br><br>RT | Hematological 52% mucositis 34%, laryngeal 13%<br><br>Hematological 47% mucositis 43%, laryngeal 18%<br><br>Hematological 3% mucositis 34%, laryngeal 16% | Skin toxicity 5-0%, mucosal 5-0%, larynx toxicity 1-6%, dysphagia 15-3%, subcutaneous 11-1%<br><br>Skin toxicity 1-0%, mucosal 3-0%, larynx toxicity 17-6%, dysphagia 22-3%, subcutaneous 9-1%<br><br>Skin toxicity 2-1%, mucosal 3-1%, larynx toxicity 21-3%, dysphagia 22-2%, subcutaneous 9-2% |
| GORTEC 2000-01 [44] | PF -> RT vs<br><br>TPF -> RT | 2TD, neutropenia 17,6%, infections 5,8%, stomatitis 7,8%, thrombocytopenia 7,8%, creatinine elevation 2%<br><br>5TD, neutropenia 31,5%, infections10,9%, stomatitis 4,6%, thrombocytopenia 1,8%, creatinine elevation 0% | G4 larynx toxicity 13,6%, mucosal 0%, xerostomia 2,2%, subcutaneous 6,6%<br><br>G4 larynx toxicity 6,2%, mucosal 1%, xerostomia 6,1%, subcutaneous 4% |
| EORTC 24954-22950 [45] | PF -> RT vs<br><br>aPF -> RT (6w) | Mucositis 32%, skin reaction 6%, dysphagia 33%<br><br>Mucositis 21%, skin reaction 0%, dysphagia 20% | Mucosal 25%, neuropathy 14%, subcutaneous 31%<br><br>Mucosal 28%, neuropathy 11%, subcutaneous 28% |
| TREMPLIN [47] | TPF -> CRT vs<br><br>TPF -> Cet+RT | Mucositis 43-3%<br><br>Mucositis 52-2% | Mucosal 3,5%, xerostomia 10,3%, subcutaneous fibrosis 7%, neuropathy 3,4%, laryngoesophageal 8,6%<br><br>Mucosal 1,8%, xerostomia 8,9%, subcutaneous fibrosis 2%, neuropathy 0%, laryngoesophageal 9,0% |

TD = toxic deaths

## Table 4 Studies analyzing OPHL potentiality also for advanced laryngeal cancer

| Author year | N | Cancer staging | Treatment | OS | DSS e DFS | LC/LRC | LFP | LFS | % Complications | % Recurrence |
|---|---|---|---|---|---|---|---|---|---|---|
| Bocca, 1983 [59] | 467 | T2-T4a | OPHL type I | OS / 5 ys 75,0% | | | | | | |
| Chevalier, 1997 [60] | 61 | T1-T4a<br>T1 2<br>T2 41<br>T3 14<br>T4 4 | OPHL type II | OS / 3 ys 83%<br>OS / 5 ys 79% | | | | | | 3,0% |
| Laccourreye, 1998 [61] | 60 | T3-T4a | Neo-adjuvant CT - OPHL type II | 87,9% / 3 ys<br>72,7% / 5 ys | | 98,3% | 91,7% | | 8,3% local failure | |
| De Vincentiis, 1998 [62] | 149 | | OPHL type II<br>(CHP 98 pz<br>CHEP 51 pz) | 2 groups:<br>OS 1° 88,1%<br>OS 2° 95,0% | | | 98% | | | 6,0% |
| Bron, 2000 [63] | 69 | T1-T4a<br>pT1 10<br>pT2 30<br>pT3 9<br>pT4 5<br>local relapse15 | OPHL type II<br>13% adjuvant RT | OS / 5ys 66,5%<br>- glottic : 69,1%<br>- supraglottic : 45,6% | DSS /5 ys 80,1%<br>- glottic : 83,2%<br>- supraglottic : 51,4% | LC/5 ys 84,0%<br>LCR no RT Pz 94,5% | | 87,0% | 49,1% | 6,1% |
| Gallo, 2005 [64] | 253 | T1-T4a<br>T1 27<br>T2 147<br>T3 64<br>T4 15 | OPHL type II<br>180 CHP<br>73 CHEP | 85,8% / 3 ys<br>79,1% / 5 ys<br>57,6% / 10 ys<br>57,6% / 16 ys | | LRC 91,3% | 92,1% | | | 8,7% |
| Lima, 2006 [65] | 43 | T3-T4a glottic | OPHL type II<br>(CHEP) | | DSS / 5 ys 78,0%<br>DFS / 5 ys 83,0% | LRC / 5 ys 85,0% | | | 25,5% | |
| Laudadio, 2006 [66] | 206 | T1b-T4a<br>T1b 66<br>T2 89<br>T3 46<br>T4 5 | OPHL Type II<br>9,2% CHP<br>90,8% CHEP | pT3 88,7%<br>pT4 78,9% | DFS / 3 ys 85,4%<br>DFS / 5 ys 85,0%<br>pT3 77,6%<br>pT4a 53,8% | | | | | 15,0% |
| Rizzotto, 2015 [67] | 115 | T2-T4a<br>pT2 14<br>pT3 50<br>pT4a 51 | OPHL Type III | 78,9%/5ys<br>pT4a 80,4% | DFS 68,5% /5 ys<br>pT4a 60,8% | 69,6% / 5 ys<br>pT4a 62,7% | | LFP 78,3%<br>pT4a 59,3% | 6,1% acute<br>24,4% late | |
| Succo, 2016 [34] | 555 | pT3-pT4a | OPHL | 84,6% / 5 ys | pT4a 68,1% | pT4a 71,7% | pT4a 78,0% | 93,3% | | |

LFP= laryngeal function preservation, LFS = laryngectomy free survival, LC = local control

# OVERVIEW

The present thesis simmarizes the candidate's main research activities performed during the 4-year PhD program at the Doctoral School in Life and Health Sciences of the University of Turin (PhD Programme in Biomedical Sciences and Oncology), under the supervision of Professor Marco Volante.

The research interest has been mainly focused on the open partial laryngectomies (OPHL), procedures that still play an important role in contemporary conservative management of laryngeal cancer, closing the gap between transoral approaches on one hand and total laryngectomy or non-surgical organ preservation strategies on the other. Furthermore, with increasing utilization of organ preservation strategies to treat laryngeal cancer, OPHLs have established an important and oncologically reliable role in the management of recurrent radio-resistant laryngeal carcinoma.

The goal of my research activities was to demonstrate that is now possible to consider the horizontal partial surgical procedures as an intensity-modulated surgical system treatment of laryngeal tumors - from horizontal supraglottic laryngectomy (HSL), to supracricoid laryngectomy (SCL) and supratracheal one (STL) — which allows surgical management of the majority of endolaryngeal cancers. It can also be considered a function-sparing surgical protocol, oncologically comparable to organ-sparing protocols based on chemoradiotherapy, especially for intermediate stages of laryngeal cancer, providing a substantial reduction in the number of total laryngectomies.

I have divided this thesis into three chapter:

The *first chapter* is dedicated to oncological outcomes of open partial laryngectomies in the treatment of intermediated / advanced laryngeal tumors.

The current trend for management of laryngeal cancer indicates that pursuing therapeutic options able to preserve laryngeal functionality provides the best quality of life for patients. To realize this goal, different approaches have been pursued, in terms of chemoradiotherapy or surgical treatment. The former is able to spare laryngeal function and patient outcome seems satisfactory, nevertheless, locoregional control is compromised during long-term follow-up. On the other hand, demolitive surgery provides better control of disease, although incurring a higher percentage of laryngeal function impairment and late sequelae that hamper the patients' quality of life.

Even though preservation of laryngeal functions is one of the major advances achieved over the past decades in the management of laryngeal cancer, intermediate/advanced stage lesions still present a major challenge in terms of controlling the disease and preserving the larynx, regardless of the therapeutic option. In fact, many glottic cT3 tumors with subglottic extent (vocal cord and arytenoid fixation) often result in early pT4a for extralaryngeal extent, making their management with chemoradiotherapy or supracricoid laryngectomy difficult. Toward the end of the 1990s, a comparative analysis (unpublished data) of total laryngectomy and supracricoid specimens in relation to arytenoid fixation and subglottic swelling triggered the idea of extending the supracricoid laryngectomy downward to obtain safer margins. In 2006, this led to the introduction of a new type of open partial horizontal laryngectomy, the supratracheal laryngectomy, otherwise known as open partial horizontal laryngectomy type III, according to the recent European Laryngological Society Classification.

As recently demonstrated by Schindler et al and Rizzotto et al, this is able to spare laryngeal function without compromising locoregional control during long-term follow-up. As a consequence of the diffusion of supracricoid partial laryngectomies (open partial horizontal laryngectomy type II), the advent of supratracheal partial laryngectomies (open partial horizontal laryngectomy type III), and the consolidated role of conventional nonsurgical organ-sparing protocols, the role of total laryngectomy in the treatment of endolaryngeal neoplasms has considerably decreased.

The 5-year OS of 84.6% observed in our studies is higher than that reported in the literature for both concomitant chemoradiotherapy and induction chemotherapy followed by radiotherapy (approximately 60%). More advanced pT4a tumors had a 5-year DFS of 68.1%, a result in agreement with that obtained with total laryngectomy; of note, patients with extensive extralaryngeal spread were not considered amenable to open partial horizontal laryngectomy. These data show that a careful selection can make a good number of patients eligible for the partial modular surgical approach, even in some well selected "extreme cases." However, 5-year DFS of patients with pT4a tumors (68.1%) was significantly lower than that of patients with pT3 (87.9%), but higher than that reported for radiotherapy and/or chemotherapy, which ranges from 26% to 38%, respectively. Finally, the number of patients that were subjected to total laryngectomy for either functional or oncologic purposes was extremely low (6.2%). The high laryngectomy-free survival rate here achieved demonstrates the great potential of open partial horizontal laryngectomy approaches in preserving the larynx. In summary, “everybody loses a piece, but few lose all.”

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The *second chapter* is dedicated to functional results open partial laryngectomies in the treatment of intermediated / advanced laryngeal tumors.

The real Achilles heel of open partial horizontal laryngectomies is represented by a greater proportion of functional problems compared with non-surgical treatment options
Benito et al reported that persistent slight dysphagia and aspiration pneumonia still represent major complications in patients undergoing open partial horizontal laryngectomy type II. The same findings were observed in the our cohort of patients; furthermore, the voice was significantly deteriorated, and generally quite hoarse and breathy, especially in open partial horizontal laryngectomy type III.

General, swallowing-related, and voice-related QOL were comparable in patients who underwent OPHL type IIa or type IIIa with no statistically significant difference between the two groups.

Perceived QOL is strictly related to patient’s expectation, stretching the importance of precise and exact information on functional outcomes during the preoperative and postoperative counseling. This information is also essential to guide patients in the choice of which type of surgery to undergo.

The *third chapter*, finally, is dedicated to the importance of Informed Consent about these procedures.

Nowadays, open partial horizontal laryngectomies (OPHLs) are well-established procedures for treatment of laryngeal cancer. Their uniqueness is the possibility to modulate the intervention intraoperatively, according to eventual tumour extension. An OPHL procedure is not easy to understand: there are several types of procedures and the possibility to modulate the operation can produce confusion and lack of adherence to the treatment from the patient. Even if the surgery is tailored to a patient's specific lesion, a unified consent form that discloses any possible extensions, including a total laryngectomy, is still needed. The patient-surgeon relationship is based on trust. A correct Informed Consent permits to improve the level of patient-surgeon cooperation and to avoid any possible litigation by improving comprehension of the procedure and reaching complete agreement on surgical planning.

## Overview of the subtasks / projects

| Chapter, paper | Working hypothesis | Aim | Results | Conclusions |
|---|---|---|---|---|
| **1** | | | | |
| **1.1** | The current surgical treatment guidelines for laryngeal cancer in its intermediate/advanced categories distinguish T3 lesions in those amenable to partial versus total laryngectomy. On the other hand, total laryngectomy remains the first therapeutic option for the T4a category, leaving non-surgical organ preservation protocols for selected patients refusing surgery. A lack of evidence-based clear-cut consensus still exists on how to differentiate T3-T4a patients amenable to laryngeal conservation surgery from those requiring total laryngectomy | To identify subcategories in cT3-cT4a supraglottic/glottic cancers, describing their different spreading patterns, and local and loco-regional recurrence modes. | Five-year OS, DSS, DFS, LRC, LC, FFL, LFS were significantly better in anterior tumors (subcategories I and III) when compared to the corresponding posterior ones (subcategories II and IV). | Anterior cT3 tumors are manageable by OPHL, and this approach could also be proposed in the treatment of early anterior cT4aN0. Despite promising results, OPHLs should be considered under investigation in posterior cT3 tumors due to clinical and biological behavior similar to cT4a tumors. |
| **1.2** | Even though some of OPHL surgical techniques date back more than half a century and their use in some part of the world is progressively expanding, a comprehensive classification has not been attempted in the literature | To propose a classification as basis for obtaining a common language among the head and neck surgical community and to present this classification system as a simple and intuitive teaching instrument, and a tool to be able to compare surgical series with each other and with non-surgical data. | The classification identifies three types of surgical procedures based on the lower limit of resection (Type I → Supraglottic laryngectomies; Type II → Supracricoid laryngectomies; Type III → Supratracheal laryngectomies). Moreover, each type may be extended to adjacent laryngeal and/or pharyngeal sites; the extension of surgical removal is indicated by abbreviations (+ARY → | The principles chosen to distinguish one procedure from others have been essentially based on laryngeal anatomy and the lower extent of surgical resection. In this way, we subdivided OPHLs according to the cranio-caudal extension of resection, focusing on the accessorial elements (arytenoids and crico-arytenoid |

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| | | | to involve one arytenoid (specifying the side of resection; +BOT → to involve the base of tongue; +PIR → to involve one piriform sinus (specifying the side of resection); +CAU → to involve one crico-arytenoid unit composed by arytenoid, crico-arytenoid joint, and underlying hemicricoid plate (specifying the side of resection).<br>For Type II and III OPHLs, the suffix "a" means that the suprahyoid epiglottis has been spared, while the suffix "b" indicates its removal. | units, base of tongue, piriform sinuses) removed or not together with the essential ones. |
| **1.3** | OPHL have been increasingly more adopted by head and neck surgeons as a type of function preserving surgery for the treatment of early (glottic T1b–T2; supraglottic T2) or locally advanced (glottic and supraglottic selected T3) laryngeal tumors. Many surgeons have shown that SCL, when faced with the planned sacrifice of the larynx compared to other therapeutic options, provides good, reproducible loco-regional control, and preserves laryngeal function, with the tracheostomy eventually closed in almost all patients | To demonstrate the safety and reproducibility of oncologic and functional outcomes of subtotal laryngectomies on a large number of patients, while introducing the concept that function-sparing surgical protocols permit, especially for intermediate stages of disease, a substantial reduction in the number of total laryngectomies. Long-term oncological and functional results from a retrospective study on 469 patients over a 10-year period of subtotal laryngectomies (SL), 399 supracricoid partial laryngectomies (SCL) and 70 supratracheal partial laryngectomies (STL) are presented | The mean follow-up time was 97 months (range 60–165 months). The observed long-term results were: SCL, 5-year OS and DFS: 95.6, and 90.9%, respectively; 2-year post-operative LFP: 95.7%; STL, 5-year OS and DFS: 80 and 72.9%, respectively; 2-year postoperative LFP: 80%. The performance status scale for LFP showed very high 2-year scores, with no significant differences depending on the type and extent of surgery. The adopted type of function-sparing surgery provided OS and DFS rates that were somewhat better than those reported in studies based on organ-sparing protocols with chemoradiotherapy. The rate of total laryngectomy of completion in this series was 4.4%. | In comparison with organ-sparing protocols, inclusion criteria of surgical protocols are usually less stringent; the mortality rate is likely to be lower (zero in our experience); the rate of acute and late morbidities is nearly same or lower; the number of total laryngectomies for oncological or functional purposes is significantly less; functional outcomes are good (with the only variable the poorer quality of voice) although survival rates are even higher |

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| **1.4** | Laryngeal squamous cell carcinoma (SCC) accounts for the 1.9% of cancers worldwide. Most of these (up to 60%) are diagnosed in early stages (T1-T2, N0). For these larynx preserving/conserving option is preferable. Beyond transoral laser microsurgery (TLM), open partial horizontal laryngectomy (OPHL) is a function-sparing surgical technique to treat them. | To perform a retrospective analysis of clinical outcomes of 216 patients who underwent OPHL for glottic cT2 laryngeal cancer from 1995 to 2011. | 5 years OS, DSS, LRC, LC, LFP and LFS rates were 93.1%, 98.0%, 97.1%, 97.5%, 97.8% and 98.5%, respectively. Disease controls are significantly affected by previous treatment and type of surgery employed. | Although TLM for cT2 laryngeal cancer with unimpaired vocal cord mobility still represents a sound option, OPHL with a modular approach offer higher local control and laryngeal preservation rates, for selected patients with impaired mobility of vocal cord combined to an involvement of the paraglottic space |
| **1.5** | Cancer of the larynx in the intermediate/advance stage still presents a major challenge in terms of controlling the disease and preserving the organ. Among therapeutic options, open partial horizontal laryngectomy (OPHL) is proposed as function-sparing surgical technique. | To perform a retrospective analysis of clinical outcomes of 555 patients with laryngeal cancer staged pT3–pT4a who underwent either supracricoid or supratracheal OPHL. | 5 years OS, DSS, LRC, LC, LFP rates were 84.6%, 84.2%, 86.3%, 90.6% and 91.2%, respectively. DFS, LRC, LC and LFP prevalences were significantly affected by pT4a staging (68.1%, 71.7% and 78.0% respectively), while pN+ influenced only DFS (≤72.6%) and LRC (≤79.6%). | In cases of laryngeal tumors at intermediate and selected advanced stage, also with sub-glottic extension, the choice of OPHL with a modular approach can be considered effective in terms of prognostic and functional results. |
| **1.6** | Laryngeal cancer management should pursue function-sparing therapeutic options. Even though demolitive surgery provides better control of disease at intermediate to advanced stages when compared to chemoradiotherapy, it does not preserve laryngeal function. Supratracheal partial laryngectomy has been described as a function-sparing surgical technique for laryngeal cancer with subglottic extension. | To perform a retrospective analysis of clinical outcomes of 115 patients who underwent supratracheal partial laryngectomy. | At 5 years, OS, DFS, and LRC rates were 78.9%, 68.5%, and 69.6%, respectively; DFS and LRC prevalences were greatly affected by pT4a classification (49.0% and 51.4%, respectively); and LFP was maintained in 78.3% of patients despite being affected by pT4a classification (59.3%) and age > or = 65 (64.6%). | For cases with glottic tumors and with subglottic extension, the choice of supratracheal partial laryngectomy versus chemoradiotherapy can be considered to be effective in terms of prognostic and functional results |

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| **1.7** | 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. | To focus on the indications and contraindications, both local and general, for STPL 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 OS, DSS, DFS and 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 LFP and 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%). | 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. |
| **2** | | | | |
| **2.1** | Patients undergoing STL could experience dysphonia and some degree of dysphagia with aspiration. In the literature, different studies reported long-term functional outcomes after SCL, showing satisfactory functional results, but with inevitable significant alterations of both swallowing and voice, requiring several months to restore these functions. | To report preliminary long-term results of swallowing, voice, and quality of life (QOL) after STL | Aspiration was found in 10, 2, and 5 patients, respectively, for liquids, semisolids, and solids. Neoglottis motility was generally preserved, whereas vibration was impaired. Aerodynamic measures showed a poor performance. Perceptual assessment revealed highly dysphonic voices. In only 8 patients, a harmonic structure was visible in the spectrograms. Aspiration pneumonia occurred in 2 patients. Preoperative weight was maintained in 16 patients. Generic, voice-related, and swallowing-related QOL revealed satisfied patients. | After STL, swallowing was sufficiently restored and QOL was satisfactory, whereas the voice was severely impaired even if oral communication was well preserved. |
| **2.2** | Supracricoid laryngectomies (SCLs) are conservative organ-sparing surgical techniques for the treatment | To analyse the literature on functional results after SCLs as knowledge on functional results will | The analysis of the length of hospital stay, feeding-tube removal time and time to eventual tracheotomy | There is a need for clearer clinical recommendations on early post-surgical management, tracheal- |

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| | of selected T2–T4 laryngeal carcinomas. Although these procedures allow preserving the larynx and its functions, in several countries SCLs are not adopted in oncological protocols. One of the possible reasons to account for this choice is the complexity of post-surgical in-hospital management and the variability in functional results | help in focusing on what is needed in the future to reach more standardized post-surgical procedures and homogeneous outcomes. | decannulation showed a marked variability across authors and centres. The review on swallowing functional outcomes showed marked variability, as well as a lack of consensus on how to assess swallowing after SCLs. The analysis of voice functional outcomes also revealed a marked variability; surprisingly, the tools applied in the assessments were very often not adequate for substitution voice. Literature review showed that voice- and swallowing-related quality of life are often satisfactory but the variability among centres is still too large | cannula and feedingtube removal criteria, voice- and swallowing-assessment protocol, rehabilitation need and timing. |
| **2.3** | Open partial horizontal laryngectomies (OPHLs) are conservative surgical techniques for the treatment of selected laryngeal carcinomas. In particular, OPHL type II or supracricoid laryngectomy and OPHL type III or supratracheal laryngectomy are indicated in the treatment of T2 to T4 laryngeal tumors with glottic and subglottic extension.<br>Both voice and swallowing functions are affected by these types of surgery and patients could experience dysphonia and some degree of dysphagia, with a possible impact on QOL. | To compare long-term swallowing, voice results, and quality of life (QOL) after open partial horizontal laryngectomy (OPHL) type IIa and type IIIa. | Significant differences were found only for the residue with solids and for the intelligibility parameter of the overall quality impression and intelligibility, additive and unnecessary noise, speech fluency, and presence of voiced segments scale with patients of the OPHL type IIIa group showing worse performances than the OPHL type IIa group | Patients who underwent OPHL type IIa and type IIIa show comparable long-term functional outcomes. OPHL type IIIa represents a valid surgical alternative to OPHL type IIa. |

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| **2.4** | After open partial horizontal laryngectomy (OPHL), many patients experience deterioration of laryngeal function over time | To evaluate laryngeal functional outcome at least 10 years after surgery in a cohort of 80 elderly patients. | The incidence of aspiration pneumonia (AP) and objective/subjective laryngeal functional assessments were carried out. Eight patients experienced AP including four with repeated episodes. A significant association was observed between AP and severity of dysphagia (p <0.001). Dysphagia was more pronounced than in a normal population of similar age but less than would be expected. There was a significant association between type of intervention and grade of dysphagia / dysphonia; difference in voice handicap was found, depending on the extent of glottic resection. | After OPHL, laryngeal function was impaired but this did not significantly affect quality of life. AP is more frequent in the initial post-operative period, decreasing in subsequent years. |
| **2.5** | Surgical and non-surgical treatment for laryngeal cancer can lead to voice impairment, with a severe impact on oral communication. This aspect can play a critical role affecting communication-related quality of life (QOL). People aging with verbal communication disabilities face demanding challenges in areas such as maintaining social roles, identity and accessing daily services. The telephone is certainly one of the most impactful interaction tools within verbal communication<br>Laryngeal cancer treatment may impact on the control of both pitch and intensity of voice, with a significant | To investigate telephonic voice intelligibility in patients treated for laryngeal cancer using different approaches, by a cross-sectional outcome study | Regarding words, the poorest intelligibility was noted for type II open partial horizontal laryngectomies, followed by total laryngectomies. The best intelligibility was found for transoral laser microsurgery, followed by radiotherapy alone. For sentences, the poorest intelligibility was noted for type II open partial horizontal laryngectomies, followed by chemo-radiotherapy. The best intelligibility was found for radiotherapy alone and transoral laser microsurgery. | More aggressive surgery as well as chemo-radiotherapy correlated with significantly poorer outcomes. Transoral laser microsurgery or radiotherapy alone ensured the best telephonic voice intelligibility. Intermediate-advanced T stages at diagnosis also showed significantly poorer intelligibility outcomes, suggesting that T stage represents an independent negative prognostic factor for voice intelligibility after treatment |

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| | deterioration of voice quality, prosody and – as a consequence – intelligibility. | | | |
| **2.6** | The management of head and neck cancer in the elderly has been historically heterogeneous, often marred by many prejudices, mainly based on both patient age and general health perceptions.<br>Nowadays, the exclusion of elderly patients from standard therapeutic options is becoming less justifiable, taking advantage potentially of all therapeutic alternatives available after a proper screening. It is therefore essential to better establish the risk to which the patient is subjected for each proposed therapeutic option, be it surgical or non surgical | To compare patient outcomes and to identify predictive factors that can be used by surgeons to choose the most appropriate treatment option | Patients affected with more advanced tumour and hence treated by invasive open neck surgeries (above all TL) are more prone to develop complications and undergo fatal outcome than those with early disease treated by laser microsurgery, independently of age at surgery | Elderly patients affected by laryngeal cancer can be treated similarly to younger patients, keeping in mind that more invasive surgeries are associated with a higher risk of developing complications. The advantages of mini-invasive surgery make it a possible first choice treatment in very old and frail patients suffering from laryngeal cancer, especially considering the recent success in treatment of some advanced stage tumours. Furthermore, comorbidities, by themselves, should not be used as exclusion criteria for subjecting an elderly patient to a different treatment that is from standard therapy. |
| **3** | | | | |
| **3.1** | Open partial horizontal laryngectomies (OPHLs) are well-established procedures for treatment of laryngeal cancer. Their uniqueness is the possibility to modulate the intervention intraoperatively, according to eventual tumour extension. An OPHL procedure is not | To review the English literature on informed consent, and to propose comprehensive Information and Consent Forms for OPHLs. | The Information Form is intended to answer any possible questions about the procedure, while remaining easy to read and understand for the patient. It includes sections on laryngeal anatomy and physiology, surgical aims and indications, alternatives to surgery, complications, and physiology of the | The primary goal of OPHLs is always oncological safety. For this reason, the surgeon must be allowed to extend the procedure as far as needed, according to the possible extensions reported 5 |

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| | easy to understand: there are several types of procedures and the possibility to modulate the intervention can produce confusion and lack of adherence to the treatment from the patient. Even if the surgery is tailored to a patient’s specific lesion, a unified consent form that discloses any possible extensions, including a total laryngectomy, is still needed. | | operated larynxThe Consent Form is written in a “modular” way: the surgeon defines the precise extension of the lesion, chooses the best OPHL procedure and highlights all possible expected extensions specific for the patient. Our intention, providing these forms both in Italian and in English, is to optimise communication between the patient and surgeon, improving surgical procedure arrangements and preventing any possible misunderstandings and medico-legal litigation. | |

# FIRST CHAPTER

# Paper 1

## *Treatment of T3–T4a laryngeal cancer by open partial horizontal laryngectomies: prognostic impact of different pT subcategories*

**ABSTRACT**

*Background:* The aim of this retrospective study was to identify subcategories in cT3-cT4a supraglottic/glottic cancers, describing their different spreading patterns, and local and loco-regional recurrence modes.

*Methods*: Patients (N=489) who underwent open partial horizontal laryngectomies (OPHLs) were retrospectively classified as: subcategory I (anterior pT3 with normal arytenoid mobility), subcategory II (posterior pT3 with impaired/absent mobility), subcategory III (anterior pT4 with normal mobility), and subcategory IV (posterior pT4 with impaired/absent mobility).

*Results:* Five-year overall, disease-specific, disease-free survivals, loco-regional, local control, freedom from laryngectomy, and laryngectomy-free survival were significantly better in anterior tumors (subcategories I and III) when compared to the corresponding posterior ones (subcategories II and IV).

*Conclusions*: Anterior cT3 tumors are manageable by OPHL, and this approach could also be proposed in the treatment of early anterior cT4aN0. Despite promising results, OPHLs should be considered under investigation in posterior cT3 tumors due to clinical and biological behavior similar to cT4a tumors.

## INTRODUCTION

The current surgical treatment guidelines for laryngeal cancer in its intermediate/advanced categories distinguish T3 lesions in those amenable to partial versus total laryngectomy.[1] On the other hand, total laryngectomy remains the first therapeutic option for the T4a category, leaving non-surgical organ preservation protocols for selected patients refusing surgery. Nevertheless, to complicate matters further, a lack of evidence-based clear-cut consensus still exists on how to differentiate T3-T4a patients amenable to laryngeal conservation surgery from those requiring total laryngectomy. Different factors related to both the tumor and the patient[2, 3] should indeed be considered when making an appropriate selection between patients treatable by the wide spectrum of open partial horizontal laryngectomies (OPHLs)[4] and those requiring organ sacrifice. One possible source of confusion is related to the great heterogeneity of T3-T4a categories including a wide gamut of different lesions ranging from T3 with minimal versus massive paraglottic space involvement (with normal or impaired/fixed vocal cord and arytenoid mobility), T3 with preepiglottic space infiltration, T3 with thyroid cartilage erosion, T4 with purely anterior extralaryngeal extension, and T4 with posterior-inferior spreading through the lateral portion of the cricothyroid membrane and the crico-thyro-arytenoid space. The contemporary endoscopic[5, 6] and imaging[2, 7] work-ups have dramatically reduced the diagnostic uncertainty level in the pre-treatment setting. Notwithstanding this, no endoscopic technique or imaging refinement is as yet able to objectively quantify the degree and causes of reduced/absent motility of the vocal cord/crico-arytenoid unit.[8]

Nowadays, several surgical and non-surgical options are available for treatment of T3-T4a laryngeal cancer, with comparable results in terms of loco-regional control, overall, and laryngectomy-free survival.[9-11] Some large series published by different authors[12-16] have shown that OPHLs[4] allow sound and reproducible oncological outcomes to be obtained. Furthermore, these techniques are characterized by a high laryngectomy-free survival, relatively low morbidity and mortality rates, and acceptable functional outcomes, if a careful preoperative patient selection is carried out.

The aim of this multi-institutional retrospective study on T3-T4a laryngeal cancer patients treated by OPHLs was to identify, in the vast group of these lesions, some homogeneous subcategories describing their different patterns of spreading and related modes of local, and loco-regional recurrence.

## PATIENTS AND METHODS

### *Patients*

After comprehensive preoperative counseling, 479 patients (Table 1) underwent surgery between January 2000 and December 2012 at the Hospitals of Vittorio Veneto, Martini of Turin, and Policlinic Hospital of Modena. As previously described,[15] patient selection was based on superficial and deep tumor extent, assessed by endoscopic and imaging evaluation performed less than 3 weeks before surgery. Computed tomography (CT) or magnetic resonance (MR) imaging was used to define infiltration of the cartilaginous framework, involvement of the pre-epiglottic (PES) and/or paraglottic spaces (PGS), as well as extralaryngeal spreading. Pre- and intraoperative videolaryngoscopic examination, by flexible endoscope in the office, and 0° and 70° rigid endoscopes in the operating theater, were employed to evaluate both vocal cord/arytenoid mobility and superficial tumor extent. Concerning arytenoid mobility, 293 patients showed impaired mobility/fixed vocal cord with mobile arytenoid, and 186 presented both vocal cord and arytenoid fixation. Patient characteristics, distribution according to the involved laryngeal sites, as well as their pT and pN categories, are reported in Table 1.

The general eligibility criteria for OPHL were a histological diagnosis of intermediate/advanced (cT3-cT4a) categories of glottic and supraglottic laryngeal squamous cell carcinoma (SCC), and Karnofsky index[17] higher than 80. Exclusion criteria were: purely supraglottic T3 with limited extension to the PES (and therefore amenable to OPHL type I or transoral laser microsurgery), previous treatment(s) for laryngeal carcinoma with curative intent, severe diabetes mellitus, severe bronchopulmonary chronic obstructive disease, neurological problems impairing the ability to expectorate and/or swallow, or severe cardiac disease.

*pT subcategories*

Clinical, endoscopic, radiologic, surgical, and pathological reports were retrospectively assessed to divide patients into four subcategories based on a laryngeal compartmentalization using a vertical virtual plane tangential to the arytenoid vocal process and perpendicular to the ipsilateral thyroid lamina. We defined anterior and posterior laryngeal compartments as the portions located, respectively, anteriorly or posteriorly to such a plane (Fig. 1). The four subcategories identified are therefore as follows:

I) Supraglottic/glottic/subglottic pT3, involving the anterior laryngeal compartment, with PES and anterior PGS involvement with/without inner cortex thyroid infiltration, but with normal arytenoid mobility (n=233 patients) (Fig. 2);

II) Supraglottic/glottic/subglottic pT3, involving the posterior laryngeal compartment, with infiltration of the whole PGS with/without inner cortex thyroid invasion, and with impaired (reduced or absent) arytenoid mobility (n=157 patients) (Fig. 3);

III) Supraglottic/glottic/subglottic pT4a, involving the anterior laryngeal compartment, with extralaryngeal extension (through the thyro-hyoid membrane, thyroid cartilage, and/or crico-thyroid membrane), but with normal arytenoid mobility (n=60 patients) (Fig. 4);

IV) Supraglottic/glottic/subglottic pT4a, involving the posterior laryngeal compartment, with extralaryngeal extension (through or around the posterior portion of the thyroid lamina, through the lateral crico-thyroid membrane, cricoid cartilage, and/or at the level of the crico-thyroid-arytenoid space), and with impaired (reduced or absent) arytenoid mobility (n=29 patients) (Fig. 5).

*Surgical procedures*

All 479 patients underwent OPHL types II-III according to the European Laryngological Society Classification[8] for curative purposes. Indications and contraindications of such procedures have already been described in previous studies.[12, 14, 15, 18, 19] The different types of surgical operation performed are reported in Table 2.

Neck dissection (ND), graded according to the American Academy of Otolaryngology – Head and Neck Surgery Foundation Classification,[20] was performed in 419 patients (87.5%), and was unilateral in 347 (82.8%) and bilateral in 72 (17.2%). ND was performed electively (ND levels II-IV) in 368 cN0 patients (87.8%) and for curative purposes in 51 cN>0 (12.2%). In 391 patients (93.3%), level VI or unilateral paratracheal lymph node clearance was added. No ND was performed in 60 cN0 patients (12.5%).

*Adjuvant treatments*

Based on pathological findings, 62 patients (12.9%) were subjected to adjuvant radiotherapy. The indications were: pN+>1 (n=43 patients), gross extralaryngeal extension (n=17, of whom six showed positive margins), and positive margins elsewhere (n=2). A large volume encompassing the primary site and all draining lymph nodes were irradiated with a dose of up to 54 Gy. Regions at higher risk for malignant dissemination received a 12 Gy boost (total, 66 Gy; range, 62–68 Gy).

Furthermore, chemotherapy was added in 37 patients who received 100 mg/m$^2$ of cisplatin on days 1, 22, and 43, concomitantly with radiotherapy because of a higher risk of local recurrence (five with Delphian nodes pN+, 20 pN2 with extracapsular spread, and 12 more extended pT4a showing positive/close margins toward pre-laryngeal tissues).[21]

*Statistical methods*

Clinical, endoscopic, and radiologic follow-up was performed for a mean of 5.3 years (range, 6 months–16.4 years). Overall (OS), disease-free (DFS), disease-specific (DSS) survivals, local (LC) and loco-regional (LRC) controls with OPHL alone, laryngectomy-free (LFS), and laryngo-esophageal dysfunction-free survivals (LEDFS)[22] were assessed by Kaplan–Meier curves. Log-rank (LR) and, for early events, Gehan-Breslow-Wilcoxon (GBW) tests were used to compare Kaplan–Meier estimates among the different subcategories. The end points considered were: the date of death (OS); the date of the first recurrence (DFS); the date of death from disease (DSS); the date of the first local recurrence (LC); the date of the first loco-regional recurrence (LRC); the date of salvage total laryngectomy or the date of death (LFS); the date of salvage total laryngectomy or the date of tracheostomy and/or PEG for functional reasons or the date of death (LEDFS). The association of prognostic factors for recurrence and subcategories was evaluated by odds ratio, meanwhile the corresponding incidences were compared by chi-squared ($\chi$2) test.

All analyses were performed with GraphPad Prism version 6.0e (GraphPad Software, San Diego, CA, USA), with $p<0.05$ as the threshold for statistical significance.

## RESULTS

### *Pathology*

Pathology reports showed close margins (<2 mm on the specimen side) in 59 cases (12.3%) and positive margins (negative at frozen sections but positive at the definitive histopathologic examination) in 16 (3.3%).

Comparison between clinical and pathological staging showed up-staging of the primary tumor in 73 (15.2%) cT3 lesions that became pT4a (49 in subcategory III and 24 in subcategory IV), while 6 cT4a tumors became pT3 (3 in subcategory I and 3 in subcategory II).

In total, 428 patients (89.3%) had been staged as cN0. In contrast, 40 (9.3%) of them became pN+ after ND. Overall, lymph node metastases were detected in 72 (15%) patients of whom 41 (8.6%) had multiple metastases (Table 1).

### *Patterns of failure*

In total, 70 (14.6%) patients developed recurrences: 28 (40%) were local, 18 (25.7%) regional, and 4 (5.7%) loco-regional. Seven (10%) had local and distant recurrences, 2 (2.8%) were regional and distant, whereas 10 (14.3%) developed distant metastasis only. One patient (1.4%) developed both loco-regional and distant recurrences.

### *Survival and disease control according to different subcategories*

The 5-year estimates of the abovementioned oncologic outcomes for each subcategory are reported in Table 3. OS was significantly higher ($p<0.01$, with LR and GBW tests) in patients affected by anterior tumors (subcategories I and III, 92.7%) when compared with those treated for posterior ones (subcategories II and IV, 82.3%) (Fig. 6A). Moreover, anterior pT3 tumors (subcategory I) had better OS than posterior pT3 tumors (subcategory II, $p<0.001$, with LR and GBW tests), although no significant difference was detected among pT4 tumors (subcategories III vs. IV). Finally, OS was hampered by T classification in anterior tumors (subcategories I vs. III, $p<0.01$, with LR and GBW tests), but not in posterior ones (subcategories II vs. IV).

In the same way, DSS was affected by the described laryngeal compartmentalization: it was 96.3% in anterior (subcategories I and III) and 90.1% in posterior tumors (subcategories II and IV) ($p<0.05$, with LR and GBW tests) (Fig. 6B). A statistically significant difference was also demonstrated when comparing anterior (subcategory I) and posterior (subcategory II) pT3 tumors ($p<0.05$, with LR and GBW tests), but not when analyzing pT4 tumors (subcategories III vs. IV), even though they had a similar trend. Finally, no difference in terms of DSS was detected by comparison of pT3 and pT4 tumors located in the same laryngeal compartment (subcategories I vs. III and II vs. IV).

DFS was significantly reduced in posterior (subcategories II and IV, 78.8%) compared to anterior tumors (subcategories I and III, 88.3%) ($p<0.05$, with LR and GBW tests) (Fig. 6C). Likewise, posterior pT3 (subcategory II) had worse DFS ($p<0.05$, with LR and GBW tests) than anterior pT3 tumors (subcategory I), although no significant difference was detected among subcategories III and IV. Moreover, patients treated for pT4 tumors had more recurrences than those with pT3 neoplasms independently from the antero-posterior localization of the disease (subcategories I vs. III, $p<0.01$; subcategories II vs. IV, $p<0.05$, with LR and GBW tests).

LRC was not significantly different between anterior (subcategories I and III, 88.6%) and posterior tumors (subcategories II and IV, 83.3%) (Fig. 6D). Nevertheless, it was better in subcategory I than in subcategory II ($p<0.05$, with LR test), although pT4 (subcategories III and IV) had comparable results. Finally, T status affected LRC of anterior tumors (subcategories I vs. III, $p<0.01$, with LR and GBW tests), but not that of posterior ones (subcategories II vs. IV).

Likewise, LC was similar in anterior (subcategories I and III, 92.7%) and posterior tumors (subcategories II and IV, 88.1%) (Fig. 6E). Again, subcategory I had better control than subcategory II ($p<0.05$, with LR test), whereas no significant difference was detected when comparing pT4 (subcategories III vs. IV).

Patients affected by anterior tumors were less prone to fatal outcomes and had less need of salvage total laryngectomy than those with posterior ones (LFS 90.1% for subcategories I and III and 75.7% for subcategories II and IV; $p<0.001$ with LR test and $p<0.01$ with GBW test) (Fig. 6F). Subcategory I had better LFS than subcategory II ($p<0.001$, with LR and GBW tests), but no significant difference was detected between subcategories III and IV. Finally, LFS was higher in anterior pT3 than in anterior pT4 tumors ($p<0.01$, with LR and GBW tests), whereas posterior pT3 had better LFS with respect to posterior pT4 tumors as an early event only ($p<0.05$, with GBW test).

Similarly, the LEDFS was higher in anterior (subcategories I and III, 88.8%) than in posterior tumors (subcategories II and IV, 74.9%, $p<0.001$, with LR test and $p<0.01$, with GBW test) (Fig. 6G). Again, despite no significant difference being detected between pT4 tumors (subcategories III vs. IV), anterior pT3 (subcategory I) had better LEDFS than posterior pT3 tumors (subcategory II, $p<0.001$, with LR and GBW tests). Furthermore, only anterior tumors were affected by T classification: anterior pT4 (subcategory III) had worse LEDFS ($p<0.001$, with LR and GBW tests) than anterior pT3 (subcategory I).

*Correlation between each subcategory and factors affecting loco-regional recurrence*

The associations between positive or close margins, pN+, level VI pN+, extracapsular spread (ECS) and subcategories have been evaluated and results are summarized in Table 4.

Tumor localization was generally associated with the occurrence of ECS alone: its risk of occurrence was indeed higher in posterior (subcategories II and IV) than in anterior tumors (subcategories I and III) ($p<0.05$). Despite being not significantly different, the occurrence of ECS appeared to be more frequent in subcategory IV.

The prevalence of positive margins was homogeneous amongst the subcategories, but their occurrence was significantly more frequent in pT4a when compared with pT3 tumors (subcategory III vs. I, $p<0.05$; subcategory IV vs. II, $p<0.001$). Similarly, no statistically significant difference was detected in terms of pN+ prevalence amongst the subcategories, but lymph node involvement at level VI was more common in patients affected by pT4a tumors, with respect to those with pT3 tumors (subcategory III vs. I, p<0.001; subcategory IV vs. II, p<0.01).

DISCUSSION

The last two decades have gradually witnessed a paradigm shift in the treatment of laryngeal cancer, with a progressively increasing significance given to organ and function preservation.[9-11, 15, 16] Focusing on advanced stages, all the therapeutic approaches, non-surgical as well as surgical by OPHLs, have demonstrated that larynx preservation is feasible, even though some disappointing long-term results of chemoradiotherapy (CRT) protocols deserve further evaluation and investigation.[9, 23]

Despite the undoubted advantages deriving from the laryngeal function preservation approach in terms of quality of life, laryngeal oncology has struggled to develop like other subspecialties in oncology, probably because of the major push towards organ preservation by non-surgical modalities. In fact, this paper clearly demonstrates that excellent results can be obtained even though the application of surgical function sparing strategies like OPHLs maintained that particular accuracy in their indications and limits are observed. From this perspective, the implementation of correct OPHL indications, rather than the surgical technique itself, is probably one of the most important keys to success in this type of surgery.

Assuming that total laryngectomy is the safest treatment for laryngeal cancer in intermediate and advanced stages, any therapeutic approach attempting to preserve the larynx should be based on careful case selection, where a pivotal role is taken by patient- and tumor-related parameters. For this reason, meaningful direct comparisons between the oncologic and functional outcomes of CRT, total laryngectomy and OPHLs are lacking in the current literature for the very reason that they are quite difficult, if not impossible, to be comprehensively made. For the innate diversity (in terms of staging, comorbidity, willingness, age, gender, profession, previous treatments, etc.) of those patients considered amenable to one treatment versus another, a true comparison of crude data like survival or swallowing/voice (just to mention the most obvious) is far beyond the real possibilities of any prospective or retrospective analysis.

OPHL can be offered to patients as a valuable alternative to preserve part of the larynx and its functions, even in advanced T categories, avoiding the negative physical and psychosocial impacts of a permanent tracheostomy[15, 16, 19]. After a strict selection of patients (based on the assessment of good general and functional conditions, the absence of clinically positive neck nodes and a good compliance to an intensive rehabilitation protocol), different types of partial laryngectomy can be proposed. When a patient accepts a conservative surgical management approach, in fact, an OPHL type I, IIa, IIb, IIIa or IIIb may be performed guided by intraoperative evaluations confirmed by frozen sections. This kind of flexibility and customized surgical approach requires specific expertise and, therefore, centralization of such cases in sufficiently large reference centers.

Further aspects to be considered during pre-treatment multidisciplinary visit are the well-known absolute contraindications to OPHL type II and III, which are based on T and N stage.

In our experience, these are represented by: i) lesions extended to base of tongue or pyriform sinus; ii) lesions with major invasion of pre-epiglottic space involving the hyoid bone, lesion involving the inter-arytenoid space, the posterior commissure and both arytenoid cartilages; iii) large extralaryngeal spread of cancer involving thyroid gland, strap muscles, cervical skin, internal jugular vein or common carotid artery; and iv) lesions reaching the first tracheal ring.

The suspected presence of clinically positive nodes >cN1 is not an absolute contraindication. However, it does not represent a good indication to OPHL due to the probable need for a post-operative RT: the first goal of a function sparing surgical approach should indeed be to get a single-shot therapy.

In the present series, stringent clinical-radiological selection criteria have been adopted to identify homogeneous cT3 and cT4 subcategories that may be treated by OPHL type II – III with the best chance of success. For both supraglottic and glottic T3 and T4 tumors, the most crucial prognosticator appears to be involvement of the posterior PGS, usually associated with reduced mobility or fixation of the ipsilateral arytenoid. This simple criterion of anterior vs. posterior laryngeal compartmentalization has herein been demonstrated to be a useful adjunctive parameter to be included in preoperative therapeutic planning.

In fact, when dealing with anterior T3 tumors with normal vocal cord/arytenoid mobility (subcategory I), OPHL compares favorably with transoral laser microsurgery (TLM) (whose local control has been shown to be in the range of 44–72% for glottic and 70–87% for supraglottic tumors),[24-27] and with CRT (whose 2-year laryngo-esophageal dysfunction-free survival has been reported to be around 40%).[28] The inner thyroid lamina infiltration does not negatively impact on the possibility to attain adequate disease control by such an open-neck conservative approach, while this is definitely the case for TLM and the issue is still debated for CRT.

Considering anterior T4 tumors (subcategory III), OPHL allows quite favorable oncologic outcomes that can only be compared with those described after total laryngectomy. Here the difference is in terms of a better quality of life and function preservation of the larynx. Interestingly, our series highlights that there is not a great difference in terms of OS, DSS, and LFS between subcategory I and III when these lesions have been addressed by OPHL.

In contrast, the posterior lesions are much more troublesome and definitely represent the most difficult clinical scenario. Posterior T3 tumors with vocal cord/arytenoid fixation (subcategory II) have been shown to offer very poor outcomes when treated by either TLM or CRT. Even using OPHLs, the oncologic outcomes are significantly worse in this subcategory when compared to anterior tumors (OS $p<0.001$, DSS $p<0.05$, and DFS $p<0.001$).

OPHLs for T3 cancer affecting arytenoid motility requires a detailed knowledge of tumor growth and diffusion patterns. Traditionally, arytenoid fixation was adopted as an exclusion criterion for OPHLs. However, in a study on 77 cases, Katilmis et al. focused on the possible different causes of arytenoid fixation: involvement of intrinsic laryngeal muscles with insertion on the arytenoid, crico-arytenoid joint invasion, and recurrent nerve infiltration.[29] Beyond these, another cause of reduced/absent arytenoid mobility is represented by the tumor mass effect, which is present in about 60% of supraglottic lesions. Therefore, an adequate preoperative endoscopic and imaging work-up able to reliably distinguish among such different causes of arytenoid fixation is strongly warranted and might in future greatly help in subclassifying these lesions according to more detailed etiologies. This may also mean that posterior T3 tumors could be considered more similar to T4 from an oncologic as well as from a functional point of view. Even from an anatomic perspective, posterior T3 tumors can present cricoarytenoid joint invasion, cricoid plate infiltration, as well as lateral cricoarytenoid muscle involvement, or perineural spreading along the recurrent nerve. These factors allow tumors to grow outside the laryngeal box, towards the hypopharynx and cervical soft tissues. Once the tumor has gained the thyro-cricoarytenoid gateway, it is indeed almost outside the larynx and, in this sense, it is prognostically more similar to T4 cancer. Moreover, in posterior T3-T4 tumors, the risk of occurrence of lymph nodes with ECS is 2.5 times higher than in anterior lesions, and the occurrence of close margins is 2.4 times higher in anterior pT4 than in pT3, and 8.1 times higher in posterior lesions. In light of this, OPHL should be reserved for very carefully selected cases of posterior T3 (and even less frequently in posterior T4 or subcategory IV) since, even from a functional point of view, OPHL type III + CAU (removal of one cricoarytenoid unit) definitively represents an "extreme" conservative surgery with several technical difficulties and sometimes unpredictable outcomes. Therefore, in posterior T3-T4 tumors, total laryngectomy (with adjuvant CRT or RT) should remain the mainstay of treatment.

Another advantage of OPHLs type II – III is their respectable functional outcomes whose occurrences have been summarized in Table 5. As a matter of fact, use of OPHL allows quite good results to be obtained in terms of the composite end point represented by LEDFS. Even from this point of view, anterior pT3 (subcategory I) had better LEDFS than posterior pT3 tumors (subcategory II, $p<0.001$, with LR and GBW tests).

Recently, comparing CRT versus primary surgery, Timme et al. showed that some selected patients with locally advanced laryngeal cancer can be offered non-surgical organ preservation without compromising survival.[28] However, these have higher rates of laryngeal and esophageal dysfunction than those obtained by OPHLs.

## CONCLUSIONS

OPHLs type II – III for intermediate/locally advanced laryngeal cancer provide good oncological and functional outcomes only if strict patient and tumor selection criteria are followed. Concerning the cT3 category, anterior tumors sparing the posterior PGS and not affecting arytenoid mobility are definitely manageable by such a surgical approach with excellent oncologic outcomes. OPHLs could also be offered to patients affected by early anterior cT4aN0, strongly motivated to avoid total laryngectomy and declining concurrent CRT.

Even though associated with more than promising results, probably due to the strict criteria used to select the subset of patients more suitable for partial laryngectomies, this conservative surgical approach should be carefully applied in cases of cT3 tumors reaching the posterior PGS and causing arytenoid fixation. In fact, the subset of patients belonging to subcategory II comprises tumors characterized by biological behavior as well as oncologic results that appear very similar to those of T4a cancers.

Anyway, a new method of selecting cases amenable to OPHL should first keep in mind the absolute local and general contraindications to this type of surgery.

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**Table 1 – Epidemiologic and clinical characteristics of patients treated by OPHL in the present series (N=479).**

| | | No. of patients (%) | |
|---|---|---|---|
| **Age** | Mean±standard deviation | | 60.0±9.2 |
| | Range | | 16-83 |
| **Gender** | Male | | 434 (90.6%) |
| | Female | | 45 (9.4%) |
| **Karnofsky** | 100 | | 298 (62.2%) |
| | 90 | | 181 (37.8%) |
| **Arytenoid mobility** | Normal | | 293 (61.2%) |
| | Impaired/fixed | | 186 (38.8%) |
| **pTN** | | **Glottic** | **Supraglottic** |
| pT3 | N0 | 290 (60.5%) | 46 (9.6%) |
| | N1 | 15 (3.1%) | 8 (1.7%) |
| | N2 | 18 (3.8%) | 13 (2.7%) |
| pT4a | N0 | 69 (14.4%) | 2 (0.4%) |
| | N1 | 8 (1.7%) | 0 (0.0%) |
| | N2 | 7 (1.5%) | 3 (0.6%) |

**Table 2 – Surgical procedures performed**

| | No. of patients (%) | | | |
|---|---|---|---|---|
| **OPHL type** | **Subcategory I (N=233)** | **Subcategory II (N=157)** | **Subcategory III (N=60)** | **Subcategory IV (N=29)** |
| IIa | 33 (14.2%) | 15 (9.6%) | 7 (11.7%) | 4 (13.8%) |
| IIa + ARY | 125 (53.6%) | 69 (43.9%) | 11 (18.3%) | 6 (20.7%) |
| IIb | 19 (8.2%) | 6 (3.8%) | 6 (10%) | - (0%) |
| IIb + ARY | 49 (21%) | 37 (23.6%) | 19 (31.7%) | 5 (17.3%) |
| IIIa | 1 (0.4%) | 2 (1.3%) | 3 (5%) | 1 (3.4%) |
| IIIa + CAU | 6 (2.6%) | 28 (17.8%) | 10 (16.7%) | 10 (34.5%) |
| IIIb | - (0%) | - (0%) | 2 (3.3%) | 1 (3.4%) |
| IIIb + CAU | - (0%) | - (0%) | 2 (3.3%) | 2 (6.9%) |

***Legend*** **–** IIa: supracricoid partial laryngectomy with crico-hyoido-epiglottopexy; IIb: supracricoid partal laryngectomy with crico-hyoidopexy; IIIa: supratracheal partial laryngectomy with tracheo-hyoido-epiglottopexy; IIIb: supratracheal partial laryngectomy with tracheo-hyoidopexy; ARY: extension to one arytenoid; CAU: extension to one cricoarytenoid unit.

**Table 3 – Oncologic outcomes stratified according to subcategory**

| | Subcategory | | | |
|---|---|---|---|---|
| | I | II | III | IV |
| OS | 95% | 82.8% | 82.9% | 79.9% |
| DSS | 97% | 90.7% | 93.6% | 86.5% |
| DFS | 91.5% | 81.2% | 74.6% | 64.2% |
| LRC | 91.9% | 84.2% | 74.6% | 77.3% |
| LC | 96% | 89.1% | 78.1% | 81.6% |
| LFS | 93% | 77.7% | 77.2% | 64.1% |
| LEDFS | 93.1% | 76.6% | 70.4% | 64.7% |

***Legend*** **–** OS = overall survival; DSS = disease specific survival; DFS = disease-free survival; LRC = loco-regional control; LC = local control; LFS = laryngectomy-free survival; LEDFS = laryngo-esophageal dysfunction free survival

**Table 4 –** **Prognostic factors for recurrences. ODDS Ratio and $\chi 2$ analyses amongst subcategories.**

ODDS Ratio

| Subcategories | II vs. I | IV vs. III | III vs. I | IV vs. II | II+IV vs. I+III |
|---|---|---|---|---|---|
| Close margins | 0.65 | 2.20 | 2.41 | 8.13 | 0.93 |
| Positive margins | 2.70 | 1.40 | 3.12 | 1.61 | 2.08 |
| pN+ | 1.69 | 2.13 | 1.74 | 2.20 | 1.32 |
| Lev VI+ | 3.77 | 2.32 | 11.69 | 7.20 | 2.14 |
| ECS | 2.03 | 7.51 | 1.09 | 4.05 | 2.53 |

$\chi 2$

| Subcategories | II vs. I | IV vs. III | III vs. I | IV vs. II | II+IV vs. I+III |
|---|---|---|---|---|---|
| Close margins | 0.349 | 0.172 | 0.032 | 0.000 | 0.907 |
| Positive margins | 0.196 | 0.899 | 0.312 | 0.927 | 0.233 |
| pN+ | 0.514 | 0.470 | 0.330 | 0.179 | 0.353 |
| Lev VI+ | 0.106 | 0.418 | 0.000 | 0.006 | 0.118 |
| ECS | 0.292 | 0.062 | 0.766 | 0.076 | 0.047 |

**Fig. 1 Anatomical drawings representing the anterior and posterior laryngeal compartments defined by a vertical plane tangential to the arytenoid vocal process and perpendicular to the ipsilateral thyroid lamina: A) axial; B) sagittal views.**

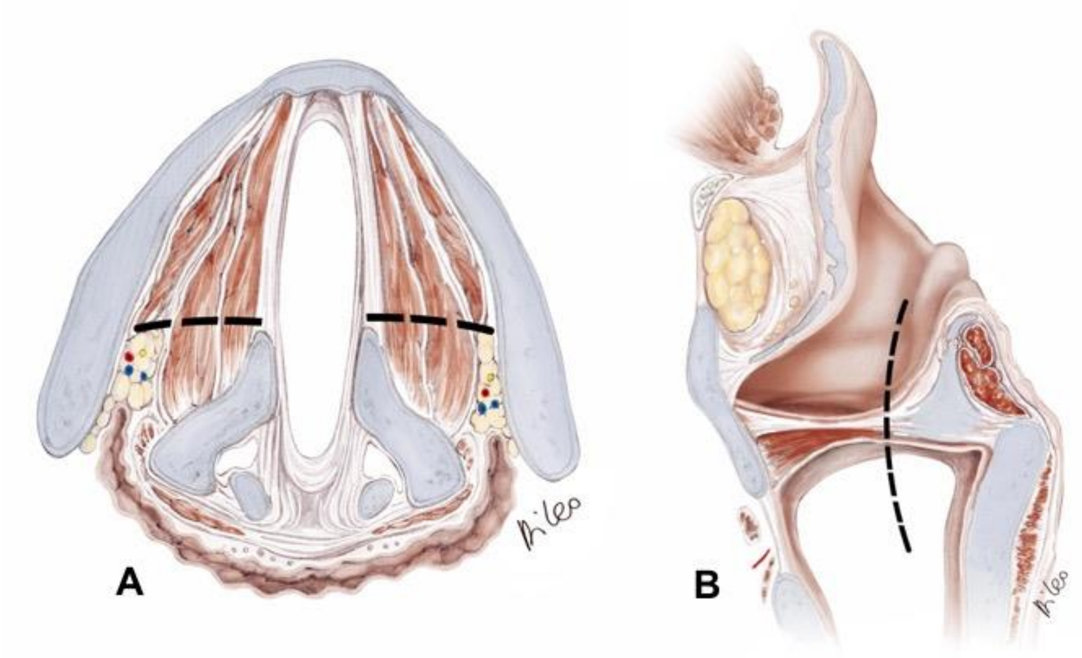


**Fig. 2 Anatomical drawings representing the possible tumor presentations in subcategory I. A) Supraglottic cT3 extending to the PES and anterior commissure; B) supraglottic cT3 with PES and anterior PGS involvement; C) glotto-supraglottic cT3 with anterior PGS and infrapetiole region involvement; D) glottic cT3 with anterior PGS involvement; E) glottic cT3 with anterior PGS, internal thyroid lamina, and anterior commissure involvement; F) glottic-subglottic cT3 with anterior PGS and subglottic mucosa involvement**.

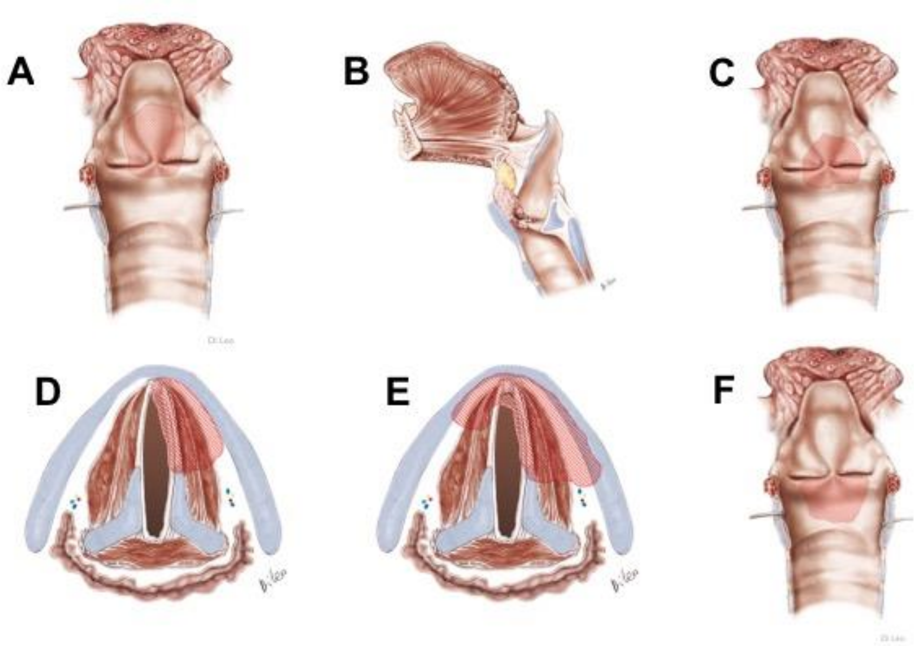


**Fig. 3 Anatomical drawings representing the possible tumor presentations in subcategory II. A) Supraglottic cT3 with superior and posterior PGS and arytenoid involvement; B) glottic cT3 with whole PGS involvement; C) glottic cT3 with whole PGS and internal thyroid lamina involvement; D) glotto-subglottic cT3 with posterior PGS and crico-arytenoid joint involvement**.

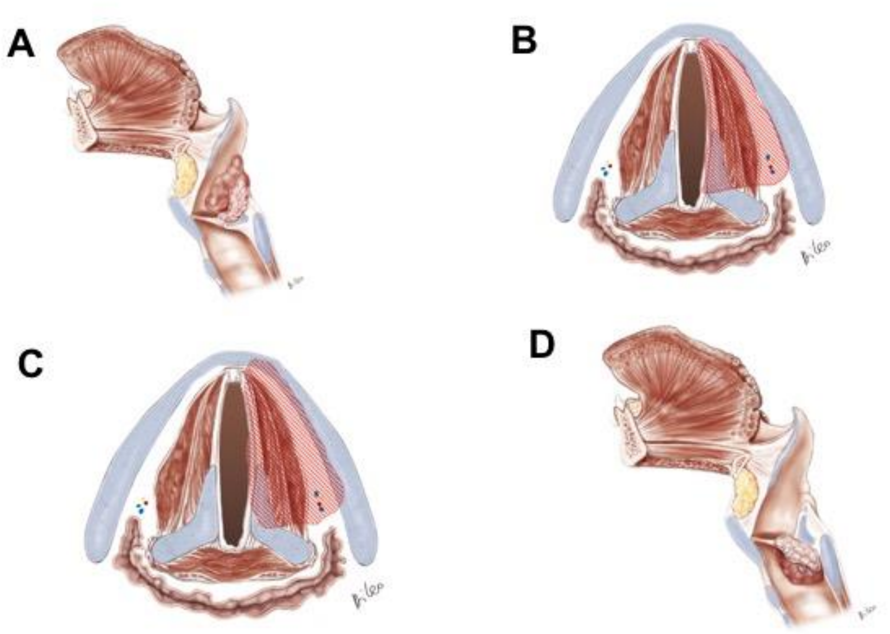


**Fig. 4 Anatomical drawings representing the possible tumor presentations in subcategory III. A) Anterior supraglottic cT4a with extension through the thyro-hyoid membrane and thyroid cartilage; B) anterior glottic cT4a with extension through the thyroid cartilage and crico-thyroid membrane.**

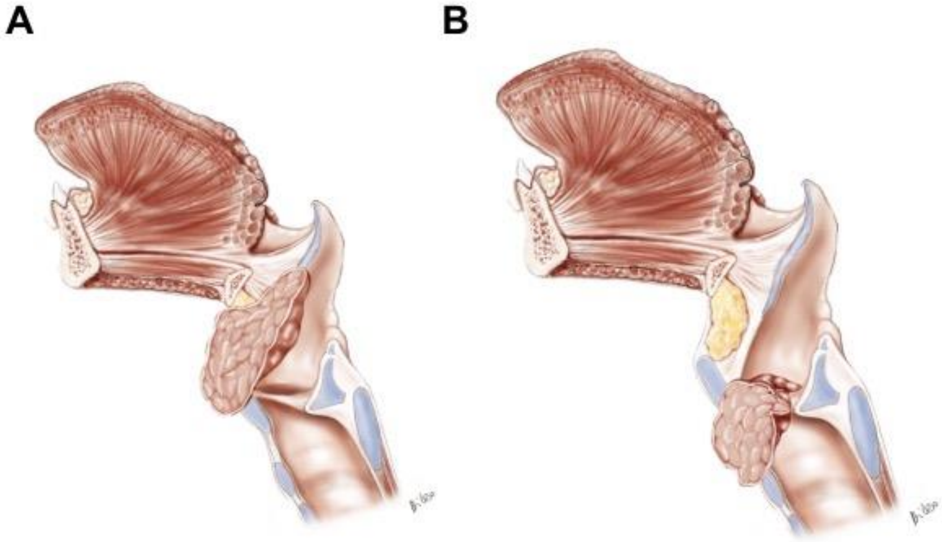


**Fig. 5 Anatomical drawings representing the possible tumor presentations in subcategory IV. A) Posterior glottic cT4a with extension through the crico-thyroid membrane; B) posterior transglottic cT4a with extension through the thyroid cartilage and cricoid involvement.**

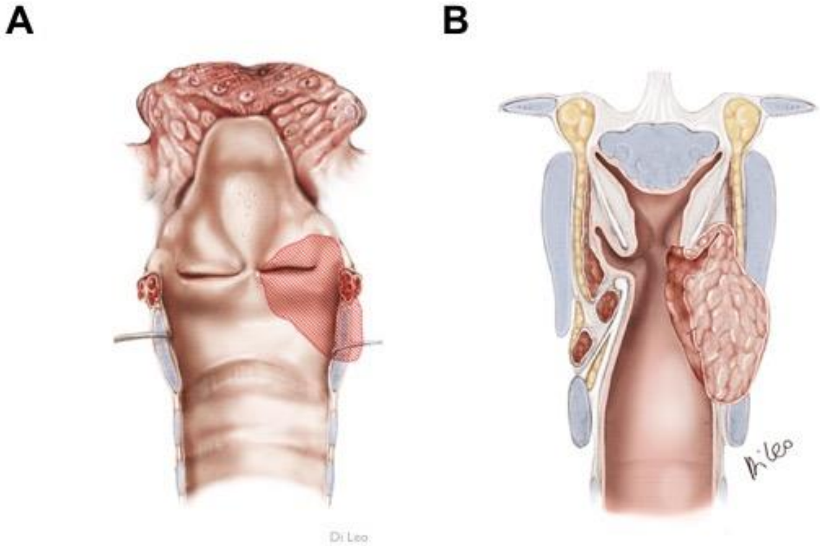
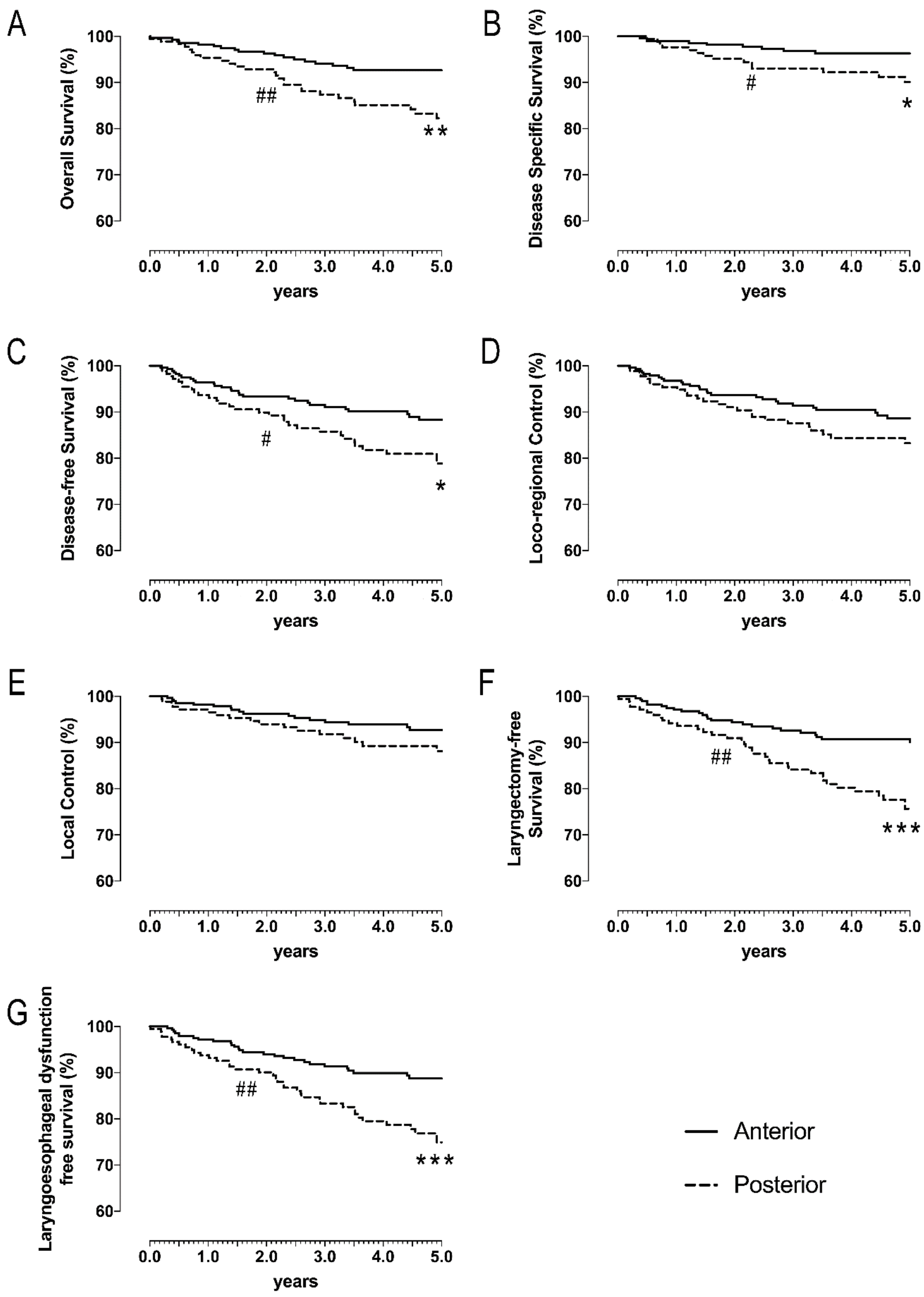


**Fig. 6 A) Overall survival, B) disease-specific survival, C) disease-free survival, D) locoregional control, E) local control, F) laryngectomy-free survival, and G) laryngo-esophageal dysfunction-free survival for the entire cohort. Log-Rank test: *p<0.05; **p<0.01; ***p<0.001. Gehan-Breslow-Wilcoxon test: #p<0.05; ##p<0.01.**



# Paper 2

## *Open partial horizontal laryngectomies: a proposal for classification by the working committee on nomenclature of the European Laryngological Society*

*Abstract*

We present herein the proposal of the European Laryngological Society working committee on nomenclature for a systematic classification of open partial horizontal laryngectomies (OPHL). This is based on the craniocaudal extent of laryngeal structures resected, instead of a number of different and heterogeneous variables present in existing nomenclatures, usually referring to eponyms, types of pexy, or inferior limit of resection. According to the proposed classification system, we have defined three types of OPHLs: Type I (formerly defined horizontal supraglottic laryngectomy), Type II (previously called supracricoid laryngectomy), and Type III (also named supratracheal laryngectomy). Use of suffixes "a" and "b" in Type II and III OPHLs reflects sparing or not of the suprahyoid epiglottis.

Various extensions to one arytenoid, base of tongue, piriform sinus, and crico-arytenoid unit are indicated by abbreviations (ARY, BOT, PIR, and CAU, respectively). Our proposal is not intended to give a comprehensive algorithm of application of different OPHLs to specific clinical situations, but to serve as the basis for obtaining a common language among the head and neck surgical community. We therefore intend to present this classification system as a simple and intuitive teaching instrument, and a tool to be able to compare surgical series with each other and with non-surgical data.

*Introduction*

Open partial laryngectomies still play an important role in contemporary conservative management of laryngeal cancer, closing the gap between transoral approaches on one hand and total laryngectomy or non-surgical organ preservation strategies on the other [1, 2]. Furthermore, with increasing utilization of organ preservation strategies to treat laryngeal cancer, OPHLs have established an important and oncologically reliable role in the management of recurrent radio-resistant laryngeal carcinoma [3, 4]. Even though some of these surgical techniques date back more than half a century [5–14] and their use in some part of the world is progressively expanding, a comprehensive classification of open partial laryngectomies has not been attempted in the literature. At the same time, the European Laryngological Society (ELS) has established the nomenclature for transoral glottic [15, 16] and supraglottic resections [17], nowadays commonly used in papers and meetings at least all over Europe, and we therefore felt that a similar effort was needed also for open partial laryngectomies. Traditionally, open partial laryngectomies have been placed in three subgroups:

1. Vertical partial laryngectomies: This approach has been used for treatment of glottic carcinomas. By dividing the thyroid cartilage in the midline or in a paramedian sagittal plane, access to the glottis is achieved, allowing for resection of one or both vocal cords, the anterior commissure, and the adjacent portions of the thyroid cartilage. Open cordectomy via a midline thyrotomy approach without cartilage resection may be considered the least invasive type of procedure in this subgroup. All other interventions include some degree of thyroid cartilage sacrifice. Some of these techniques include the use of local or free flaps to reconstruct the glottis and improve phonation. Many different subtypes of this approach have been described in the medical literature, and have been coined with the names of their describers [18]. However, they do not represent the object of the present nomenclature and will not be further addressed in this paper.

2. Horizontal partial laryngectomies: This approach has been, and still is, widely used to resect tumours arising from the supraglottic structures of the larynx. The procedure is closely linked to the name of Alonso [5] who popularised it in the 1950s [19]. The indications include tumours of the supraglottic endolarynx with at least one unaffected arytenoid cartilage, without extension to the glottic plane.

3. Atypical open partial laryngectomies: Apart from the previous two major subgroups, some additional and “atypical” procedures, not suitable for categorisation in the “vertical” or “horizontal” subgroups, have been

published over the years. These include subtotal laryngectomy (regarded by some authors as a “near total” laryngectomy due to the natural postoperative persistence of tracheotomy) [20], combined endoscopic and open approaches [21], and procedures using free microvascular flaps to reconstruct major laryngeal defects following partial laryngectomy [22–24].

This generally accepted classification, however, is not suitable to implement innovative partial procedures that apply the idea of transverse (horizontal), drawer-like, resections to non-supraglottic carcinomas, i.e. to glottic and subglottic tumours. This concept was first suggested by Majer and Rieder in Vienna [8] and became popular through routine clinical application to intermediate category tumours of the glottis and infrahyoid supraglottis in France [12, 25] and Italy [11, 26], and later in the USA [27] and other parts of the world. While many of the traditionally used vertical partial procedures have meanwhile become obsolete due to the widespread use of transoral procedures, these interventions, usually referred to as “supracricoid partial laryngectomies”, have now gained major importance for the treatment of intermediate and selected advanced laryngeal carcinomas. In fact, this type of laryngeal surgery is now the surgical standard for laryngeal cancer that is not accessible via a transoral route. To date, the terminology used in the literature to classify these surgical techniques identifies only the inferior limit of resection (e.g., supraglottic, supracricoid, and supratracheal laryngectomies) or the type of pexy accomplished to achieve laryngeal reconstruction (e.g., crico-hyoidoepiglottopexy, crico-hyoidopexy, and so on). As a result of such heterogeneous nomenclature, variants of every procedure are left vaguely undescribed. A working party of the Nomenclature Committee of the ELS was established to provide systematic and widespread nomenclature for a range of laryngological surgical procedures including transoral laryngeal resections and open partial laryngectomies. The authors of this proposal attempt to establish a comprehensive but straightforward classification system of these surgical procedures. The aim is not to define or restrict therapeutic indications but, using a common system, to aid in teaching these procedures to residents and novices, and in interpreting and comparing the postoperative results achieved by different institutions.

**Principles of classification**

The common denominator of every open partial laryngectomy described herein is its modulated resection in a cranio-caudal direction, being the horizontal upper and inferior limits of excision the most adequate to be used for description of each surgical procedure. For this reason, we have comprehensively indicated these techniques with the term OPHL. In order to simplify the nomenclature of the different types of OPHL, and to clarify the extent of surgical removal, the present classification identifies three types of surgical procedures based on the lower limit of resection:

- Type I → Supraglottic laryngectomies
- Type II → Supracricoid laryngectomies
- Type III → Supratracheal laryngectomies

Moreover, each type may be extended to adjacent laryngeal and/or pharyngeal sites; the extension of surgical removal is indicated by abbreviations as follows:

- +ARY → to involve one arytenoid (specifying the side of resection)
- +BOT → to involve the base of tongue
- +PIR → to involve one piriform sinus (specifying the side of resection)
- +CAU → to involve one crico-arytenoid unit composed by arytenoid, crico-arytenoid joint, and underlying hemicricoid plate (specifying the side of resection)

For Type II and III OPHLs, the suffix “a” means that the suprahyoid epiglottis has been spared, while the suffix “b” indicates its removal.

**Classification**

*OPHL Type I* (*horizontal supraglottic laryngectomy*):

Entails the resection of the whole supraglottis, including the pre-epiglottic space and the upper half of the thyroid cartilage. Inferiorly, the resection encompasses the petiole of the epiglottis, down to the anterior commissure, and the ventricular folds. Posteriorly, the limit of resection passes in front of the arytenoids, sectioning the ventricular and aryepiglottic folds. Superiorly, the incision transects the valleculae along the posterior aspect of the hyoid bone (Fig. 1a, b). Larynx reconstruction is accomplished by a thyro-hyoidopexy. In individual cases, resection of the hyoid bone may be necessary. In these cases, the pexy will approximate the inferior thyroid and the base of tongue. Wound complications and pharyngo-cutaneous fistulae as a consequence of a disruption of this pexy are more frequently encountered as in thyro-hyoidopexy. Therefore, this variant should only be used if the tumour reaches the hyoid bone. A partial hyoidectomy can be also considered in these cases.

*OPHL Type I+ARY* (*horizontal supraglottic laryngectomy extended to one arytenoid*): Represents an extension of the former procedure to one arytenoid. To prevent aspiration and enhance the loudness of the voice, the disconnected vocal fold should be fixed postero-medially to the cricoid plate. “Left” or “right” specify the side of the removed arytenoid.

- *OPHL Type I+BOT* (*horizontal supraglottic laryngectomy extended to the base of tongue*): Represents an extension of the classic OPHL Type I to a limited portion of the base of tongue.
- *OPHL Type I+PIR* (*horizontal supraglottic laryngectomy extended to the piriform sinus*): Represents an extension of the OPHL Type I to the medial and/or lateral aspects of the piriform sinus.
- *OPHL Type II* (*supracricoid laryngectomies*): Entails the resection of the entire thyroid cartilage, with the inferior limit represented by the upper edge of the cricoid ring. The differences between the various subtypes of OPHL Type II are related to the amount of supraglottis removed and their extension, if any, to include one arytenoid.
- *OPHL Type IIa* (*supracricoid laryngectomy with cricohyoido-epiglottopexy*): Superiorly, the thyro-hyoid membrane is entered horizontally, and the pre-epiglottic space and epiglottic cartilage are transected so that the suprahyoid part of the epiglottis is spared. On both sides, the inferior constrictor muscles are incised, the piriform sinuses are dissected, the inferior horns of thyroid cartilage cut, and the ventricular and vocal folds divided down to the lower limit of

resection in the subglottic region. Larynx reconstruction is achieved by crico-hyoido-epiglottopexy (Fig. 2a, b).

- *OPHL Type IIa+ARY* (*supracricoid laryngectomy with crico-hyoido-epiglottopexy extended to one arytenoid*): Represents an extension of OPHL Type IIa to one arytenoid. “Left” or “right” specify the side of the removed arytenoid.
- *OPHL Type IIb* (*supracricoid laryngectomy with cricohyoidopexy*): Superiorly, the thyro-hyoid membrane is horizontally divided along the lower border of the hyoid bone. The posterior aspect of the hyoid is dissected, and the valleculae and the entire epiglottis are included in the surgical specimen. Laterally and inferiorly the procedure is carried out as in OPHL Type IIa. The entire supraglottis and the pre-epiglottic space are removed. Larynx reconstruction is achieved by crico-hyoidopexy (Fig. 3a, b).
- *OPHL Type IIb+ARY* (*supracricoid laryngectomy with crico-hyoidopexy extended to one arytenoid*): Represents an extension of OPHL Type IIb to one arytenoid. “Left” or “right” specify the side of the resected arytenoid.
- *OPHL Type III* (*supratracheal laryngectomies*): Entails the resection of the entire supraglottic, glottic, and part of the subglottic sites, sparing both or at least one functioning crico-arytenoid unit (i.e. half of the posterior cricoid plate, with the corresponding arytenoid and the intact inferior laryngeal nerve of the same side). Inferiorly, the limit of resection encompasses the cricoid ring and/or part of the cricoid plate and/or the first two tracheal rings. The various types of OPHL Type III differ each other for the amount of supraglottis resected and for the postero-lateral extension, if any, to include one crico-arytenoid unit. Laryngeal reconstruction is accomplished by either tracheo-hyoidoepiglottopexy or tracheo-hyoidopexy.
- *OPHL Type IIIa* (*supratracheal laryngectomy with tracheo-hyoido-epiglottopexy*): Inferiorly, after the section of ventricular and vocal folds, the cricoid ring is divided on both sides, medially to the crico-thyroid joints, from the cricoid plate. The inferior limit of the resection is either the membrane between the cricoid cartilage and the first tracheal ring or the second/third

tracheal ring. Laryngeal reconstruction is achieved by tracheo-hyoido-epiglottopexy (Fig. 4a, b).

- *OPHL Type IIIa+CAU* (*supratracheal laryngectomy with tracheo-hyoido-epiglottopexy extended to one cricoarytenoid unit*): Represents an extension of OPHL Type IIIa to one crico-arytenoid unit (Fig. 5). “Left” or “right” specify the side of the resected crico-arytenoid unit.
- *OPHL Type IIIb* (*supratracheal laryngectomy with tracheo-hyoidopexy*): Represents the complete removal of thyroid cartilage, epiglottis and other supraglottic structures except for the arytenoids, and part of the cricoid cartilage up to the first two tracheal rings. Laryngeal reconstruction is obtained by a tracheo-hyoidopexy (Fig. 6a, b).
- *OPHL Type IIIb+CAU* (*supratracheal laryngectomy with tracheo-hyoidopexy extended to one crico-arytenoid unit*): Represents an extension of OPHL Type IIIb to one crico-arytenoid unit (Fig. 5). “Left” or “right” specify the side of the resected crico-arytenoid unit.

**Discussion**

Classification is defined as the systematic arrangement of different entities into categories according to differing characteristics. A good classification should make life more efficient and facilitate the study of the corresponding units or elements. It should also be able to draw meaningful comparisons, allow scientists and clinicians to apply a common language, be easy to learn, use, and subsequently expanded if needed. In recent years, traditional open partial laryngectomies have been largely replaced by transoral laser microsurgery. For most T1 and some T2 lesions of the larynx, this minimal access approach has been shown to be oncologically reliable while significantly reducing the complication rates of laryngeal surgery. However, intermediate size tumours, including some T2 and most T3 lesions, arising from the anterior commissure and the infrahyoid portion of the epiglottis, frequently cannot be removed safely via a transoral approach. For these tumours, OPHLs have gained major clinical importance in many parts of Europe as they allow for complete and safe resection of intermediate and selected advanced primary neoplasms of the glottic and supraglottic sites.

A number of reports in the international literature have already demonstrated the oncologic validity of OPHLs, both in primary and in salvage treatment scenarios, as well as their predictability and reproducibility in terms of functional outcomes. However, direct comparisons with other surgical and non-surgical treatment modalities are particularly difficult for many reasons. In fact, the literature addressing this topic is extremely abundant and a large number of treatment options have been described, coping with the different possible patterns of laryngeal tumour spread. This represents one of the most insidious caveats when trying to compare different series, since the risk is truly to compare completely different clinical entities.

We stress that the aim of our classification system is not to define or restrict surgical indications, since in the same patient the procedure chosen as the most adequate may vary according to specific preferences, while respecting both functional and oncological purposes. A comprehensive classification of OPHLs must rather help in understanding and comparing literature reports dealing with functional and oncological outcomes obtained by various OPHLs, and to possibly cumulate meta-analytic figures to retrospectively compare surgical series among one another, or surgical and non-surgical data. To this intent, the adopted system has been kept as simple as possible: its prerequisite is to offer laryngologists and head and neck surgical oncologists, especially those in training, a systematic and organized scheme of the most widely used OPHLs, as an aid in teaching and training programs

**Conclusions**

The principles chosen to distinguish one procedure from others have been essentially based on laryngeal anatomy and the lower extent of surgical resection. In this way, we subdivided OPHLs according to the cranio-caudal extension of resection, focusing on the accessorial elements (arytenoids and crico-arytenoid units, base of tongue, piriform sinuses) removed or not together with the essential ones. The declared intention of this ELS Committee for Classification project is to facilitate circulation of comparable data among surgeons and researchers on one of the most debated issues in contemporary laryngeal cancer treatment.

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**Figure 1 OPHL type I: a) frontal view b) sagittal view**

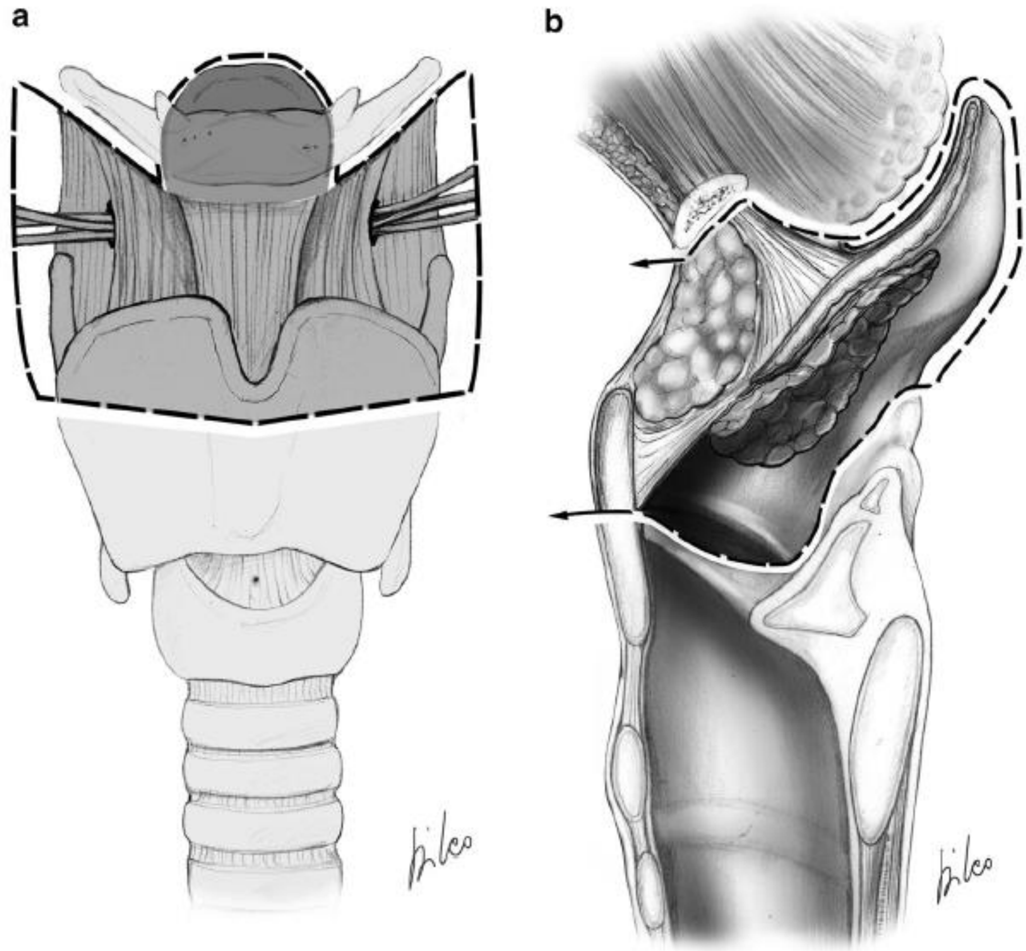


**Figure 2 OPHL type IIa: a) frontal view b) sagittal view**

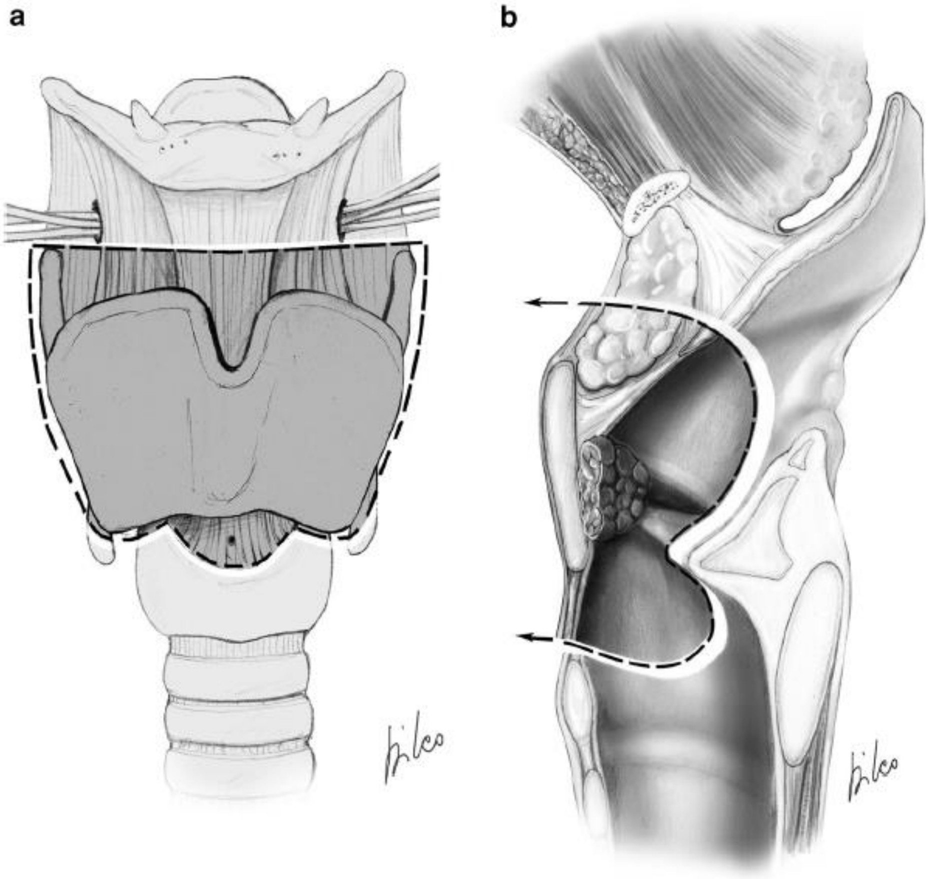


**Figure 3 OPHL type IIb: a) frontal view b) sagittal view**

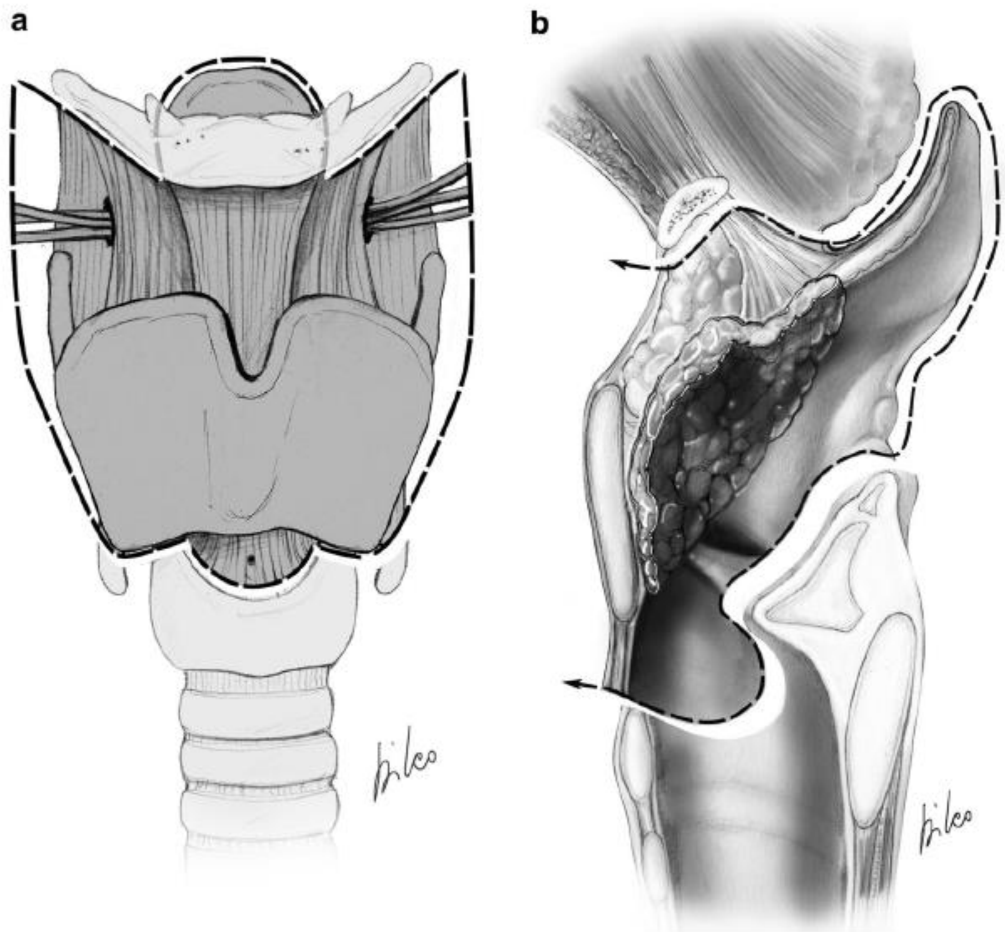


**Figure 4 OPHL type IIIa: a) frontal view b) sagittal view**

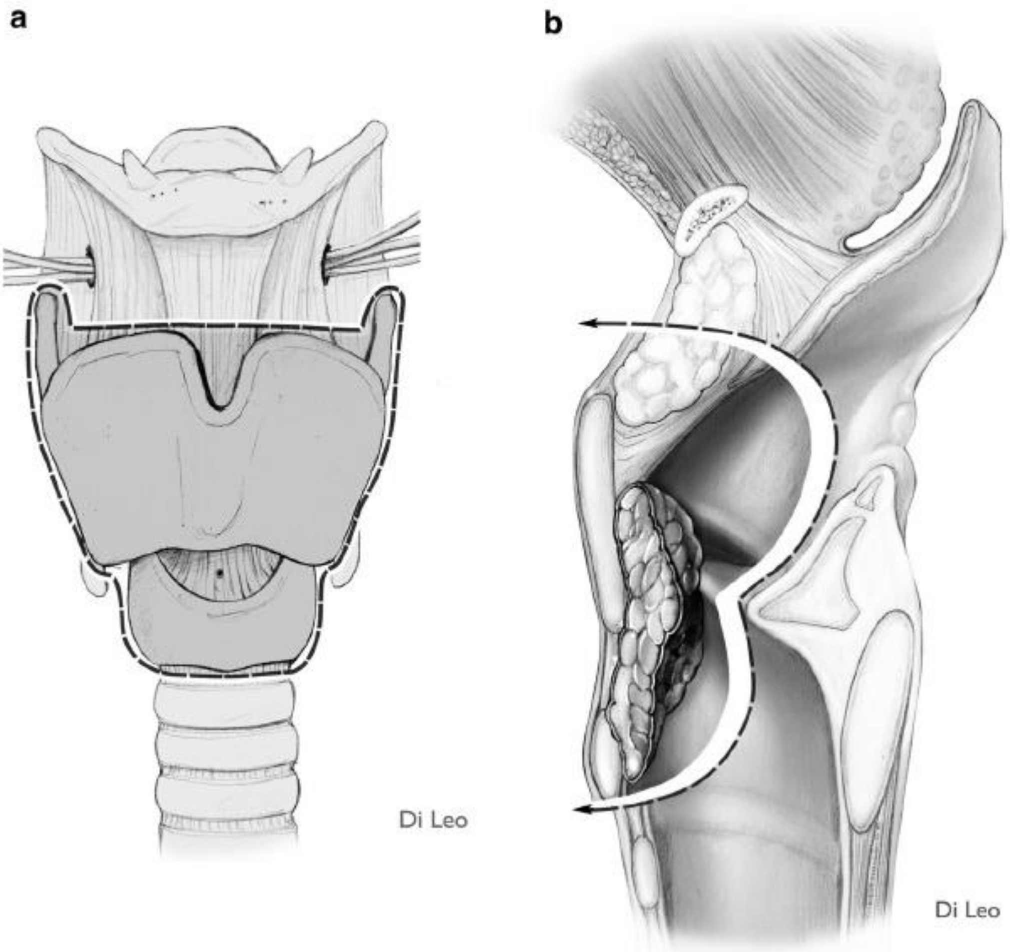


**Figure 5 OPHL type III + CAU: axial view**

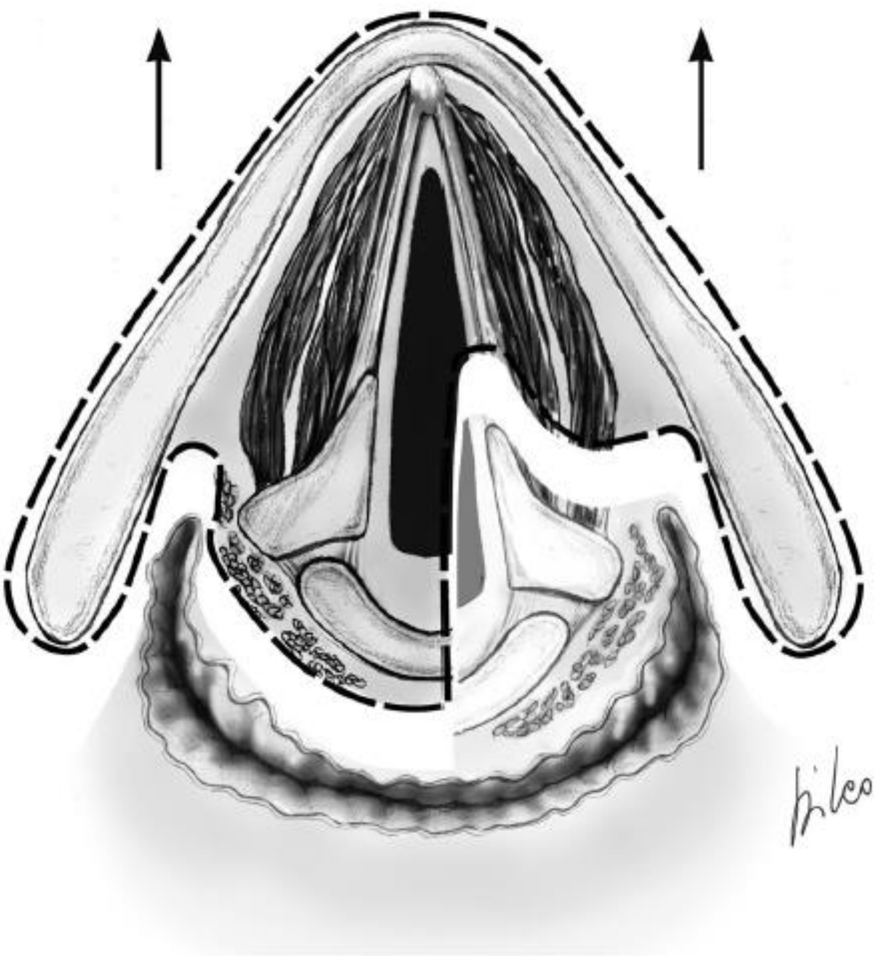
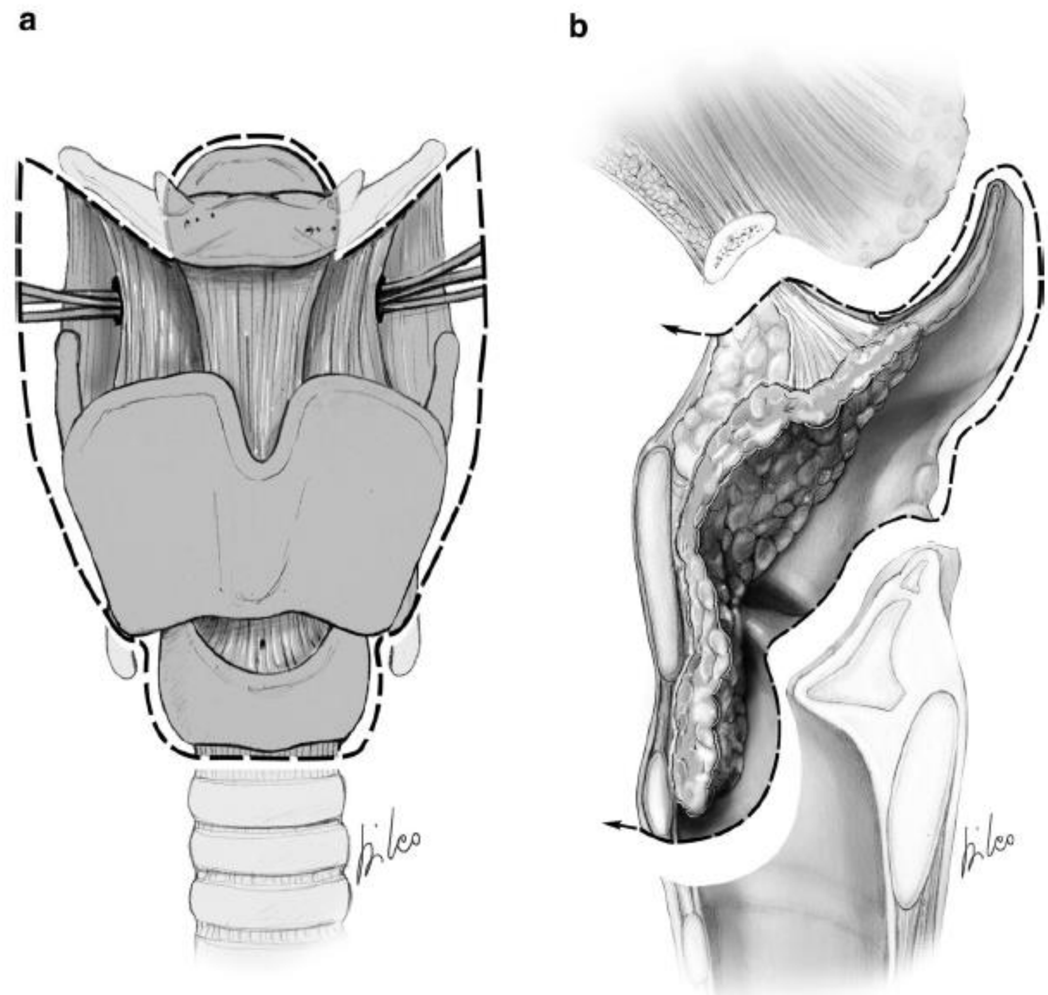


**Figure 6 OPHL type IIIb + CAU: a) frontal view b) sagittal view**



## Paper 3

### *Subtotal laryngectomy: outcomes of 469 patients and proposalvof a comprehensive and simpliWed classiWcation of surgical procedures*

*Abstract*

Long-term oncological and functional results from a retrospective study on 469 patients over a 10-year period of subtotal laryngectomies (SL), 399 supracricoid partial laryngectomies (SCL) and 70 supratracheal partial laryngectomies (STL) are presented. The mean follow-up time was 97 months (range 60–165 months). Acute complications, types and rates of late sequelae, functional results, 2-year post-operative scores of laryngeal function and quality of life are reported. The observed long-term results were: SCL, 5-year overall and disease-free survival: 95.6, and 90.9%, respectively; 2-year post-operative laryngeal function preservation: 95.7%; STL, 5-year overall and disease-free survival: 80 and 72.9%, respectively; 2-year postoperative laryngeal function preservation: 80%. The performance status scale for laryngeal function preservation showed very high 2-year scores, with no significant differences depending on the type and extent of surgery. The adopted type of function-sparing surgery provided overall and disease-free survival rates that were somewhat better than those reported in studies based on organ-sparing protocols with chemoradiotherapy. The rate of total laryngectomy of completion in this series was 4.4%. A new classification of the current horizontal partial laryngectomies is also proposed, namely "Horizontal Laryngectomy System" (HOLS), based on the extent of surgical removal of laryngeal structures.

***Introduction***

In Italy, each year around 4,040 new cases of laryngeal cancer are diagnosed [1]. Of these, 55–60% are early cancers (defined by the American Joint Committee on Cancer as T1 or T2 tumors without nodal involvement or distant metastases), while the remaining are classified as locally advanced (T3–T4, without nodal involvement), loco-regionally advanced (any T with nodal metastases) and disseminated (any T, any N with distant metastases). In Italy, starting in the 1970s following the efforts of Serafini [2], supracricoid partial laryngectomies

(SCL) have been increasingly more adopted by head and neck surgeons as a type of functionpreserving surgery for the treatment of early (glottic T1b–T2; supraglottic T2) or locally advanced (glottic and supraglottic selected T3) laryngeal tumors. Many surgeons have shown that SCL, when faced with the planned sacrifice of the larynx compared to other therapeutic options, provides good, reproducible loco-regional control, and preserves laryngeal function, with the tracheostomy eventually closed in almost all patients [3–7]. Beyond classical SCLs, in 2006 our group described a new type of horizontal partial laryngectomy, i.e., subtotal laryngectomy with tracheo-hyoido-epiglottopexy (THEP) or tracheo-hyoidopexy (THP), which, by extending the inferior limit of the resection to include a large part of the cricoid cartilage, expanded the indications of the horizontal partial laryngectomies to some T3 and select T4a supraglottic and glottic tumors.

Reported as subtotal "supratracheal laryngectomy" (STL-THEP or THP) — the term "supratracheal" was coined by A.R. Antonelli in analogy with other horizontal partial interventions on the larynx, which are named according to the inferior limit of the resection (e.g., "supraglottic", "supracricoid") — STLs have shown promising oncological and functional results [8].

By grouping together all the horizontal partial surgical procedures on the larynx, it is now possible to consider the "Horizontal Laryngectomy System" (HOLS) as an extension-modulated surgical treatment of laryngeal tumors - from horizontal supraglottic laryngectomy (HSL), to SCL and STL — which allows surgical management of the majority of endolaryngeal cancers. It can also be considered a function-sparing surgical protocol, comparable to organsparing protocols based on chemoradiotherapy.

The goal of this retrospective study was to demonstrate the safety and reproducibility of oncologic and functional outcomes of subtotal laryngectomies on a large number of patients, while introducing the concept that function-sparing surgical protocols permit, especially for intermediate stages of disease, a substantial reduction in the number of total laryngectomies. In fact, in institutions such as ours that have adopted HOLS, the number of total laryngectomies has drastically decreased.

The present study is focused on the long-term oncologic and functional results of 469 patients subjected to SCL and STL over a 10-year period, during which the conventional therapeutic alternatives for early stage tumors would have been radiotherapy alone, traditional partial laryngectomies or transoral laser endoscopic procedures, while for locally advanced tumors organ-preservation protocols with radiochemotherapy or total laryngectomy would have been applied. Based on these outcomes, and considering the preliminary results obtained with STLs, an updated classification of horizontal partial laryngectomies is proposed.

*Materials and methods*

From 1976 to the time of writing, 1,081 partial laryngectomies (supraglottic, supracricoid and supratracheal) have been performed at the Departments of Otorhinolaryngology of the Hospital of Vittorio Veneto (Italy) and the Martini Hospital in Turin (Italy). The present retrospective study has a minimum follow-up of 60 months and extends over the period 1995–2005, during which 469 patients aVected by laryngeal cancer were treated, 399 using SCL with cricohyoido-epiglottopexy (SCL-CHEP) or crico-hyoidopexy (SCL-CHP) and 70 using STL with tracheo-hyoido-epiglottopexy (STL-THEP) or tracheo-hyoidopexy (STL-THP).

The age of the patient cohort ranged from 18 to 87 years, with a median of 59.4 years. 435 patients were male (92.8%) and 34 females (7.2%). All patients had a biopsyproven laryngeal squamous cell carcinoma, previously treated or untreated, stage from I to IVa according to the 2002 UICC staging classiWcation system [9] (Table 1).

During the 3 weeks preceding surgical treatment, all patients underwent the same diagnostic work-up that included direct or indirect laryngoscopy (flexible and/or rigid videolaryngoscopy), direct microlaryngoscopy and biopsy, laryngeal and neck CT scan or MRI, bronchoscopy and esophagoscopy to rule out synchronous tumors, chest X-ray or CT scan to exclude lung tumors or distant metastases, assessment of bronchopulmonary function and of comorbidities for at-risk patients, and nutritional evaluation. Karnofsky performance status index had to be at least 80 (i.e., patient able to carry out normal activities, even though with difficulty) [10].

For 400 patients, SCL or STL was the Wrst treatment, while 69 patients (14.7%) were subjected to surgery for failure of a previous treatment of the laryngeal tumor [27 with CO2 laser transoral surgery (39.1%), 21 with radiation therapy (30.4%), 3 with open neck partial laryngectomy (4.3%), and 18 (26.1%) with cordectomy via laryngoWssure].

Exclusion criteria were, in addition to a Karnofsky index less than 80, severe diabetes mellitus, severe bronchopulmonary chronic obstructive disease and severe cardiac disease. Advanced age, even if historically an age of 70 years has been an important cut-oV age for relative surgical indication of some partial laryngectomies, in our experience it is no longer, in itself, an exclusion criterion.

After accurate selection of patients on the basis of the absence of important comorbidities and the strong desire of the patient to avoid permanent tracheostomy, age was also considered along with the patient's general condition.

The indications for SCLs and STLs according to the 2002 TNM UICC T stage are reported in Table 2. Absolute contraindications for SCLs and STLs were posterior commissure involvement, involvement of both arytenoids, massive invasion of the inferior paraglottic space with inWltration of the submucosa of pyriform sinus, or involvement of the retrocricoid area or trachea.

*Surgery*

Three hundred and ninety-nine patients underwent SCL and 70 underwent STL. The supracricoid laryngectomies included 272 SCL-CHEP (58%) and 127 SCL-CHP (27%), while the supratracheal laryngectomies included 62 STLTHEP (13.2%) and 8 STL-THP (1.7%). Removal of one arytenoid was indicated, in surgical records, by adjoining to the symbol "+A" the acronym of the laryngectomy, specifying the side, left or right, of the removed arytenoid. Neck dissection (ND), classiWed according to the classiWcation of the AAO-HNS [11], was performed in 412 patients (87.8%), and was monolateral in 279 (67.7%) and bilateral in 133 (32.3%) cases. Neck dissection was elective in 378 (91.7%) cN0 patients, and curative in 34 cN >0 patients (8.2%). No neck dissection was performed in an additional 57 patients (12.1%) with cN0 disease and glottic early cancer.

Overall, lymph-node metastases were detected in 46/412 patients (11.2%); in 25 patients (6.1%) metastases were bilateral. The pT and pN stage distribution among patients with supraglottic and glottic tumors is reported in Table 3.

In all patients, resection margins were examined intraoperatively by frozen sections; when positive, the resection was expanded until margins were negative. The margins of the surgical specimen were always checked again upon deWnitive pathology. Pathology reports indicated that the margins were either close (<3 mm) in 11 (2.3%) or positive (microinWltration) in 11 patients (2.3%).

Post-operative course and adjuvant treatments All patients were monitored for early complications (local and general) and late sequelae. Patients underwent the same rehabilitation protocol, with the obvious exception of those with serious, early complications.

The post-operative protocol consisted of the following:

(a) post-op days 1–4: insertion of an uncuZed tracheal cannula and beginning of phonation;

(b) post-op days 4–6: during daytime intermittent occlusion of the tracheostoma with a saline-soaked gauze and starting of feeding without the tracheal cannula in position.

(c) post-op day 6 onwards, the NGT was removed as soon as a good level of deglutition of both solids and liquids was achieved.

On the basis of pathological Wndings, 78 patients (16.6%) were subjected to adjuvant radiotherapy. A large volume encompassing the primary site and all draining lymph nodes at risk was irradiated with a dose of up to 54 Gy/2 Gy. Regions that were at high risk for malignant dissemination (pN + and/or ECS), or with positive resection margins received a 12-Gy boost (total 66 Gy/2 Gy–range 62–68 Gy). Eleven of 78 patients also received 100 mg of cisplatin per m2 of body-surface area on days 1, 22, and 43 of the course of radiotherapy [12, 13].

*Functional assessment*

Functional status was quantiWed at the end of the Wrst and the second post-operative year by two members of each staV, a physician and a nurse, in each department using the Performance Status Scale as reported by List et al. [14]. This is a simple, practical, clinician-rated assessment tool consisting of three subscales: speech comprehension, normalcy of diet and eating in public.

*Statistical methods*

The minimum follow-up was 60 months (mean 97, range 60–165 months). The endpoint for overall survival was the date of death (regardless of cause) or the date of the last follow-up examination for patients who were alive. For disease-free survival, patients who died of unrelated causes were considered as censored at the date of death. The endpoint for disease-free survival was the date of local/regional/distant recurrence/second primary. Regarding preservation of laryngeal function, the following criteria were adopted: for patients requiring salvage total laryngectomy, the endpoint for laryngeal function preservation was the date of eventual total laryngectomy, while for the remaining patients the functional data at the last follow-up were considered [tracheostomy (Y/N), NGT or PEG feeding (Y/N), intelligible voice (Y/N)]. The simultaneous absence of tracheostomy and NGT or PEG, and the presence of comprehensible voice were considered as preserved laryngeal function.

The curves for overall and disease-free survival were calculated from the date of the surgery using the Kaplan–Meier method. The impact on disease-free survival, tumor stage, laryngeal site of tumor, and type of surgery was assessed by univariate analysis with a log-rank test.

**Results**

*Patient cohort*

From 1 Jan 1995 to 31 Dec 2005, 469 patients were subjected to subtotal laryngectomy. After providing informed consent, all patients were always oVered the most conservative surgical or non-surgical therapy (e.g., radiotherapy, laser surgery, partial vertical laryngectomy, organ-sparing protocols with radiochemotherapy or, in advanced cases, total laryngectomy), explaining the advantages and disadvantages of each therapeutic option.

*Survival outcomes*

The mean follow-up among surviving patients was 97 months. At 5 years, overall (OS) and disease-free survival (DFS) were, respectively, 95.6 and 90.9% for SCL versus 80 and 72.9% for STL. Figure 1a and b shows the OS and DFS curves obtained using the Kaplan–Meier method according to the type of surgery. Figure 2 shows the DFS curves according to cancer stage (UICC 2002) and tumor site [supraglottic (Fig. 2a) and glottic (Fig. 2b)].

Figure 3a and b shows the loco-regional control data obtained using the Kaplan–Meier method according to the type of surgery.

**Patterns of failure**

*Supracricoid partial laryngectomies*

The overall recurrence rate was 11.0% (44/399), while the local and regional recurrence rates were 3.2% (13/399) and 2.5% (10/399), respectively. Simultaneous local and regional recurrence was observed in 7 of the 13 patients with local recurrence. The overall rate of distant metastases was 1.0% (4/399) (three in lung and one in bone). The overall frequency of second primary tumors was 4.3% (17/399).

At 5 years, the loco-regional control rate according to the type of surgery was SCL-CHEP 89.3% (243/272), SCLCHP 92.9% (118/127).

In 13 patients with local recurrence, the following salvage treatments were performed: total laryngectomy and adjuvant radiation therapy § chemotherapy in 11 patients and laser surgery in 2 cases. Three patients died from further local recurrence (average 25.5 months, range 9–42 months). At the last follow-up, 9 patients were alive and disease-free and 1 patient was alive with loco-regional disease; overall local control after salvage therapy was achieved in 9 of the 13 patients (69.2%).

Regional control was obtained in 389/399 (97.5%) patients. Recurrence in the neck was observed in 10 patients: 7 patients previously classiWed as cN0, 3 patients cN > 0. Seven of these patients at the time of primary resection did not receive ND, whereas two patients underwent one ipsilateral and one bilateral neck dissection each.

Eight recurrences in the neck were treated with neck dissection and adjuvant radiation therapy, and two with radiation therapy § chemotherapy. Four patients died from regional recurrence (range 9–34 months, mean 24 months).

At the last follow-up, six patients were alive and diseasefree; overall, after salvage therapy neck control of disease was achieved in six of ten patients (60%).

*Supratracheal partial laryngectomies*

The overall recurrence rate was 25.7% (18/70). The local recurrence rate was 21.4% (15/70). The regional recurrence rate was 4.2% (3/70). Simultaneous local and regional recurrence was observed in 2 of 15 patients with local recurrence. No distant metastases were detected (0/70 patients). At 5 years, the loco-regional control rate according to the type of surgery was: STL-THEP 83.9% (52/62) and STL-THP 62.5% (5/8).

Local control was obtained in 60/70 (85.7%) patients. In 15 patients with local recurrence, the following salvage treatments were performed: total laryngectomy and adjuvant radiation therapy § chemotherapy in eight patients and chemotherapy in Wve cases. Ten patients died from further local recurrence (average 18.6 months, range 8–35 months). At the last follow-up, 5 patients were alive and disease-free; overall local control after salvage therapy was achieved in 5 of 15 patients (33.3%).

Regional control was obtained in 67/70 (95.7%) patients. Recurrence in the neck was observed in three cases: one patient previously classiWed as cN0 and two cN > 0 patients. All these patients, at the time of primary resection, received bilateral neck dissection. All recurrences in the neck were treated with radiation therapy § chemotherapy, and all patients died from regional recurrence (range 8–21 months and mean 15 months).

*Acute complications and late sequelae*

Overall, acute complications during hospitalization occurred in 33 of the 469 patients (7%) (Table 4). The mean hospitalization time for patients with acute complications was 32 days, which was signiWcantly longer than that of patients without acute complications (18 days; $p < 0.01$).

Late sequelae following discharge were observed in 43 of the 469 cases (9.1%). Among these, the following treatments were required: endoscopic revision by transoral CO2 laser surgery (33/43; 76.7%), open-neck revision of the pexy (4/43; 9.3%) and total laryngectomy (2/43; 4.6%). Eight late sequelae were seen in patients that had acute post-operative complications. There were no perioperative deaths.

*Preservation of laryngeal function*

At the end of the second year, preservation of a satisfactory degree of laryngeal function was achieved in 438 of the 469 cases (93.4%). The rates of preservation of laryngeal function according to the type and the extension of resection were: SCL-CHEP (with both arytenoids spared), 98/103 cases (95.1%); SCL-CHEP +A, 165/169 cases (97.6%); SCL-CHP (with both arytenoids spared), 33/36 cases (91.7%); SCL-CHP +A, 86/91 cases (94.5%); STL-THEP (with both arytenoids spared), 10/11 cases (90.9%); STLTHEP +A, 41/51 cases (80.4%); STL-THP +A, 5/8 cases (62.5%) (Table 5).

The rate of preservation of laryngeal function was slightly better for SCL compared to STL in the 461 patients that were eventually decannulated (98.3%). The mean duration of trachestomy intermittent occlusion was 24.9 days (range 4–406 days), and the average time of tracheostomy closure was 73.4 days (range 16–852 days).

In our protocol progressive closure of the tracheostomy is preferred, which occurs spontaneously in the majority of patients following occlusion. For patients, this leads to about a sensation of greater safety, especially in the first weeks after discharge, concerning small episodes of food inhalation which are relatively frequent. When the tracheostomy has almost closed, a small plastic surgery can then be performed.

Nearly all patients (466/469, 99.4%) had the NGT or PEG removed. The NGT or PEG remained in place for an average of 15.9 days (range 4–161 days) (Table 6).

438 of the 441 patients who were disease-free on the larynx swallowed almost normally at the end of the first year.

Occasional aspiration was reported in 26/469 patients (5.5%) when drinking, and by 13/469 patients (2.8%) even when eating solid foods. Overall pneumonia ab ingestis was observed in 15/469 cases (3.2%). In three cases, total laryngectomy was proposed for persistent aspiration: two patients accepted and one refused, preferring to keep the PEG and maintain voice.

Table 7 details the data concerning functional assessment. The distribution of patient scores as well as median scores for the three subscales is presented according to the type of surgery.

**Discussion**

After the first total laryngectomy performed by Billroth assisted by Heidelberg (quoted by Weir [15]) in 1873, the problem of voice preservation and airway restoration pushed the surgeons' inventive toward new function-sparing, though oncologically sound, procedures. In the present study, we considered a large series of SLs, including both SCLs (which are the most common, reproducible and consolidated type of surgical procedure) and STLs (which have more selective indications and for this reason are less numerous).

In our series of SCLs, the observed 5-year overall survival was 95.6% and was also excellent in patients with stage III cancers. Moreover, overall survival was good for patients treated with STLs (even if 15.7% of the patients experienced a recurrence after previous treatment), where the observed 5-year overall survival was 80%, compared to 86.4% in previously untreated patients.

Several oncologic and functional considerations of our cohort of patients are necessary. Based on pathologic stage, which can provide the most precise prognostic implications, 305/469 (65%) patients had early stage cancers, and most (252) were glottic cancers, while 164 cases (35%) were grouped in stages III and IV. Radiation alone combined with laser surgery could have cured about 80% of the patients with early stage disease, without resorting to tracheostomy, with better results in terms of quality of voice and swallowing, and a treatment plan that is much easier for the patient.

However, less aggressive protocols are characterized by a rate of total laryngectomy that is about 11% [16] after radiotherapy and 3–5% after laser surgery [17, 18].

The pattern of greatest failure with these protocols is seen when the tumor involves the anterior commissure (glottic T1b) [19] and the paraglottic space posteriorly (glottic T2) [17]. Thus, it can be reasonably assumed that in cases with early stage tumors, the use of less-invasive therapies would be expected, considering the slightly poorer prognostic outcomes, a greater number of total laryngectomies but generally with better quality of voice and swallowing.

The results are somewhat different for cases of locally advanced disease. In these cases, organ-sparing protocols with radiochemotherapy show prognostic results that are about 10% less with a variable but much greater percentage of total laryngectomies (from 20 to 50%); long-term functional results are also entirely unsatisfactory [20].

Thus, in terms of global morbidity, the extensive use of subtotal laryngectomy can be reconsidered for early stage disease in which there are valid and proven less-invasive surgical and non-surgical alternatives that can provide good functional results with fewer problems in functional recovery.

In these cases, subtotal laryngectomy is only justifiable for cases at risk such as T1b glottic tumors with significant involvement of the anterior commissure and/or with diYculties in exposition in direct microlaryngoscopy and/or with suspect involvement of the prelaryngeal lymph node (19), T2 glottic tumors that involve the paraglottic space superiorly and/or inferiorly and that tend to behave biologically as authentic T3 cancers [21].

The choice of subtotal laryngectomy can be considered as extremely competitive not only in prognostic terms but also in terms of functional results such as a reduction in the number of total laryngectomies, especially for intermediate stages and some advanced stages (T3 and selected T4a). There were no significant differences according to the type of surgery, SCL-CHEP or CHP and STL-THEP or THP. 5-year overall survival rate for all types of SL was about 10% higher than that reported in published studies on organ-sparing protocols based on chemoradiotherapy. Furthermore, supratracheal laryngectomy in cases at risk of close margins if treated by SCL, allowed widening the resection both downward and laterally. Moreover, the proportion of patients subjected to total laryngectomy for either functional or oncological purposes, was significantly lower (4.4%) and there was no perioperative mortality.

Our data on the patterns of failure show that SLs can be tailored to each patient, depending on the extent of the lesion, and that all types of SCL and STL (in previously untreated patients) provide similar rates of local control. This is possible since the larynx ‘tolerates’ tumor-free margins of 4–5 mm: in the present study, the radicality of surgical removal was always routinely checked intra-operatively by frozen sections.

The necessity of neck dissection in N0 tumors, mostly in glottic tumors, is worthy of comment. In our cohort of patients, 475 of 545 neck dissections were unnecessary. But in terms of regional control, it should be noted that the greatest percentage of recurrences on *N* was seen with SCL-CHEP +A, which was also the largest subgroup of patients (169/469, 36%).

This could indicate, also for N0 tumors and even in consideration of the low morbidity of selective neck dissection, that greater attention should be given to stage II and III tumors, utilizing bilateral dissection at levels II–III–IV for supraglottic tumors when the midline of the larynx is involved, and ipsilateral dissection of the same levels in lateralized supraglottic and glottic tumors.

In case of subglottic extension, homo- or bilateral paratracheal lymph node dissection should be performed considering the high prevalence of occult metastases [22].

Acute complications were seen in 7% of the patients. The most frequent were pneumonia (almost 39% of all the complications in agreement with the observations of Benito et al. [23] who reported that the most frequent complication of SL is aspiration), wound or neck infections and neck hemorrhage (36%). This observation highlights the need for careful preoperative assessment of comorbidities, especially diabetes mellitus and bronchopulmonary chronic obstructive disease.

In the present series, 159/469 patients (33.9%) were over 65 years of age, and in this subset the 5-year rate of overall survival was 88.1%, which was not significantly different from the subset of younger patients. Late sequelae occurred in 9.1% of the patients. Of these, the majority was due to laryngeal obstruction (65% of late sequelae), most of which were related to chronic edema or mucosal flaps of the neolarynx.

Only 9.3% suffered from intermittent or persistent aspiration. It should be stressed that the majority of late sequelae were rescued by one or two transoral procedures by CO2 laser. In patients that developed late sequelae, the percentage of laryngeal sparing was 95.3%, and only 2 patients had to be subjected to total laryngectomy. (The possibility to undergo reconstructive revision of the airway to resolve problems related to severe aspiration should also be mentioned; the revision of the pexy with restoration of swallowing was successfully performed in four cases in the present study).

Concerning functional results, we stress the need for a timely and vigorous rehabilitative protocol consisting:

- The use of an uncuffled tracheal cannula just at the end of surgery or in the immediate post-operative period, to favor coughing, as a defense mechanism;
- – The early (1 or 2 days post-op) starting of phonation rehabilitation, to improve the patient’s mood and favor recovery of laryngeal sensory feedback;

- – The occlusion of the tracheostomy during the daytime, starting from post-operative days 3–4, which contributes to restore laryngeal sensory feedback and improves coughing reflexes;
- – Early rehabilitation of swallowing without the tracheal cannula in position, that would hinder the rising of the laryngotracheal axis at each swallow.

In the subgroup of patients that failed previous treatment for the same laryngeal cancer, SCL and STL provided, as a rescue procedure, good local control and preservation of laryngeal function (overall survival, 60/69 patients, 86.9%; disease-free survival, 57/69 patients, 82.6%, preservation of laryngeal function, 58/69 cases, 84.1%; acute complications, 8/69 cases; 11.6%, late sequelae, 10/69 cases, 14.5%).

This fnding is in agreement with the study by Spriano et al. [24], and demonstrates that SCL and STL can be used as salvage surgery, even after organ-sparing protocols, as well as in locally extended lesions (e.g., rT2 and selected rT3).

For laryngeal cancer, since the frequency of distant metastasis is low, the cure rates will depend mainly on loco-regional control, attained by modulating the extent of surgical removal, as in HOLS. For this reason, it is important to highlight two factors. If because of the T stage there is a risk of obtaining close margins with a more limited surgical removal, it is preferable to widen the resection as follows:

1. SCL-CHEP → SCL-CHEP +A
   SCL-CHEP → SCL-CHP
   SCL-CHEP → STL-THEP

   Functional outcomes are similar, but the radicality is greater and more certain.

2. Concerning N status, it should be taken for granted that patients with supraglottic cancers greater than T1 should undergo elective neck clearance. Substantial importance should be given to level VI lymph nodes in curative and elective, either selective- or radical-modified neck dissections, whenever the cancer involves the inferior paraglottic space and/or subglottis. In these situations, even though a neck

dissection may not have been planned, exploration of the central compartment lymph nodes is recommended.

3. For all anterior tumors without posterior involvement, both SCL and STL provide very good local control. This suggests the radicality that can be obtained with SL is nearly identical to that obtained with more radical interventions. Therefore, in these cases, if not affected by disease, it is not necessary to sacrifice the crico-arytenoid units, which are fundamental for functional recovery.

4. Functional data obtained from both objective (99.4% NGT and PEG removal, 13.9% among late sequelae related to chronic/intermittent aspiration, 98.3% tracheostomy closure), and subjective (evaluation of diet, speech and eating in public) outcomes have demonstrated the validity of SL in sparing laryngeal function, albeit at the obvious expense of a “simplified” laryngeal framework. This shows the anatomical redundancy of the laryngeal structure and the vast ability of this organ to recover the essentials of its function after partial surgical mutilation, provided that tissue has been destroyed according to “functional criteria”. This latter includes the preservation of at least a single functional crico-arytenoid unit with its corresponding recurrent nerve, the integrity of the superior laryngeal nerves, the sparing of as much as possible of the pyriform sinus mucosa, adequate reconstruction of the pyriform sinus and the restoring of the airway continuity through the pexy.

5. One disadvantage of subtotal laryngectomy is the quality of voice, which is unsatisfactory in 30–40% of the cases.

**Conclusions**

With the diffusion, at least among European head and neck surgeons, of supracricoid laryngectomies, the advent of the supratracheal laryngectomies, and the consolidated role of conventional non-surgical organ-sparing protocols and endoscopic procedures, the role of total laryngectomy in the treatment of endolaryngeal neoplasms has decreased considerably. On the other hand, there is a growing proportion of patients to whom the choice between organ-sparing and surgical function-sparing protocols (open surgery and laser surgery) can now be offered. The oncological results of the two treatment strategies are nearly equivalent, a fact that is due to the application of organ-sparing protocols that avoid surgical trauma and risks, and assure laryngeal preservation.

The psychological impact of this possibility is demonstrated by the fact that the surgical arm of randomized perspective studies on organ-sparing protocols offers the only surgical alternative to total laryngectomy. While waiting for the results of a perspective, randomized study on the entire range of subtotal partial laryngectomies, our data, even though retrieved from retrospective case reports, appear to offer some considerations that may be important in patient counseling.

In comparison with organ-sparing protocols, inclusion criteria of surgical protocols are usually less stringent; the mortality rate is likely to be lower (zero in our experience); the rate of acute and late morbidities is nearly same or lower; the number of total laryngectomies for oncological or functional purposes is significantly less; functional outcomes are good (with the only variable the poorer quality of voice) although survival rates are even higher.

To fill the above gap, a randomized clinical perspective trial comparing the two treatment modalities is warranted, with the set of surgical function-preserving procedures in the surgical arm. Along these lines, our group is actively participating in a trial led by Giuseppe Spriano, from the Istituto dei Tumori of Rome (Italy). Until the results of this trial are available, our current policy with patients with early (T1b with massive invasion of the anterior commissure, T2 with posterior paraglottic space involvement or subglottic extension) or selected advanced (T3–T4a) laryngeal cancers who are candidates for surgical protocols that preserve laryngeal function is to propose the surgical or non-surgical options and allow the patient to choose the preferred treatment modality [25].

Analysis of the National Cancer Data Base [26] shows that in the US survival has decreased among patients with laryngeal cancer during the past two decades, in parallel with the increased use of organ-sparing protocols with combined chemoradiotherapy. The most notable decline in the 5-year relative survival occurred among advanced stage glottic cancers, early stage supraglottic cancers and supraglottic cancers classified as T3N0M0. In contrast, in these three tumor groups, horizontal supraglottic laryngectomy, and supracricoid and supratracheal laryngectomy provide a higher degree of loco-regional control.

In order to simplify the recording of the different types of horizontal laryngeal function-sparing procedures, and to clarify the extent of surgical removal, we propose that horizontal partial laryngectomies can be classified into three types, in a manner similar to that adopted for endoscopic cordectomies by the ELS [27]. In all three types, the extension of surgical removal is indicated by symbols as follows:

- +A → To comprise one arytenoid
- +B → Upward
- +C → Downward
- +D → Laterally

*Type I Horizontal laryngectomy* horizontal supraglottic laryngectomy → HSL

Possible extensions:

- +A → to one arytenoid
- +B → to base of tongue
- +C → to one vocal cord
- +D → to pyriform fossa mucosa

*Type II* Horizontal laryngectomies

Type IIa: supracricoid partial laryngectomy with cricohyoido-epiglottopexy and both arytenoids spared → SCL-CHEP

Possible extension:

- +A → to one arytenoid = SCL-CHEP + A

Type IIb: supracricoid partial laryngectomy with the removal of the entire epiglottis and preepiglottic space, with crico-hyoidopexy and both arytenoids spared → SCL- CHP

Possible extension:

- +A → to one arytenoid = SCL-CHP + A

*Type III* Horizontal laryngectomies

Type IIIa: supratracheal partial laryngectomy withtracheo-hyoido-epiglottopexy and both arytenoids spared → STL-THEP

Possible extension:

- +A → to one crico-arytenoid unit = STL-THEP + A

Type IIIb: supratracheal partial laryngectomy with the removal of the entire epiglottis and preepiglottic space, and with tracheo-hyoidopexy → STL-THP

Possible extension:

- +A → to one crico-arytenoid unit = STL-THP + A

The classfication system is simple, and easy to apply. The system also takes into account the need to consider an organized scheme for horizontal laryngectomies, as there are over 16 different types, and each has different indications according the degree of extension, site, pathology and grade of the lesion.

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**Table 1** **Characteristics of the 469 patients undergoing subtotal laryngectomy according to age, gender and Karnofsky performance status**

| Characteristic | *n*/*N* | % |
|---|---|---|
| Age | | |
| ≤55 | 144/469 | 30.7 |
| 55–75 | 302/469 | 64.4 |
| >75 | 23/469 | 4.9 |
| Median (year) | 59.4 | |
| Range (year) | 18–87 | |
| Gender | | |
| Male | 435/469 | 92.8 |
| Female | 34/469 | 7.2 |
| Karnofsky performance status | | |
| 100 | 301/469 | 64.1 |
| 90 | 115/469 | 24.6 |
| 80 | 53/469 | 11.3 |

**Table 2** **Indications for each type of subtotal laryngectomy according to 2002 TNM UICC clinical staging**

**Table 2** Indications for each type of subtotal laryngectomy according to 2002 TNM UICC clinical staging

| | SCL | | | | STL | | | |
|---|---|---|---|---|---|---|---|---|
| | CHEP | CHEP +A | CHP | CHP +A | THEP | THEP +A | THP | THP +A |
| Glottic | 99 | 155 | 9 | 24 | 11 | 50 | – | 8 |
| T1b | 42 | 17 | – | – | – | – | – | – |
| T2 | 54 | 112 | 6 | 15 | 2 | 9 | – | – |
| T3 | 3 | 26 | 3 | 9 | 9 | 28 | – | 4 |
| T4 | – | – | – | – | – | 13 | – | 4 |
| Supraglottic | 4 | 14 | 27 | 67 | | 1 | | |
| T1 | – | – | – | – | – | – | – | – |
| T2 | 4 | 11 | 17 | 25 | – | 1 | – | – |
| T3 | – | 3 | 10 | 41 | – | – | – | – |
| T4 | – | – | – | 1 | – | – | – | – |

*SCL-CHEP* supracricoid laryngectomy with crico-hyoido-epiglottopexy
*SCL-CHP* supracricoid laryngectomy with crico-hyoidopexy
*STL-THEP* supratracheal laryngectomy with tracheo-hyoido-epiglottopexy
*STL-THP* supratracheal laryngectomy with tracheo-hyoido-pexy

**Table 3** **Characteristics of the 469 patients undergoing subtotal laryngectomy according to post-operative pathological findings**

| pT | Glottic | | Supraglottic | |
|---|---|---|---|---|
| | *N* | % | *N* | % |
| pT1 | 40 | 8.5 | – | – |
| pT2 | 191 | 40.7 | 53 | 11.3 |
| pT3 | 86 | 18.3 | 55 | 11.7 |
| pT4 | 39 | 8.3 | 5 | 1.1 |
| pN | | | | |
| pN0 | 337 | 71.8 | 86 | 18.3 |
| pN1 | 10 | 2.1 | 11 | 2.3 |
| pN2 | 9 | 1.9 | 16 | 3.4 |
| pN3 | – | – | | |

**Table 4** **Acute post-operative complicatomns and late sequelae**

| Acute complications | *N* | % |
|---|---|---|
| Acute cervical bleeding | 4 | 12.1 |
| Acute renal failure | 1 | 3.1 |
| Blood infection | 1 | 3.1 |
| AMI | 1 | 3.1 |
| Pulmonary failure + pneumonia | 2 | 6.2 |
| Pneumonia ab ingestis | 11 | 33.3 |
| Pulmonary failure | 3 | 9 |
| Stroke | 1 | 3.1 |
| Wound infection + cardiac failure | 1 | 3.1 |
| Wound infection | 8 | 24.2 |
| Late sequelae | | |
| Frequent aspiration | 4 | 9.3 |
| Laryngeal fibrosis with stenosis | 5 | 11.6 |
| Laryngeal soft tissue stenosis + occasional aspiration | 2 | 4.7 |
| Laryngeal soft tissue stenosis | 21 | 48.8 |
| Persistent dyspnea | 5 | 11.6 |
| Recurrent cervical infection | 2 | 4.7 |
| Aspiration pneumonia | 4 | 9.3 |

**Table 5** **Preservation of laryngeal function**

| Type of surgery | *n*/*N* | % |
|---|---|---|
| SCL | | |
| CHEP | 98/103 | 95.1 |
| CHEP + A | 165/169 | 97.6 |
| CHP | 33/36 | 91.7 |
| CHP + A | 86/91 | 94.5 |
| STL | | |
| THEP | 10/11 | 90.9 |
| THEP + A | 41/51 | 80.4 |
| THP | – | – |
| THP + A | 5/8 | 62.5 |

*SCL-CHEP* supracricoid laryngectomy with crico-hyoido-epiglottopexy

*SCL-CHP* supracricoid laryngectomy with crico-hyoidopexy

*STL-THEP* supratracheal laryngectomy with tracheo-hyoido-epiglottopexy

*STL-THP* supratracheal laryngectomy with tracheo-hyoidopexy

**Table 6 Functional results according to the type of surgery**

| | SCL-CHEP | SCL-CHEP +A | SCL-CHP | SCL-CHP +A | STL-THEP | STL-THEP +A | STL-THP | STL-THP +A |
|---|---|---|---|---|---|---|---|---|
| | *N* (%) | *N* (%) | *N* (%) | *N* (%) | *N* (%) | *N* (%) | *N* (%) | *N* (%) |
| Time of initiation of deglutition | | | | | | | | |
| 3–7 days | 90 (87.4) | 152 (89.9) | 16 (44.4) | 54 (59.3) | 8 (72.7) | 39 (76.5) | – | 4 (50) |
| 8–11 days | 10 (9.7) | 12 (7.1) | 12 (33.3) | 18 (19.8) | 2 (18.2) | 9 (17.6) | – | 2 (25) |
| >11 days | 3 (2.9) | 5 (2.99) | 8 (22.2) | 19 (20.9) | 1 (9.1) | 3 (5.9) | – | 2 (25) |
| Range (days) | 3–28 days | | | | | | | |
| NGT removal/PEG removal | 466/469 (99.4%) | | | | | | | |
| Median (days) | 15.9 days | | | | | | | |
| Range (days) | 4–161 days | | | | | | | |
| Tracheal occlusion | 461/469 (98.3%) | | | | | | | |
| Median (days) | 24.9 days | | | | | | | |
| Range (days) | 4–406 days | | | | | | | |
| Surgical removal tracheostomy | 157/469 (33.5%) | | | | | | | |
| Median (days) | 96 days | | | | | | | |
| Range (days) | 16–852 days | | | | | | | |
| Spontaneous removal tracheostomy | 312/469 (66.5%) | | | | | | | |
| Median (days) | 61.5 days | | | | | | | |
| Range (days) | 19–432 days | | | | | | | |

**Table 7** **Performance status scale for head and nech cancers patients: a) Supracricoid partial laryngectomies b) Supratracheal partiale laringectomies**

| | SCL-CHEP | | SCL-CHEP +A | | SCL-CHP | | SCL-CHP +A | |
|---|---|---|---|---|---|---|---|---|
| | LFP 98/103 | | LFP 165/169 | | LFP 86/91 | | LFP 33/36 | |
| (a) Supracricoid partial laryngectomies | | | | | | | | |
| Eating in public[a] | *N* | % | *N* | % | *N* | % | *N* | % |
| 100 | 89 | 90.8 | 149 | 90.3 | 76 | 88.4 | 28 | 84.8 |
| 75 | 6 | 6.1 | 11 | 6.7 | 6 | 7 | 3 | 9.1 |
| 50 | 3 | 3.1 | 5 | 3 | 4 | 4.6 | 2 | 6.1 |
| 25 | – | – | – | – | – | – | – | – |
| 0 | – | – | – | – | – | – | – | – |
| Understandability of speech[b] | | | | | | | | |
| 100 | 62 | 63.3 | 104 | 63 | 49 | 57 | 19 | 57.6 |
| 75 | 32 | 32.6 | 52 | 31.5 | 33 | 38.4 | 11 | 33.3 |
| 50 | 4 | 4.1 | 9 | 5.5 | 4 | 4.6 | 2 | 6.1 |
| 25 | – | – | – | – | – | – | – | – |
| 0 | – | – | – | – | – | – | – | – |
| Normalcy of diet[c] | | | | | | | | |
| 100 | 79 | 80.6 | 130 | 78.8 | 60 | 69.8 | 24 | 72.7 |
| 90 | 15 | 15.3 | 22 | 13.3 | 19 | 22.1 | 5 | 15.2 |
| 80 | 3 | 3.1 | 9 | 5.5 | 5 | 5.8 | 4 | 12.1 |
| 70 | 1 | 1.0 | 3 | 1.8 | 2 | 2.3 | 1 | 3 |
| 60 | – | – | 1 | 0.6 | – | – | – | – |
| 50 | – | – | – | – | – | – | – | – |
| 40 | – | – | – | – | – | – | – | – |
| 30 | – | – | – | – | – | – | – | – |
| 20 | – | – | – | – | – | – | – | – |
| 10 | – | – | – | – | – | – | – | – |
| 0 | – | – | – | – | – | – | – | – |

| | STL-THEP | | STL-THEP + A- | | STL-THP | | STL-THP + A | |
|---|---|---|---|---|---|---|---|---|
| | LFP 10/11 | | LFP 41/51 | | LFP 0/0 | | LFP 5/8 | |
| (b) Supratracheal partial laryngectomies | | | | | | | | |
| Eating in public[a] | *N* | (%) | *N* | (%) | *N* | (%) | *N* | (%) |
| 100 | 8 | 80 | 35 | 85.4 | – | – | 3 | 60 |
| 75 | 2 | 20 | 3 | 7.3 | – | – | 1 | 20 |
| 50 | – | – | 3 | 7.3 | – | – | 1 | 20 |
| 25 | – | – | – | – | – | – | – | – |
| 0 | – | – | – | – | – | – | – | – |
| Understandability of speech[b] | | | | | | | | |
| 100 | 5 | 50 | 28 | 68.4 | – | – | 2 | 40 |
| 75 | 2 | 20 | 7 | 17.0 | – | – | 2 | 40 |
| 50 | 3 | 30 | 6 | 14.6 | – | – | 1 | 20 |
| 25 | – | – | – | – | – | – | – | – |
| 0 | – | – | – | – | – | – | – | – |
| Normalcy of diet[c] | | | | | | | | |
| 100 | 7 | 70 | 35 | 85.4 | – | – | 1 | 20 |
| 90 | 2 | 20 | 1 | 2.4 | – | – | 2 | 40 |

| | STL-THEP | | STL-THEP + A- | | STL-THP | | STL-THP + A | |
|---|---|---|---|---|---|---|---|---|
| | LFP 10/11 | | LFP 41/51 | | LFP 0/0 | | LFP 5/8 | |
| 80 | – | – | 2 | 4.9 | – | – | 2 | 40 |
| 70 | 1 | 10 | 1 | 2.4 | – | – | – | – |
| 60 | – | – | 2 | 4.9 | – | – | – | – |
| 50 | – | – | – | – | – | – | – | – |
| 40 | – | – | – | – | – | – | – | – |
| 30 | – | – | – | – | – | – | – | – |
| 20 | – | – | – | – | – | – | – | – |
| 10 | – | – | – | – | – | – | – | – |
| 0 | – | – | – | – | – | – | – | – |

*LFP* laryngeal function preservation

[a] 100 No restriction of place, food or companion (eats out at any opportunity); 75 no restriction of place, but restricts diet when in public (eats anywhere, but may limit intake to less "messy" foods, e.g. liquids; 50 eats only in the presence of selected persons in selected places; 25 eats only at home in presence of selected persons; 0 always eats alone

[b] 100 Always understandable; 75 understandable most of the time, occasional repetition necessary; 50 usually understandable, face-to-face contact necessary; 25 difficult to understand; 0 never understandable, may use written communication

[c] 100 full diet (no restriction); 90 peanuts; 80 all meat; 70 carrots and celery; 60 dry bread and crackers; 50 soft, chewable foods (e.g., macaroni, canned/soft fruits, cooked vegetables, fish, hamburger and small pieces of meat); 40 soft foods requiring no chewing (e.g., mashed potatoes, apple sauce, and pudding); 30 pureed foods (in blender), 20 warm liquids, 10 cold liquids; 0 normal feeding (tube fed)

**Figure 1** **A) Overall survival and disease –free survival probability in supracricoid laryngectomies (N = 399)**
**B) Overall survival and disease –free survival probability in supratracheal laryngectomies (N = 70)**

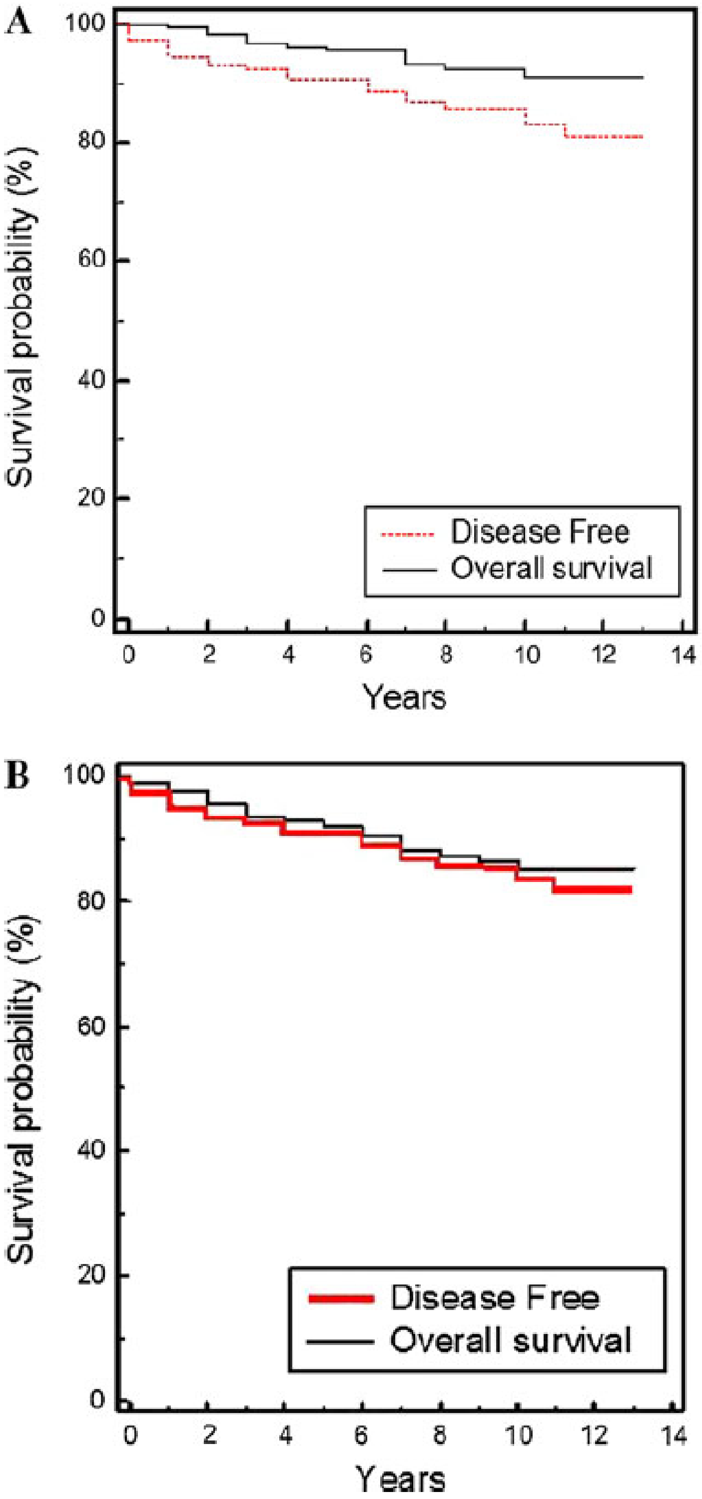


**Figure 2** **Disease-free survival probability according to stage and laryngeal site in subtotal laryngectomies (N = 469)**

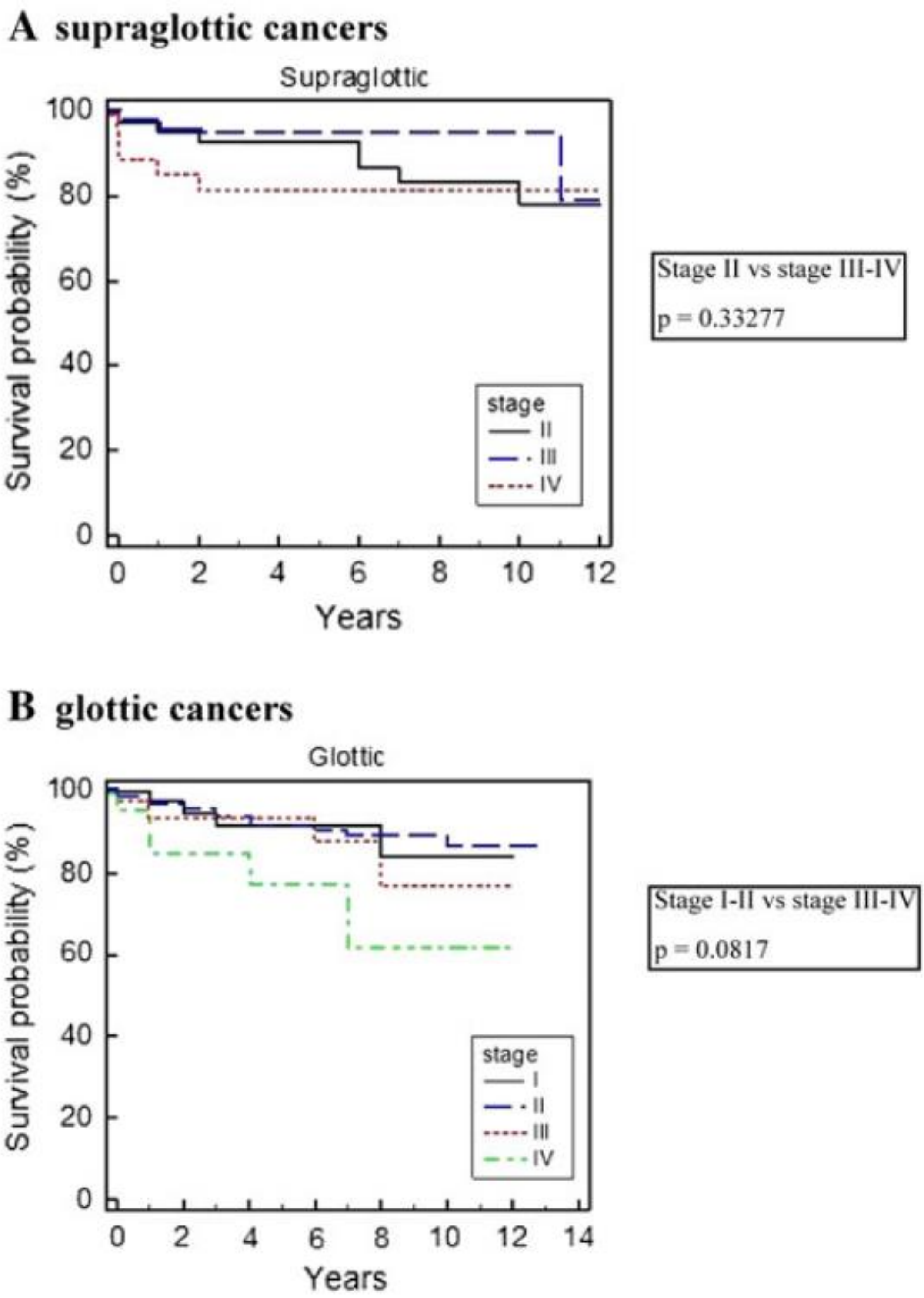
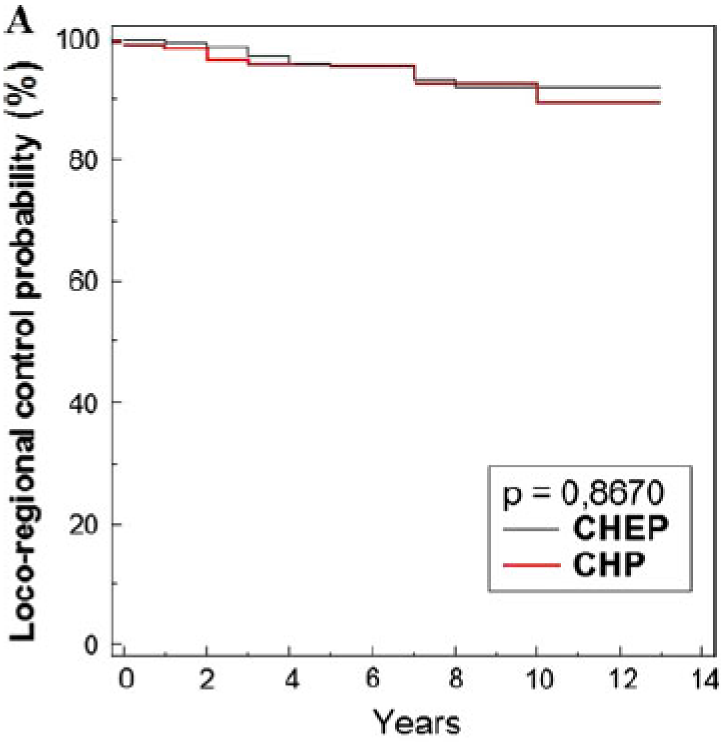
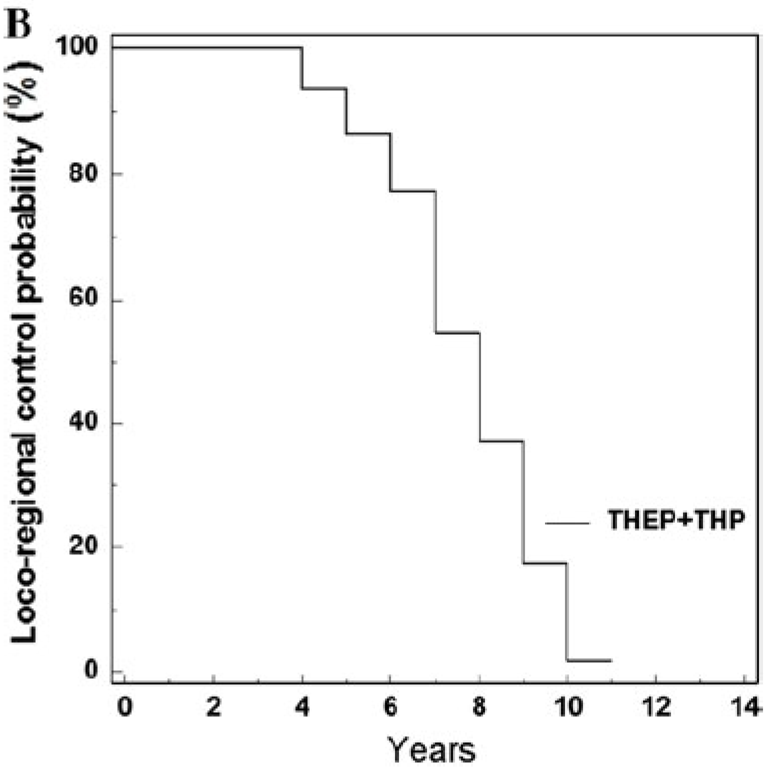


**Figure 3** **A) Locoregional control probability according to the type of surgery in supracricoid laryngectomies (N = 399)**
**B) Locoregional control probability according to the type of surgery in supratracheal laryngectomies (N = 70)**



## Paper 4

### *Benefits and drawbacks of Open Partial Horizontal Laryngectomies, Part A: early-intermediate stage glottic carcinoma*


### Abstract

*Background.* Laryngeal squamous cell carcinoma (SCC) accounts for the 1.9% of cancers worldwide. Most of these (up to 60%) are diagnosed in early stages (T1-T2, N0). For these larynx preserving/conserving option is preferable. Beyond transoral laser microsurgery (TLM), open partial horizontal laryngectomy (OPHL) is a function-sparing surgical technique to treat them.

*Methods*. We retrospectively analyzed the clinical outcomes of 216 patients who underwent OPHL for glottic cT2 laryngeal cancer from 1995 to 2011.

*Results.* 5 years overall survival, disease-specific survival, loco-regional control, local control, laryngeal function preservation, and laryngectomy-free survival rates were 93.1%, 98.0%, 97.1%, 97.5%, 97.8% and 98.5%, respectively. Disease controls are significantly affected by previous treatment and type of surgery employed.

*Conclusions*. Although TLM for cT2 laryngeal cancer with unimpaired vocal cord mobility still represents a sound option, OPHL with a modular approach offer higher local control and laryngeal preservation rates, for selected patients with impaired mobility of vocal cord combined to an involvement of the paraglottic space


### Introduction

Laryngeal squamous cell carcinoma (SCC) accounts for the 1.9% of cancers worldwide.[1] Most of these are glottic (51%) of which a great many (up to 60%) are diagnosed in early stages (T1-T2, N0, M0) due to noticeable voice changes that underlie lesions in true vocal cords.[2-4] For these locally spread laryngeal tumors laryngeal functions preserving option is preferable. As a consequence, the National Comprehensive Cancer Network Guidelines foresee the employment of either radiotherapy or partial laryngectomy. However, Misono et al. recently highlighted greater overall survival and disease-specific survival in patients whose treatment included local surgery with respect to those who receive radiotherapy alone.[3] In particular, surgical option includes either open neck partial laryngectomy and/or transoral laser microsurgery (TLM). The greater part of the former, especially in Europe, is represented by open partial horizontal laryngectomy (OPHL),[5] whereas the latter is performed usually by carbon dioxide laser.[6] The choice of procedure between open neck and transoral approches is very challenging because of the extreme heterogeneity of the lesions and variety of variables related to the patient.[7]

OPHL were able to partially spare the laryngeal functions without compromising loco-regional control[8, 9] reaching a good compromise between oncological radicality and functional outcome. To standardize, the European Laryngological Society recently proposed a classification of the more commonly adopted OPHL according to extent of resection (Type I – supraglottic, Type II – supracricoid, and Type III – supratracheal).[10]

On the other hand, the advantages of TLM in terms of laryngeal preservation rate and early and faster recovery of laryngeal functions have already been reported, as well as the negative impact on local control for T3 lesions extending laterally to the thyroarytenoid (TA) muscle, with involvement of the paraglottic space (PGS).[7, 11-14]

The heterogeneity in term of local extent and prognosis of glottic cT2 tumors is well known. In particular the impaired vocal cord mobility remains a crucial issue in the therapeutic planning. Even if accurately performed by new technologies the endoscopic evaluation is subjective and debated among specialists in distinguish the different causes of vocal cord impairment such as bulky tumor, vocal muscle infiltration, PGS involvement, and crico-arytenoid joint invasion. Moreover the early assessment of the PGS invasion represents another hot topic in the staging of glottic cancer even by means of the most sophisticated imaging studies.

Therefore, when comparing clinical and pathological staging, a significant number of cases, accordingly to the UICC/AJCC classification, show an up-staging of the primary tumor from cT2 to pT3, resulting as false negative at the preoperative imaging. In this light in 2005 Peretti and colleagues proposed to sub-classify the cT2 tumors in 5 pT subcategories in relation to the size, site and patterns of superficially and submucosally diffusion analyzed by clinical, radiologic, surgical and pathological examinations.[15] He demonstrated that

unimodal endoscopic laser resection provides a good oncological outcome in the majority of cT2; by contrast tumors, upstaged as pT3, for involvement of the PGS, represent a completely different disease which negatevely influnces the prognosis.[15]
Based on these observations, we followed the policy of staging and the proposal of sub-classification of cT2 proposed by Peretti in a cohort of patients treated by OPHL, with the aim to underline the role of OPHL in patients affected by T2 and selected T3 and compare the oncological and functional outcomes with those obtained by TLM.
Hence, a multicentric retrospective outcomes analysis of 216 patients with glottic laryngeal SCC classified as cT2 and managed by Type II–III OPHLs is presented. The analysis was conducted over a 16-year period during which TLM or radiotherapy were applied as alternative therapeutic options.[6, 16]

## Material and methods

*Patients*

All patients were from the Hospital of Vittorio Veneto (Treviso) or the Martini Hospital of Turin (Italy). Selection was based on routinely performed clinical assessment lasting 3 weeks prior surgery, in order to evaluate the superficial and depth extent of the tumor, as previously described.[8]
Inclusion criteria were: histological diagnosis of glottic cT2 laryngeal SCC, with Karnofsky index[17] higher than 80 (Table 1). 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 indication[18], has not been considered, in itself, as an exclusion criterion.
After informed consent had been obtained, 216 patients with glottic squamous cell carcinoma classified as cT2 according to the 2002 TNM classification system[19] underwent a modular function sparing surgical approach between 1 January 1995 and 31 December 2011. Thirty-nine patients (18.1%) included in the present analysis had been treated previously for laryngeal carcinoma by TLM (20/39, 51.3%), radiation therapy (12/39, 30.8%) or cordectomy (7/39, 17.9%).

Vocal fold mobility assessment resulted in 71 cases with normal vocal cord mobility, and 145 cases with impaired vocal cord mobility and mobile cricoarytenoid joint.

All patients were submitted to neck computed tomography (CT) or magnetic resonance imaging (MRI) to rule out infiltration of the cartilaginous framework and evaluate the extent of the pre-epiglottic space and/or paraglottic space.

The preoperative records, radiologic images as well as all surgical specimens were retrospectively reviewed to allow the re-classification of all cases, accordingly to the UICC/AJCC classification. Moreover after the final histology the entire cohort of cT2-pT3 were divided into five subtypes as suggested by Peretti and colleagues (Fig.1).[15]

*Surgery*

Open neck procedures were classified according to the European Laryngological Society Classification:

- Type IIa (supracricoid partial laringectomy/crico-hyoido-epiglottopexy) = 76/216 (35.2%)
- Type IIa + ARY = 102/216 (47.2%)
- Type IIb (supracricoid partial laringectomy/crico-hyoido-pexy) = 12/216 (5.55%)
- Type IIb + ARY = 12/216 (5.55%)
- Type IIIa (supratracheal partial laryngectomy/tracheo-hyoido-epiglottopexy) = 1/216 (0.5%)
- Type IIIa + CAU = 13/216 (6.0%), where "+ARY" represents the removal of one arytenoid and "+CAU" the removal of one cricoarytenoid unit.

The indications adopted for Type II OPHLs were the classical ones, applied according to tumor extent, now being accepted and advocated by numerous Authors.[5, 20-24] Although definitions for the Type III OPHLs were only recently introduced,[8] the precise indications for tumors at the cT2 classification were lesions with anterior or lateral subglottic extension, spreading downward above the conus elasticus and reaching the cricoid ring.

In all patients, resection margins were examined intraoperatively with frozen sections: when positive, the resection was expanded until the margins were negative. The margins of the surgical specimen were always checked again upon definitive pathology. The interventions were conducted using the principles of a modular approach. The resection is always prepared in standard mode and the larynx is opened from the side less affected by disease. At this point, under visual control, the subsites involved are removed and the resection can be enlarged as follows: (1) Type IIa/b → Type IIa/b + ARY; (2) Type IIIa → Type IIIa + CAU; (3) Type IIa → Type IIb; (4) Type IIa + ARY → Type IIIa + CAU.

Neck dissection (ND), graded according to the American Academy of Otolaryngology - Head and Neck Surgery Foundation classification,[25] was performed in 204 patients (94.4%), and was monolateral in 168/204 (82.4%) and bilateral in 36/204 (17.6%) cases. ND was elective (ND levels II-IV) in 198 cN0 patients (97.1%) and curative (ND levels II-V + Internal Jugular Vein in one case) in 6 cN>0 patients (2.9%). In nine patients, whole level VI or unilateral paratracheal lymph node clearance was added. No ND was performed in an additional 12 patients (5.55%, elderly and/or cN0 disease or in previously treated neck) (Table1).

*Postoperative care*

All patients were monitored for early complications (local and general) and late sequelae. Patients underwent the same rehabilitation protocol, apart from those with serious early complications. The postoperative protocol was in accord with our previous report.[8]

Briefly: (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 was achieved (day 6 onwards). Post-operative aspiration was graded in accordance with Pearson's scale (0 = none; I = occasional cough but no clinical problems; II= constant cough worsening with meal or swallowing; III= pulmonary complications).[26]

*Adjuvant treatments*

On the basis of pathological findings (pN+ and/or extracapsular spread extension, positive margins), 9 patients (4.2%) were subjected to adjuvant radiotherapy. The indications for adjuvant therapy were: 5 N+ (1 pN1 and 4 pN2, all with extracapsular spread) and 4 cases with positive margins.

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 9 patients (5 pN+ with extracapsular spread, and 1 multiple positive margins toward cricoid) also received 100 $mg/m^2$ cisplatin on days 1, 22, and 43 of the course of radiotherapy.[27]

*Larynx oncologic and functional assessment*

All patients were followed for a mean period of 5.71 years with periodic videolaryngoscopic examinations, scheduled every 3 months in the first 3 years and with decreasing frequency in the subsequent period.

During the 5 postoperative years, Pearson's Scale evaluation was repeated and larynx functional status was evaluated with the Performance Status Scale.[28]

The latter is a simple, practical, clinician-rated assessment tool consisting of three subscales: speech comprehension, normalcy of diet and eating in public, graduated from 0 to 100 on the basis of predefined parameters.

*Statistical methods*

Overall survival (OS), disease free survival (DFS), disease specific survival (DSS), locoregional control (LRC), local control (LC), laryngectomy-free survival (LFS) and laryngeal function preservation (LFP), were assessed by means of Kaplan-Meier curves. Log-rank and Gehan-Breslow-Wilcoxon tests (for early events) were used to compare Kaplan-Meier estimates between groups (cT2 subtypes, clinical history of previous treatment, type of surgery, and age). The end points considered were obtained as the length of time from the date of diagnosis to: OS) the date of death; DFS) the date of the first recurrence; DSS) the date of death from the disease; LRC) the date of the first locoregional 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 5.00 (GraphPad Software, San Diego CA), with $p < .05$ as the significant cutoff.

**RESULTS**

*Pathology, survival and disease control*

Comparison between clinical findings (CT-scan or MRI) and pathological staging proved up-staging on the primary tumor from cT2 to pT3 in 36 cases (16.7%). The review of radiologic images after the definite histology showed a suspect PGS involvement in only 21 patients. Pathology reports indicated close margins (<2 mm) in 9/216 cases (4.2%) and positive margins in 4/216 cases (1.9%). Six patients (2.7%) developed recurrence between 11 and 33 months. The recurrences were observed in 5 out 180 pT2 (2.7%) and 1 out 36 pT3 (2.7%).

In particular, in the subtype I no recurrences were observed. In the subtype II, one local recurrence was observed among 13 patients. The patient was successfully treated by TLM and was free from recurrence at 46 months. In the subtype III, 3 out of 40 patients (7.5%) experienced local (1), regional (1), or locoregional (1) recurrences. Salvage therapy for local recurrence included total laryngectomy and adjuvant chemoradiation therapy. The first patient died of other disease 15 months later; the second patient showed a second recurrence 22 months later and died of the disease 8 months later, while the third is free of disease at 32 months. Among the patients with regional recurrence (neck), both were previously classified as pN0. At the time of primary resection, both received monolateral neck dissection. One recurrence was observed at the VI level. Recurrences in the neck were treated with surgery and radiation therapy; one patient died due to regional recurrences 22 months later, and one is alive and disease-free. In the subtype IV, 1 out of 116 patients (0.8%) experienced both local and regional recurrences. The patient was previously classified as pN0 and was treated with surgery, including total laryngectomy, and radiation therapy; the patient died due to distant metastases. In the subtype V (cT2/pT3), among 36 patients, there is a patient (previously classified as pN0) suffering of both local and regional recurrences (2.7%). Salvage therapy included total laryngectomy and adjuvant chemoradiation therapy, but the patient died of the disease 14 months later. Overall, lymph node metastases were detected in 9/204 patients (4.4%), of whom 4 (2.0%) had multiple metastases

The 5-year OS, DSS, LRC and LC were 93.1%, 98.0%, 97.1%, and 97.5%, respectively (Fig. 2). A total of 13 patients had died: 4 of them for the laryngeal cancer and 9 for unrelated causes (Table 2). As DFS and LRC were overlapping in our patient cohort, we reported LRC only in our analyses.

Although DSS prevalence 5 years after surgery was not affected by any of the variables analyzed, the history of previous treatment and the employment of more invasive surgery provided little but significant impairments in both local and regional control (the former also as early event, $p < .01$, Gehan-Breslow-Wilcoxon test) (Fig. 3).

*Postoperative course and morbidity*

Overall acute complications during hospitalization occurred in 18 out 216 patients (8.3%) and there were no perioperative deaths. The mean hospitalization time for patients with acute complications was 29 ± 6 days, which was significantly longer than that for patients without acute complications (19 ± 4 days). Late sequelae following discharge were observed in 26 out of 216 cases (12.0%) (Table 3). All were successfully treated with TLM (8/10, 80%), and injective laryngoplasty using Vox-implants, which successfully treated dysphagia (2/10, 20%).

*Laryngeal function preservation*

At 5 years after surgery, LFP was maintained in 97.8% of patients whereas the use of total laryngectomy was avoided in the 98.5% (figure 4). In addition, we evaluated whether pT subtypes, previous treatment, age, and the type of surgery could affect LFP or even the use of total laryngectomy (Table 4). None of these variables were able to significantly affect the preservation of laryngeal function. Nevertheless, the history of previous treatment induced a slight but significant early enhancement in the number of total laryngectomy within the first two years from the OPHL ($p < .05$, Gehan-Breslow-Wilcoxon test).

After the first post-operative month, normal swallowing (Pearson’s scale Grade 0) was achieved in 134 patients (62.0%), Grade I and II were observed in 43 (19.9%) and 35 (16.2%) patients, respectively, while aspiration pneumonia (AP) (Pearson’s Grade III) was recorded in 4 patients (1.9%). After the second year, a satisfactory degree of laryngeal function (i.e. List's scale: eating in public >50, understandability of speech >50, normalcy of diet >70)[28] was achieved in 179 out of 211 patients without local disease (84.8%). Out of the 211 patients evaluated for subjective aspiration with the Pearson's scale,[26] 95 (45.0%) had no aspiration (Grade 0), 94 (44.5%) had occasional cough without clinical problems (Grade I), 20 (9.5%) had constant cough that worsened during meals (Grade II), and 2 patients (0.9%) had frequent pulmonary complications (Grade III). All patients had the NG tube or gastrostomy removed. The NG tube remained in place for an average of 18.5 days (range 9–130 days).

Overall, AP was observed in 6/216 cases (2.8%), 4 cases during hospitalization and 2 cases during follow-up. Completion total laryngectomy for persistent aspiration was not required in any patient. Two patients were subjected to the endoscopic procedure of injective laryngoplasty using Vox implants, which successfully resolved the dysphagia.

The mean time to intermittent occlusion of the tracheostomy was 22.6 days (range 5–166 days), and the average time to tracheostomy closure was 71.4 days (range 21–198 days). In our protocol, progressive closure of the tracheostomy is preferred, and occurs spontaneously in the majority of patients following occlusion. For patients, especially in the first weeks after discharge, this leads to a sensation of greater safety concerning minor episodes of food inhalation, which are relatively frequent. When the tracheostomy has almost closed, minor plastic surgery can then be performed.

## DISCUSSION

In the early 1970s, by systematically applying whole organ sections in the study of total laryngectomy specimens, Kirchner and Oloffson et al. well described the patterns of spread of laryngeal cancer.[29, 30] PGS invasion is a critical point of weakness, above all when the lesion reaches base and roof of the ventricle: this constitutes the gateway for the tumor spreading toward the thyroarytenoid space and cricoarytenoid joint. These lesions, even though clinically defined as cT2, are actually pT3, showing a more aggressive behavior.

According to the literature about transoral laser treatment for intermediate staged glottic cancer (T2/T3), TLM has shown a signicant increase of recurrences in those cases with involvement of PGS and impairment and/or fixation of the true vocal cord. In a study of 55 patients with glottic cT2, Peretti et al.[15] concluded that TLM can be considered effective when the pT2 stage has been confirmed. By contrast in cT2/pT3 patients, after the first transoral resection that allows the correct pT staging, additional treatment should always be considered. Ambrosch[6] reported in a cohort of 167 patients treated by TLM local control rate of 74% and laryngectomy rate of 13.4% was observed in the 97 patients staged pT2 while a 5-year local control rate of 68% and laryngectomy rate of 14.3% was observed in the 70 patients staged pT3. Canis et al reported a retrospective study of 391 previously untreated patients affected by cT2/T3 glottic: they noted a 93% larynx preservation rate among pT2a and 83% among pT2b and pT3 tumors.[7, 13-15]

The preoperative under-staging, in the glottic cT2 category, occurs with some frequency because of radiologic data misinterpretation among suspicious involvement of PGS; the lack of sensitivity on early PGS involvement is greater using CT-scan compared to MRI

Therefore intermediate stage glottic cancer requires patients for TLM to be selected very carefully, reserving open neck surgery or non-surgical treatments for patients in whom a up-staging of the lesion is presumed.

In our series, upstaging of cT2 to pT3 was found in specimens from 16.7% of cases, in whom early invasion of the PGS was not detected by imaging before the operation. The misdiagnosis of selected cT2 lacking the assessment of the PGS may possibly explain the gap in term local control between OPHLs and TLM as therapeutic options.

Our data show that the outstanding oncological outcomes obtained by OPHL reproduced by other Authors [31, 32] justify the open-neck procedures in terms of local control particularly in selected pT3 lesions. In fact in this cohort any variables analyzed have shown a negative impact on the end points evaluted.

By contrast the functional outcomes in terms of complications rate and hospitalization time are negatively influenced in some cases after OPHL. Persistent slight dysphagia and aspiration pneumonia still represent major complications in patients undergoing OPHLs, especially Type III while voice was significantly deteriorated, and generally quite hoarse and breathy.[20, 21, 23] Moreover, the functional outcome of OPHLs, especially for extended interventions (Type IIb, Type III) is generally associated with slower recovery a longer hospitalization compared to TLM.

For this reason, despite the excellent oncological results, the surgeon faced with intermediate staged tumors must be considered TLM as alternative option for all pT2, especially in elderly and fragile patients no fit for OPHL. In case of risk lesions (subtype V → cT2/pT3) the TLM could play a role of a definitive staging procedure with outstanding precision in microscopically detecting deep neoplastic invasion and consequently, possible patterns of cancer progression.

When discussing conservative surgical options with the patient affected by cT2 tumor with unimpaired mobility of vocal cord, he should be clearly informed that TLM is equally as safe with respect to open neck surgery, with a more rapid recovery and with less impact on quality of life, even if the further complementary represented by re-resection and/or open neck procedures should be kept in mind in case of upstaging to pT3.

In conclusion, our results demonstrate that, in every case of glottic cT2, OPHL with a modular approach can be considered a very safe option. Considering that OPHLs determine more dysfunctional sequelae compared to TLM, the open neck options should be essentially aimed at carefully selected patients affected by glottic cT2 with impaired mobility of vocal cord and suspected extension to the PGS.

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**Table 1.** **Characteristics of the 216 patients undergoing open partial horizontal laryngectomies according to age, sex, Karnofsky performance status, pathological grade and pT sub-category**

| | No. of Patients (%) |
|---|---|
| **Age, y** | |
| Mean | 59.8±9.9 |
| Range | 23-87 |
| | |
| **Sex** | |
| Male | 201/216 (93.1%) |
| Female | 15/216 (6.9%) |
| | |
| **Karnofsky Performance Status** | |
| 100 | 128/216 (59.3%) |
| 90 | 65/216 (30.1%) |
| 80 | 23/216 (10.6%) |
| | |
| **Pathological Grade** | |
| pT2 | 180/216 (83.3%) |
| pT3 | 36/216 (16.7%) |
| | |
| pN0 | 195/204 (95.6%) |
| pN1 | 5/204 (2.5%) |
| pN2 | 4/204 (2.0%) |
| | |
| **Level VI pN+** | 1/9 (11.1%) |
| | |
| **pT sub-Category** | |
| I | 11/216 (5.1%) |
| II | 13/216 (6.0%) |
| III | 40/216 (18.5%) |
| IV | 116/216 (53.7%) |
| V | 36/216 (16.7%) |

**Table 2 Cause of death**

| | No. of patients (%) |
|---|---|
| Laryngeal cancer | 4/216 (1.8) |
| Postoperative death | 0/216 (0.0) |
| II primary cancer | 4/216 (1.8) |
| Unrelated to laryngeal cancer | 5/216 (2.3) |
| Total deaths | 13/216 (6.0) |

**Table 3 Acute postoperative complications and late sequelae**

| Complications | No. of patients (%) |
|---|---|
| Acute complications | |
| Cervical bleeding | 5/216 (2.3) |
| Aspiration pneumonia | 4/216 (1.8) |
| Wound infection | 5/216 (2.3) |
| Others | 4/216 (1.8) |
| Late sequelae | |
| Laryngeal soft tissue stenosis | 23/216 (10.6) |
| Aspiration pneumonia | 2/216 (0.9) |
| Dyspnea | 1/216 (0.5) |

**Table 4** **Five years incidences and Kaplan-Meier estimates stratified laryngeal function preservation and laryngectomy-free survival**

| Variables | No. of patients | Laryngeal function preservation | | Laryngectomy-free survival | |
|---|---|---|---|---|---|
| | | Incidence (%) | Estimates (%) | Incidence (%) | Estimates (%) |
| pT subtypes | | | | | |
| I | 11/216 | 11/11 (100) | 100 | 11/11 (100) | 100 |
| II | 13/216 | 13/13 (100) | 100 | 13/13 (100) | 100 |
| III | 40/216 | 38/40 (95.0) | 93.8 | 39/40 (97.5) | 97.4 |
| IV | 116/216 | 115/116 (99.1) | 99.1 | 115/116 (99.1) | 99.1 |
| V | 36/216 | 35/36 (97.2) | 96.9 | 35/36 (97.2) | 96.9 |
| Previous treatment | | | | | |
| Untreated | 177/216 | 175/177 (98.9) | 98.6 | 176/177 (99.4) | 99.4 |
| Treated | 39/216 | 37/39 (94.9) | 94.6 | 37/39 (94.9) | 94.6* |
| Age, y | | | | | |
| <65 | 144/216 | 140/144 (97.2) | 94.7 | 141/144 (97.9) | 100 |
| ≥65 | 72/216 | 72/72 (100) | 97.8 | 72/72 (100) | 100 |
| Open partial horizontal laryngectomy | | | | | |
| Type IIa | 178/216 | 175/178 (98.3) | 98.0 | 176/178 (98.9) | 98.8 |
| Type IIb | 24/216 | 23/24 (95.8) | 95.8 | 23/24 (95.8) | 95.8 |
| Type IIIa | 14/216 | 14/14 (100) | 100 | 14/14 (100) | 100 |

* Log-rank test = $p < .05$.

**Fig. 1 Drawing representing of T2 glottic carcinoma subtypes: (I) pT2 with superficial supraglottic extension to the base and roof of the ventricle and/or ventricular band; (II) pT2 with superficial lateral subglottic extension; (III) pT2 with anterior supracommissural and/or subcommissural extension; (IV) pT2 with deep thyroarytenoid muscle infiltration; (V) pT3 for superior and/or inferior paraglottic space invasion lateral to the thyroarytenoid muscle**

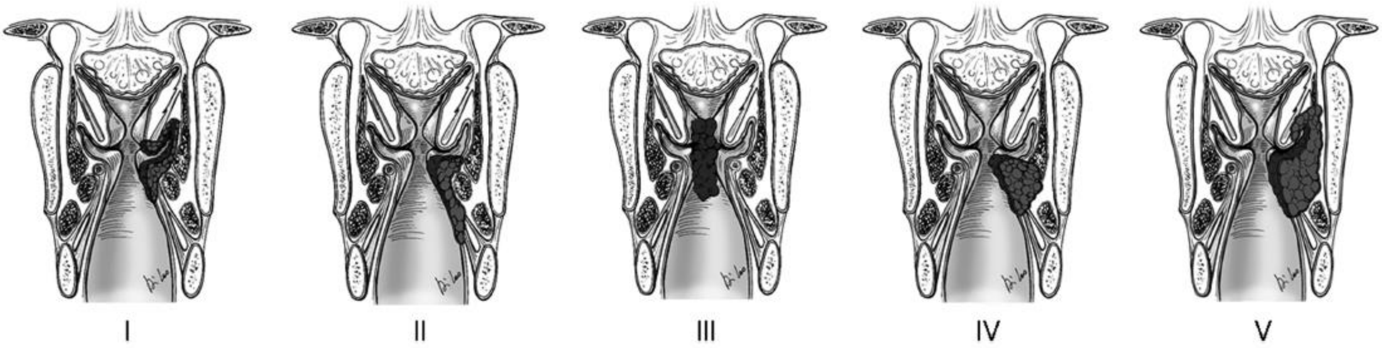


**Fig. 2. End point analysis (overall survival, disease specific survival, loco-regional control, and local control) of the patient cohort using Kaplan–Meier curves.**

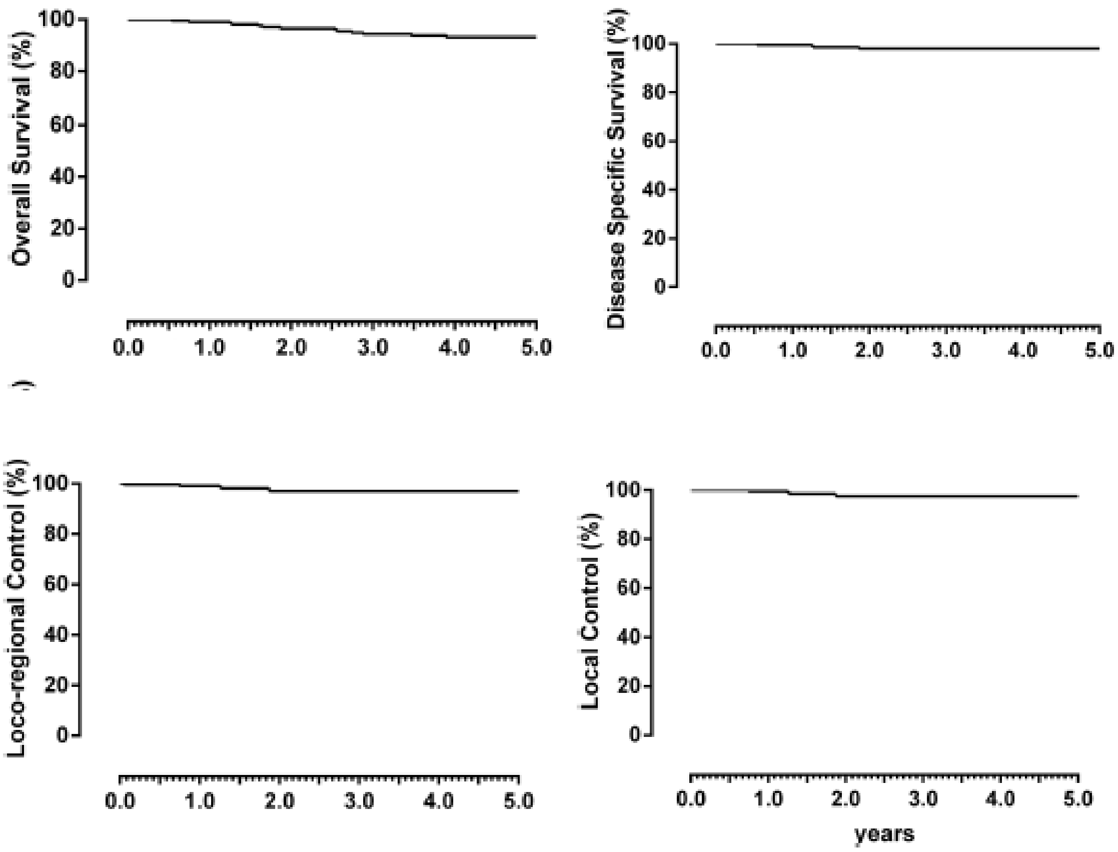
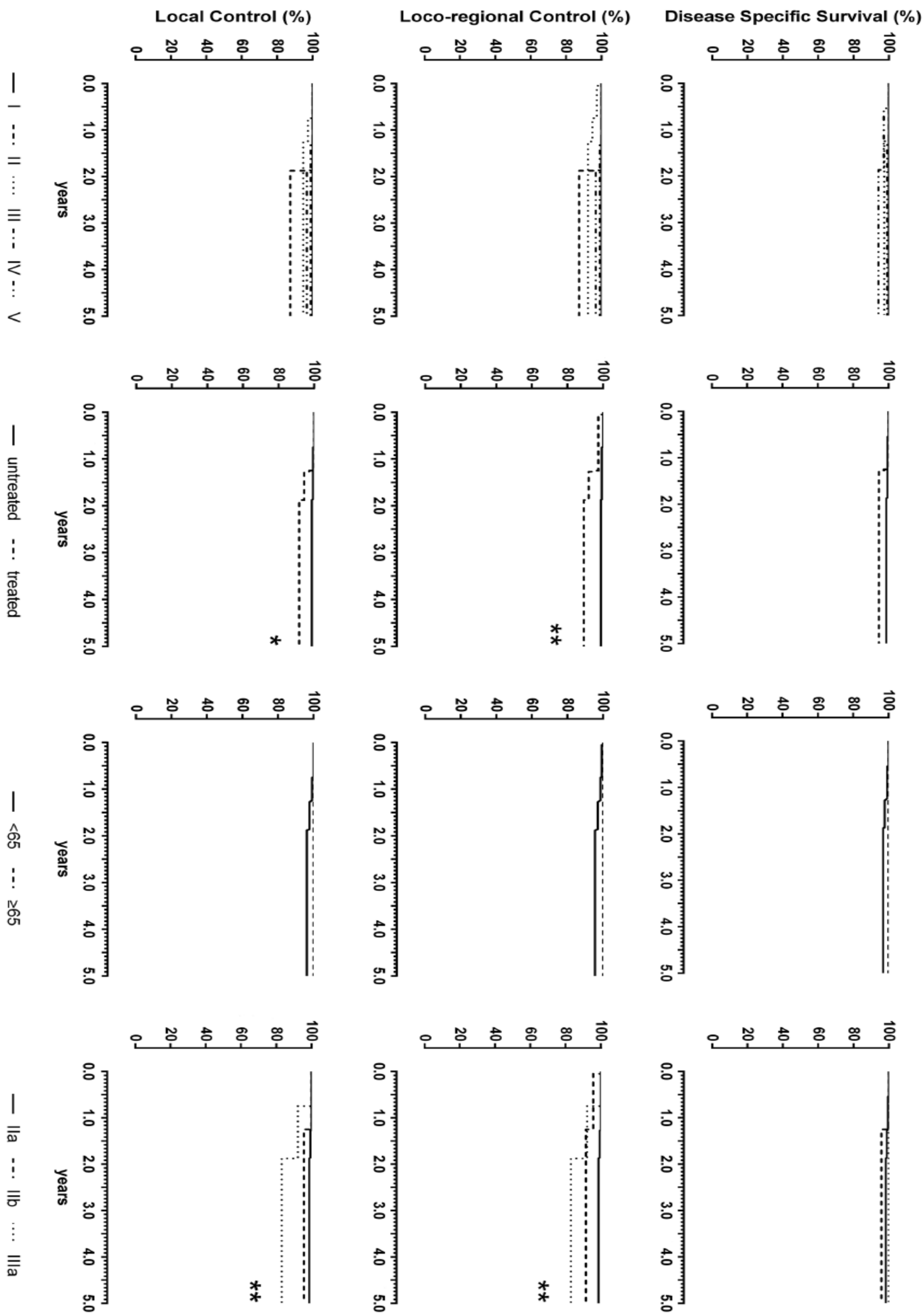
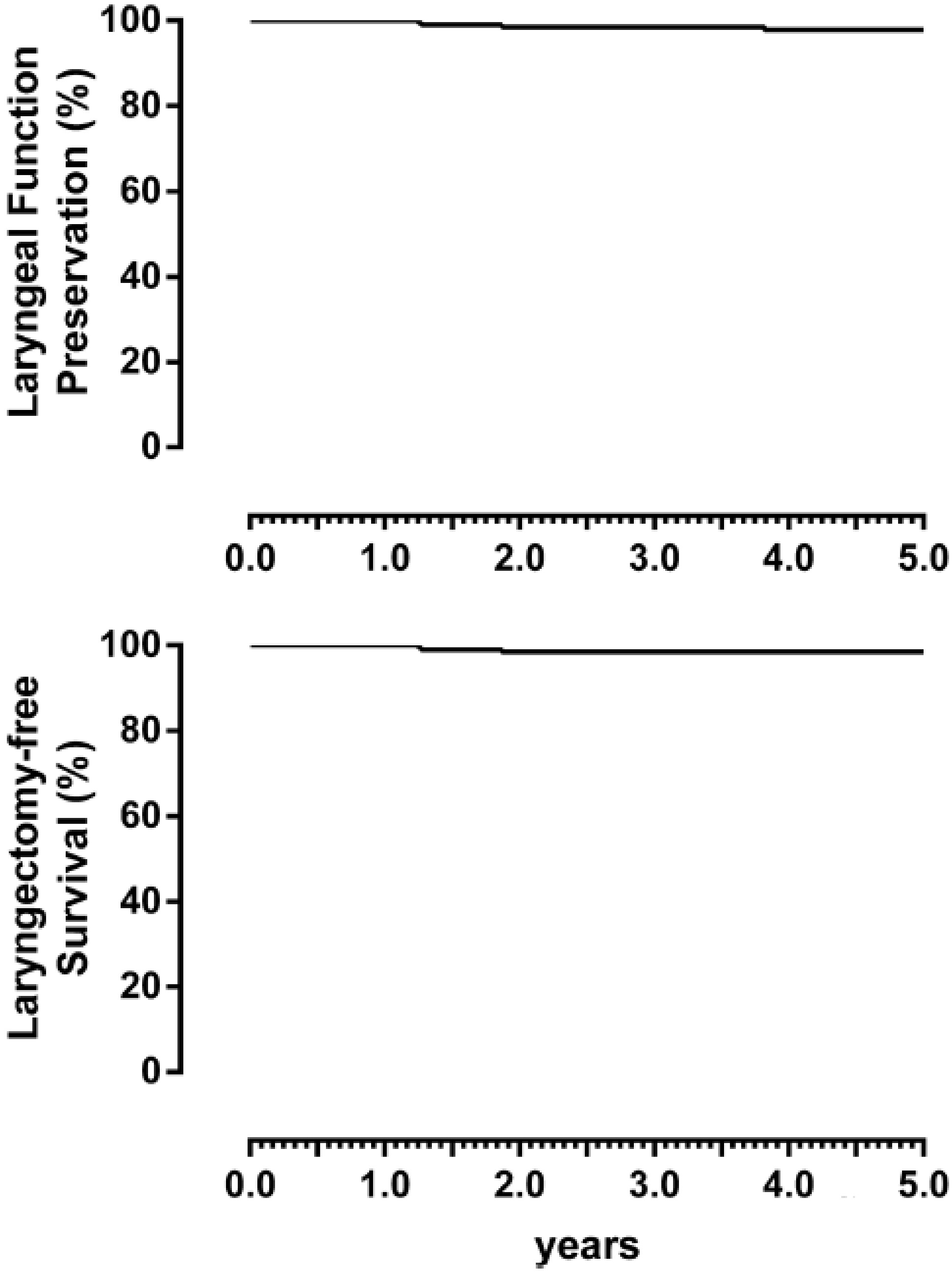


**Fig. 3. Patient cohort stratification for pT subtypes (first column), history of previous treatment (second column), age (third column), and type of surgery (fourth column) using Kaplan–Meier curves. The end points considered were (from top to bottom) disease specific survival, loco-regional control, and local control. * = $p < .05$; ** = $p < .01$**



Disease Specific Survival (%)
Loco-regional Control (%)
Local Control (%)
years
I
II
III
IV
V
untreated
treated
<65
≥65
IIa
IIb
IIIa
*
**

**Fig.4 End point analysis of laryngeal function preservation and laryngectomy-free survival in the patient cohort using Kaplan–Meier curves.**



# Paper 5

## *Benefits and drawbacks of Open partial Horizontal Laryngectomy, Part B: intermediate and selected advanced stage laryngeal carcinoma*


### Abstract

*Background*. Cancer of the larynx in the intermediate/advance stage still presents a major challenge in terms of controlling the disease and preserving the organ. Among therapeutic options, open partial horizontal laryngectomy (OPHL) is proposed as function-sparing surgical technique.

*Methods*. We analyzed the clinical outcomes of 555 patients with laryngeal cancer staged pT3–pT4a who underwent either supracricoid or supratracheal OPHL.

*Results.* 5 years overall survival, disease-free survival, loco-regional control, local control, and laryngeal function preservation rates were 84.6%, 84.2%, 86.3%, 90.6% and 91.2%, respectively. Disease-free survival, loco-regional control and laryngeal function preservation prevalences were significantly affected by pT4a staging (68.1%, 71.7% and 78.0% respectively), while pN+ influenced only disease-free survival (≤72.6%) and loco-regional control (≤79.6%).

*Conclusions*. in cases of laryngeal tumors at intermediate and selected advanced stage, also with sub-glottic extension, the choice of OPHL with a modular approach can be considered effective in terms of prognostic and functional results.


INTRODUCTION

The first and basic common step in the management of laryngeal squamous cell carcinoma (SCC) is assessment of the type, extent, and pattern of growth of the neoplasm. The second step is the choice of treatment that should be as conservative as possible, above all for surgical approaches. In fact, after the first total laryngectomy performed by Professor Theodor Billroth on December 31, 1873,1 the problems of voice preservation and airway restoration spurred surgeons toward the development of organ/function-sparing, although oncologically sound, procedures. Currently, their use represents the common trend among therapeutic approaches,[2–4] having significantly increased the survival from laryngeal SCC, although poor prognosis and loss of laryngeal functions are still common features of advanced-stage disease. Generally, open neck demolitive or “partial functional laryngectomies” represents the surgical procedure of choice. Especially in Europe, most are included in the group of open partial horizontal laryngectomies. The literature addressing this topic is rich, and a number of surgical procedures have been introduced based on the different patterns of endolaryngeal tumor site and spread.[5–9] Recently, the European Laryngological Society proposed a classification of the more commonly adopted procedures according to the extent of resection,[10] including 3 types of open partial horizontal laryngectomy: type I5supraglottic, type II5supracricoid, and type III5supratracheal. The latter, described in 2006, is based on resection of the entire glottic and subglottic sites and of the thyroid cartilage, sparing both or at least 1 functioning cricoarytenoid unit.11 In our practice, open partial horizontal laryngectomy type III expands the indications suggested by the National Comprehensive Cancer Network and Italian Head and Neck Society guidelines for the treatment of laryngeal cancer with conservative surgery (T1–T2, N0, or selected T3): some glottic cT3 (ie, subglottic extension and cricoarytenoid joint invasion) and some supraglottic cT3 (ie, large transglottic extension) became manageable by open partial horizontal laryngectomy, showing promising oncologic and functional results.[12,13] With great caution, the same intervention can be considered as an upfront option in very limited cT4a cases, with minimal anterior extralaryngeal extension, when adjuvant treatment would not be reasonably indicated. In this study, we present a multicentric retrospective outcome analysis of 555 patients with supraglottic/glottic laryngeal SCC in the intermediate/advanced stage, managed by open partial horizontal laryngectomy type II or III. The analysis was conducted over a 16-year period, during which organ-preservation protocols with chemoradiotherapy or total laryngectomy were applied as conventional therapeutic options for similar locally advanced tumors.[2,4]

## MATERIALS AND METHODS

### *Patients*

Five hundred fifty-five patients (512 men and 43 women) were treated at the Hospital of Vittorio Veneto, Treviso, or at the Martini Hospital of Turin. Selection was based on clinical and radiologic evaluation performed within 3 weeks from surgery, in order to assess the superficial and deep extent of the tumor, as previously described.12 Inclusion criteria were histological diagnosis of intermediate/advanced-stage glottic or supraglottic laryngeal SCC, with Karnofsky index14 higher than 80. The tumors were glottic (considering also those with transglottic extensions, but clearly arising from glottis) in 506 patients and supraglottic in 49 patients. The distribution of patients in relation to vocal fold mobility was as follows: 30 showed a normal or impaired (19 supraglottic pT3 and 11 supraglottic pT4a) mobility, 443 had a fixed vocal cord with mobile cricoarytenoid joint (15 supraglottic pT3; 4 supraglottic pT4a; 152 transglottic pT3; 207 glottic pT3; and 65 glottic pT4a), and 82 presented fixation of both vocal cord and cricoarytenoid joint (48 glottic-subglottic pT3; 33 glottic pT4a; and 1 transglottic pT3; Table 1). 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 cutoff for relative surgical indication,15 has not been considered, in itself, an exclusion criterion.

### *Surgery*

After informed consent had been obtained, 555 patients were selected to undergo a modular function-sparing surgical approach from January 1, 1995, to December 31, 2011. Despite that most of these cases were already included in previous reports,[9,12] the preoperative and intraoperative records and the pathological reports were reviewed to allow proper reclassification according to the 2002 TNM classification system.[16] Ninety-six patients (17.2%) included in the present analysis had been treated previously for laryngeal carcinoma by CO2 transoral laser surgery (38 of 96; 39.5%), (chemo)radiation therapy (35 of 96; 36.4%), open partial laryngectomy (8 of 96; 8.3%), or cordectomy (15 of 96; 15.6%).

Resections were classified according to the European Laryngological Society Classification, 10 in which "+ARY" represents the removal of 1 arytenoid and "+CAU" the removal of 1 cricoarytenoid unit. In particular, only type II and III open partial horizontal laryngectomies were performed: type IIa (supracricoid partial laryngectomy/cricohyoidoepiglottopexy), 62 (11.1%); type IIa+ARY, 243 (43.8%); type IIb (supracricoid partial laryngectomy/cricohyoidopexy), 32 (5.8%); type IIb+ARY, 117 (21.1%); type IIIa (supratracheal partial laryngectomy/tracheohyoidoepiglottopexy), 9 (1.6%); type IIIa+CAU, 82 (14.8%); type IIIb (supratracheal partial laryngectomy/tracheohyoidopexy), 4 (0.7%); and type IIIb+CAU, 6 (1.1%).

The indications adopted for type II (a+b) open partial horizontal laryngectomies were the classical ones, applied according to tumor extent, now being accepted and advocated by numerous authors.[6,7,9,17] Although definitions for type III (a+b) open partial horizontal laryngectomies were only recently introduced, their indications and contraindications were already described in our previous study for tumors in the intermediate/selected advanced T classification.[12] Additional contraindications for type III (a+b) open partial horizontal laryngectomies were supraglottic T4a tumors reaching the base of the tongue or invading the hyoid bone. In all patients, resection margins were examined intraoperatively with frozen sections: when positive, the resection was extended until the margins were negative. As the interventions followed the principles of a modular approach, the resection was always prepared in a standard fashion and the larynx was opened from the side less affected by the disease. At this point, under visual control, the subsites involved were removed and the resection could be easily enlarged as follows: (1) type IIa/b → type IIa/b+ARY; (2) type IIIa/b → type IIIa/b1CAU; (3) type IIa → type IIb; (4) type IIa/b1ARY → type IIIa/b+CAU; and (5) type IIIa → type IIIb. The margins of the surgical specimen were always checked again upon definitive pathology. Neck dissection, graded according to the American Academy of Otolaryngology – Head and Neck Surgery Foundation classification, was performed in 503 patients (90.6%), and was monolateral in 324 cases (64.4%) and bilateral in 179 cases (35.6%). Neck dissection was elective (neck dissection levels II–IV) in 447 patients with cN0 disease (88.9%) and curative (neck dissection levels II–V1internal jugular vein in 1 case) in 56 patients with >cN0 disease (11.1%). In 123 patients, level VI or unilateral paratracheal lymph node clearance was added. No neck dissection was performed in an additional 52 patients (9.4%; in the elderly and/or those with cN0 disease or in previously treated necks).

*Postoperative care*

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 1–4); (2) intermittent occlusion of the tracheostomy with saline-soaked gauze and the start of feeding without the tracheal cannula in place (days 4–6); and (3) nasogastric (NG) tube removal as soon as a good level of swallowing of both solids and liquids was achieved (day 6 onward).12 Postoperative aspiration was graded in accordance with Pearson's scale18 (05none; I5occasional cough but no clinical problems; II5constant cough worsening with meal or swallowing; and III5pulmonary complications).

*Pathology*

All patients suffered from a biopsy-proven supraglottic or glottic laryngeal SCC, which was classified as pT3 or pT4a, according to the 2002 TNM classification system16 (Table 1). Furthermore, pathology reports indicated close margins (<2 mm) in 13 cases (2.3%) and positive margins at the definitive histopathologic examination in 5 cases (0.9%). Four hundred ninety-nine patients (89.9%) had been staged as cN0 by palpation and neck CT scan or MRI. Overall, lymph node metastases were detected in 71 of 555 patients (12.8%), of whom 40 (7.2%) had multiple metastases. Furthermore, the comparison between clinical and pathological staging showed upstaging of the primary tumor in 83 cases (14.9%) and lymph nodes in 15 cases (2.7%).

*Adjuvant treatments*

On the basis of pathological findings (pN1 and/or extracapsular spread, extralaryngeal extent, positive margins), 72 patients (12.9%) were subjected to adjuvant radiotherapy. The indications for adjuvant therapy were: 40 N1 (14 level VI pN1, 26 pN2), 27 cases with extralaryngeal extent (3 supraglottic pT4a and 24 glottic pT4a), and 5 glottic pT3 cases with positive margins. Despite that 113 patients had pT4a tumors, the majority displayed only a limited extralaryngeal spread, which was manageable with strap muscles and thyroid resection (isthmus6ipsilateral lobe) as well as central compartment neck dissection. For this reason, adjuvant radiotherapy was added only in those cases with more extensive extralaryngeal extent. 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). Furthermore, chemotherapy was also scheduled in selected patients because of a higher risk of local recurrence: 42 of 72 (9 level VI - Delphian node pN1, 6 pN2 with extracapsular spread, and 27 with more extended pT4a showing close margins toward prelaryngeal tissues) received 100 mg/m2 cisplatin on days 1, 22, and 43 of the course of radiotherapy.[19]

*Larynx functional assessment*

Pearson's scale evaluation was repeated and larynx functional status was evaluated with the Performance Status Scale throughout 5 postoperative years. The latter is a simple, practical, clinician-rated assessment tool consisting of 3 subscales: speech comprehension, normalcy of diet, and eating in public, graduated from 0 to 100 on the basis of predefined parameters.

*Statistical methods*

Overall survival (OS), disease-free survival (DFS), disease-specific survival (DSS), locoregional control, local control, laryngectomy-free survival, and laryngeal function preservation were assessed by means of 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, type of surgery, and age). The endpoints considered were obtained as the length of time from the date of diagnosis to: OS, the date of death; DFS, the date of the first recurrence; DSS, the date of death from the disease; locoregional control, the date of the first locoregional recurrence; local control, the date of the first local recurrence; laryngectomy-free survival, the date of total laryngectomy; laryngeal function preservation, the date of total laryngectomy or presence of tracheostomy; NG tube, gastrostomy feeding; or nonintelligible voice. Unpaired t test was used to compare hospitalization time of patients. All analyses were performed with GraphPad Prism version 5.00 (GraphPad Software, San Diego CA), with $p<.05$ as the significant cutoff.

## RESULTS

A cohort of 555 patients undergoing type II or III open partial horizontal laryngectomies was considered (Table 1). Current or former smokers made up 93% of the cohort. Patients were followed for a mean period of 5.57 years.

### *Survival and disease control*

The 5-year OS, DSS, DFS, locoregional control, and local control were 84.6%, 92.8%, 84.2%, 86.3%, and 90.6%, respectively (see Figure 1). At the last follow-up, a total of 89 patients (16.0%) had died, 39 (7.0%) for the index cancer, and 50 (9.0%) for unrelated causes (Table 2).

### *Patterns of failure*

Within 5 years of surgery, 66 patients (11.9%) developed a recurrence: 40 (60.6%) were local, 5 (7.6%) locoregional, and 21 (31.8%) regional.

Local recurrences were observed in 35 of 459 untreated patients (7.6%) and 10 of 96 pretreated patients (10.4%). Among them, 8 of 45 (18.7%) had inferior paraglottic space involvement, 4 of 45 (0.8%) had internal thyroid lamina involvement, 10 of 45 (22.2%) had transglottic extension, 3 of 45 (6.7%) had subglottic extension and inclusion of a cricoarytenoid joint, 2 of 45 (4.4%) had surface extension as far as the inferior edge of the cricoid ring, 15 of 45 (33.3%) had extralaryngeal extension (9 of 15 anterior and 6 of 15 posterior), and 3 of 45 (6.7%) showed surface extension toward the posterior commissure. As a result of type III open partial horizontal laryngectomies, the typical sites of local failure inside the larynx were the mucosa at the junction between the residual larynx and trachea (6 of 20; 30.0%), the mucosa at the level of the posterior commissure (4 of 20; 20.0%), and the contralateral CAU (2 of 20; 10.0%), whereas outside the larynx (8 of 20; 40.0%) the tumor typically recurred at the level of the outer surface of the residual larynx. 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 29 of 45 patients (64.4%), radiation therapy, and/or chemotherapy in 11 of 45 (24.4%), and laser surgery in 5 of 45 (11.1%). Overall, 17 of 45 patients (37.7%) died of laryngeal cancer from progression of disease (average, 18.1 months; range, 3–42 months), 7 of 45 patients (15.6%) died of other disease, whereas at the last follow-up 1 of 45 patients (2.2%) was alive with the disease and 20 of 45 patients (44.4%) were alive and disease-free. Overall, local control after salvage therapy at 5 years was achieved in 27 of 45 patients (60.0%). Recurrence in the neck was observed in 26 of 555 cases (4.67%), 19 (3.4%) of whom were previously classified as cN0 and 7 (1.3%) as >cN0. At the time of primary resection, 2 of 26 patients (7.7%) had received unilateral neck dissection, and 14 of 26 (53.8%) had bilateral neck dissection. In 8 of 26 patients (30.8%), recurrence was observed at level VI. Four of 26 recurrences (15.4%) in the neck were treated with surgery alone, 20 of 26 (76.9%) with surgery and adjuvant radiation therapy and/or chemotherapy, and 2 of 26 (7.7%) with chemotherapy. Eleven of 26 patients (42.4%) died because of regional recurrences (range, 6–38 months; mean, 16.3 months), and 2 of 26 (7.7%) for other diseases. At the last followup, 3 of 26 patients (11.5%) were alive with disease and 1 of 26 patients (3.8%) were alive and disease-free.

*Correlation of pT category, pN category, and type of surgery with overall survival, disease-free survival, and locoregional control*

Because intermediate/advanced laryngeal carcinomas greatly differ in surgical indications and prognosis, analyses were conducted on the basis of pathological staging in order to obtain homogeneous prognostic data. By stratifying the chart data, we evaluated whether pT, pN, and type of surgery could affect the OS, DFS, and locoregional control endpoints in terms of prevalence (see Figure 2). Five years after surgery, OS was significantly affected by pT and pN classifications. In fact, it was 87.8% and 71.2% in pT3 and pT4a patients, respectively, whereas it was only 51.5% in pN _2 patients, although similar in pN0 (88.3%) and pN1 (88.5%). Moreover, the extent of surgery affected OS (87.7%, 84.6%, 74.3%, and 72.0% for patients undergoing type IIa, type IIb, type IIIa, and type IIIb open partial horizontal laryngectomy surgery, respectively). At any rate, no significant differences were detected considering the DSS endpoint (from 94.6% of open partial horizontal laryngectomy type IIb to 87.6% of open partial horizontal laryngectomy type IIIa). DFS was significantly affected by locoregional staging and surgical approach. In fact, patients with pT4a disease had 68.1% DFS if compared with 87.9% of pT3; similarly pN1 patients (72.6% pN1 and 71.1% pN _2) had worse outcome than pN0 (88.2%). As a consequence, type III open partial

horizontal laryngectomies (66.6% IIIa and 70.0% IIIb) were less effective than type II (85.1% IIa and 91.8% IIb) in maintaining patients free from disease.
The same pattern was also evident for the locoregional control endpoint: 71.7% pT4a versus 89.7% pT3; 72.0% pN1 and 79.6% pN _2 versus 89.8% pN0; 72.1% open partial horizontal laryngectomy type IIIa, and 70.0% IIIb versus 87.6% type IIa and 92.5% IIb.
We also assessed the impact of previous treatment and age _65 without observing any significant differences (data not shown).

*Postoperative course and morbidity*

Overall, acute complications during hospitalization occurred in 61 of 555 patients (11.0%) and there were 3 perioperative deaths (2 myocardial infarctions and 1 stroke). The mean hospitalization time for patients with acute complications was significantly longer than that for patients without acute complications (3266 days vs 2165 days; p<.001). Late sequelae after discharge were observed in 85 of 555 cases (15.3%; Table 3). All were successfully treated with transoral CO2 laser surgery (68 of 85; 80%), revision of the pexy (2 of 85; 2.3%), injective laryngoplasty using Vox-implants, which successfully treated dysphagia (5 of 85; 5.8%), completion laryngectomy (5 of 85; 5.8%), or other endoscopic procedures (5 of 85; 5.8%).

*Laryngeal function preservation*

Five years after surgery, the laryngeal function preservation rate was 92.6% (514 of 555 patients), whereas laryngectomy-free survival resulted in 93.3% (524 of 555 patients; see Figure 3). In addition, we evaluated whether laryngeal function preservation could be affected by local or regional staging, presence of previous treatment, or age _65 years (see Figure 4). Patients affected by advanced pT stage were significantly more prone to laryngeal function loss (78.0%) than those with intermediate pT stage (94.2%), whereas pN status had no impact.
The type of surgery and age affected laryngeal function preservation at 1 year, whereas no differences were detected at subsequent visits. Although the log-rank test did not provide significant results in the comparison between younger (92.6%) and older patients (88.5%), we could appreciate a significant difference using the Gehan–Breslow–Wilcoxon test.

Finally, laryngeal function preservation was not biased by previous treatments (data not shown).
After the first postoperative month, normal swallowing (Pearson's scale grade 0) was achieved in 333 patients (60.0%), grade I and II were observed in 115 (20.7%) and 91 patients (16.4%), respectively, whereas aspiration pneumonia (Pearson's grade III) was recorded in 16 patients (2.9%). After the second year, a satisfactory degree of laryngeal function was achieved in 460 of 555 patients without local disease (82.9%). Of the 528 patients evaluated for subjective aspiration by the Pearson's scale, 227 patients (43%) had no aspiration (grade 0), 231 patients (43.8%) had an occasional cough without clinical problems (grade I), 62 patients (11.7%) had a constant cough that worsened during meals (grade II), and 8 patients (1.4%) had frequent pulmonary complications (grade III). Nearly all patients (547 of 555; 98.6%) had the NG tube or gastrostomy removed. The NG tube remained in place for an average of 19.5 days (range, 11–161 days).
Overall, aspiration pneumonia was observed in 41 of 555 cases (7.4%), 16 cases during hospitalization and 25 cases during follow-up, which required a percutaneous gastrostomy (PEG). In another 3 patients (0.5%), a prophylactic PEG was performed in view of their advanced age. Overall, in 30 of them, PEG was removed within the first postoperative year. In 14 cases, it was maintained because of repeated episodes of aspiration pneumonia and severe dysphagia for liquids. In 7 cases, total laryngectomy was proposed for persistent aspiration: 5 patients accepted this treatment whereas 2 refused, preferring to keep the PEG and maintain their voice. Five patients underwent endoscopic injective laryngoplasty using the Vox implant, which successfully resolved dysphagia, allowing the PEG removal
The mean time to intermittent occlusion of the tracheostomy was 24.6 days (range, 3–406 days), and the average time to tracheostomy closure was 82.4 days (range, 23–489 days). In our protocol, progressive closure of the tracheostomy is preferred, and occurs spontaneously in the majority of patients after occlusion. For patients, especially in the first weeks after discharge, this leads to a sensation of greater safety concerning minor episodes of food inhalation, which are relatively frequent. When the tracheostomy has almost closed, minor plastic surgery can then be performed.

## DISCUSSION

Even though preservation of laryngeal functions is one of the major advances achieved over the past decades in the management of laryngeal cancer, intermediate/advanced stage lesions still present a major challenge in terms of controlling the disease and preserving the larynx, regardless of the therapeutic option.[2–4,6,7,9,20–23] In fact, many glottic cT3 tumors with subglottic extent (vocal cord and arytenoid fixation) often result in early pT4a for extralaryngeal extent, making their management with chemoradiotherapy or supracricoid laryngectomy difficult. Toward the end of the 1990s, a comparative analysis (unpublished data) of total laryngectomy and supracricoid specimens in relation to arytenoid fixation and subglottic swelling triggered the idea of extending the supracricoid laryngectomy downward to obtain safer margins. In 2006, this led to the introduction of a new type of open partial horizontal laryngectomy, the supratracheal laryngectomy, otherwise known as open partial horizontal laryngectomy type III, according to the recent European Laryngological Society classification.[10] As recently demonstrated by Schindler et al[13] and Rizzotto et al,[12] this is able to spare laryngeal function without compromising locoregional control during long-term follow-up. As a consequence of the diffusion of supracricoid partial laryngectomies (open partial horizontal laryngectomy type II), the advent of supratracheal partial laryngectomies (open partial horizontal laryngectomy type III), and the consolidated role of conventional nonsurgical organ-sparing protocols, the role of total laryngectomy in the treatment of endolaryngeal neoplasms has considerably decreased.

In this study, we have analyzed the outcomes of 555 patients affected by intermediate/advanced stage laryngeal SCC undergoing different forms of open partial horizontal laryngectomy. At surgery, the resection was tailored under visual control to obtain disease-free safe margins, which can be as close as only 4 to 5 mm. It is noteworthy that such intraoperative flexibility can be useful to address the heterogeneity of tumors on the base of their true extent. In fact, in our series, upstaging from cT3 to pT4a was found in 14.9% of specimens, generally because of the full thickness involvement of the thyroid lamina, and from cN0 to pN1 in 3% of cases, in spite of preoperative neck CT and/or MRI. This fact might explain the difference in terms of local control between concomitant chemoradiation and open partial horizontal laryngectomies in the management of intermediate stage cancer of the larynx. In fact, the present data on survival and local disease control confirm the results of our previous analysis,[12] but greatly differ from those of nonsurgical approaches. The 5-year OS of 84.6% observed in the present study is higher than that reported in the literature for both concomitant chemoradiotherapy and induction chemotherapy followed by radiotherapy (approximately 60%).[4,24] More advanced pT4a tumors had a 5-year DFS of 68.1%, a result in agreement with that obtained with total laryngectomy; of note, patients with extensive extralaryngeal spread were not considered amenable to open partial horizontal laryngectomy. These data show that a careful selection can make a good number of patients eligible for the partial modular surgical approach, even in some well selected "extreme cases." However, 5-year DFS of patients with pT4a tumors (68.1%) was significantly lower than that of patients with pT3 (87.9%), but higher than that reported for radiotherapy and/or chemotherapy, which ranges from 26% to 38%, respectively.[4,24] Finally, the number of patients that were subjected to total laryngectomy for either functional or oncologic purposes was extremely low (6.2%) and there were only 3 perioperative deaths. The high laryngectomy-free survival rate here achieved demonstrates the great potential of open partial horizontal laryngectomy approaches in preserving the larynx. In summary, "everybody loses a piece, but few lose all."

The real Achilles heel of open partial horizontal laryngectomies is represented by a greater proportion of functional problems compared with nonsurgical treatment options. Benito et al[25] reported that persistent slight dysphagia and aspiration pneumonia still represent major complications in patients undergoing open partial horizontal laryngectomy type II. The same findings were observed in the present cohort of patients; furthermore, the voice was significantly deteriorated, and generally quite hoarse and breathy, especially in open partial horizontal laryngectomy type III.[13] Despite the inclusion of the less extended open partial horizontal laryngectomy type II, no differences in terms of acute complication and late sequelae were found with respect to our previous analysis.[12] In fact, 19 of 41 cases of aspiration pneumonia occurred in elderly patients. Fortunately, these phenomena are not frequent, tend to self-restraint, and to be well-tolerated by patients. On the other hand, a statistically significant decrease in hospitalization time could be achieved by better tailoring surgery to the extent of tumor. Indeed, a mean hospitalization time of 32 and 21 days, with and without acute complications, respectively, was observed, in contrast to 38 and 24 days reported by Rizzotto et al[12] for open partial horizontal laryngectomy type III. The oncologic and functional results obtainable by open partial horizontal laryngectomy approaches are very robust and repeatable. Many experiences reported in the past 20 years support this claim.[5–9] The gold standard indications are: supraglottic cT3 (open partial horizontal laryngectomy type IIb ± ARY); glottic cT3 with vocal cord fixation (open partial horizontal laryngectomy type IIa ± ARY); and glottic cT3 with vocal cord fixation ± arytenoid fixation and also subglottic extension (open partial horizontal laryngectomy type IIIa ± CAU). In the latter case, the option of a supracricoid partial laryngectomy would be very much at risk of leaving positive margins as the section line passes through a cricoarytenoid joint. A different and more cautious approach is required for anterior cT4a tumors with fullthickness involvement of the thyroid lamina and/or minimal extralaryngeal extension: by adopting open partial horizontal laryngectomy, the radicality is the same as for total laryngectomy, provided that patient selection is meticulous. In fact, after thorough workup, the surgeon must be able to anticipate with a high accuracy if free margins can be obtained, thus minimizing the need to resort to a total laryngectomy. In all cases with subglottic extension or spread of the tumor toward the posterior commissure that require an open partial horizontal laryngectomy type III, a critical ethical issue arises. In fact, in many specialized centers, these cases are considered to be "amenable with total laryngectomy" and, therefore, are directed to nonsurgical treatment in order to spare the larynx. When discussing a conservative surgical option with the patients, they should be clearly informed that if the resection margins are positive at frozen sections, the intervention will be converted to a total laryngectomy. This decision-making process would indeed exclude the alternative of concurrent chemoradiation, which has the grade A recommendation according to the Scottish Intercollegiate Guidelines Network. In conclusion, herein we demonstrate that, in case of supraglottic tumors with glottic involvement, any subtype of glottic cT3, and some carefully selected glottic tumors with subglottic extension, open partial horizontal laryngectomy with a modular approach can be considered a viable treatment option not only in prognostic terms but also in terms of functional results, although the occurrence of aspiration pneumonia should not be neglected.

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**Table 1.** **Characteristics of the 556 patients undergoing OPHLss according to age, gender, Karnofsky performance status and pathological grade**

| **Age (years)** | | **pT – p N** | | |
|---|---|---|---|---|
| Mean | 59.9±9.4 | *pT* | *Supraglottic* | *Glottic* |
| | | pT3 | 34/49 (69.4%) | 408/507(80.5%) |
| **Gender** | | pT4a | 15/49 (30.6%) | 98/507 (19.3%) |
| Male | 511/556 (91.9%) | | | |
| Female | 45/556 (8.1%) | *pN* | | |
| | | pN0 | 37/49 (75.5%) | 406/454(89.4%) |
| **Karnofsky Performance Status** | | pN1 | 7/49 (14.3%) | 27/454 (6.0%) |
| 100 | 327/556 (58.8%) | pN2 | 5/49 (10.2%) | 21/454 (4.6%) |
| 90 | 158/556 (28.4%) | | | |
| 80 | 71/556 (12.8%) | Level VI pN+ | | 14/123 (11.4%) |

**Table 2** **Cause of death**

| Cause | No. of patients (%) |
|---|---|
| Laryngeal cancer | 39/555 (7.0) |
| Postoperative death | 3/555 (0.5) |
| Second primary cancer | 31/555 (5.6) |
| Others causes | 16/555 (2.9) |
| Total deaths | 89/555 (16.0) |

**Table 3 Acute post-operative complications and late sequelae**

| Complications | No. of patients (%) |
|---|---|
| Acute complications | |
| Cervical bleeding | 18/555 (3.2) |
| Aspiration pneumonia | 16/555 (2.9) |
| Wound infection | 14/555 (2.5) |
| Postoperative death | 3/555 (0.5) |
| Others | 10/555 (1.8) |
| Late sequelae | |
| Laryngeal soft tissue stenosis | 54/555 (9.7) |
| Aspiration pneumonia | 25/555 (4.5) |
| Dyspnea | 6/555 (1.1) |

**Figure 1** **Endpoint analysis (overall survival, disease-specific survival, disease-free survival, locoregional control and local control of the patient cohort using Kaplan-Meier curves**

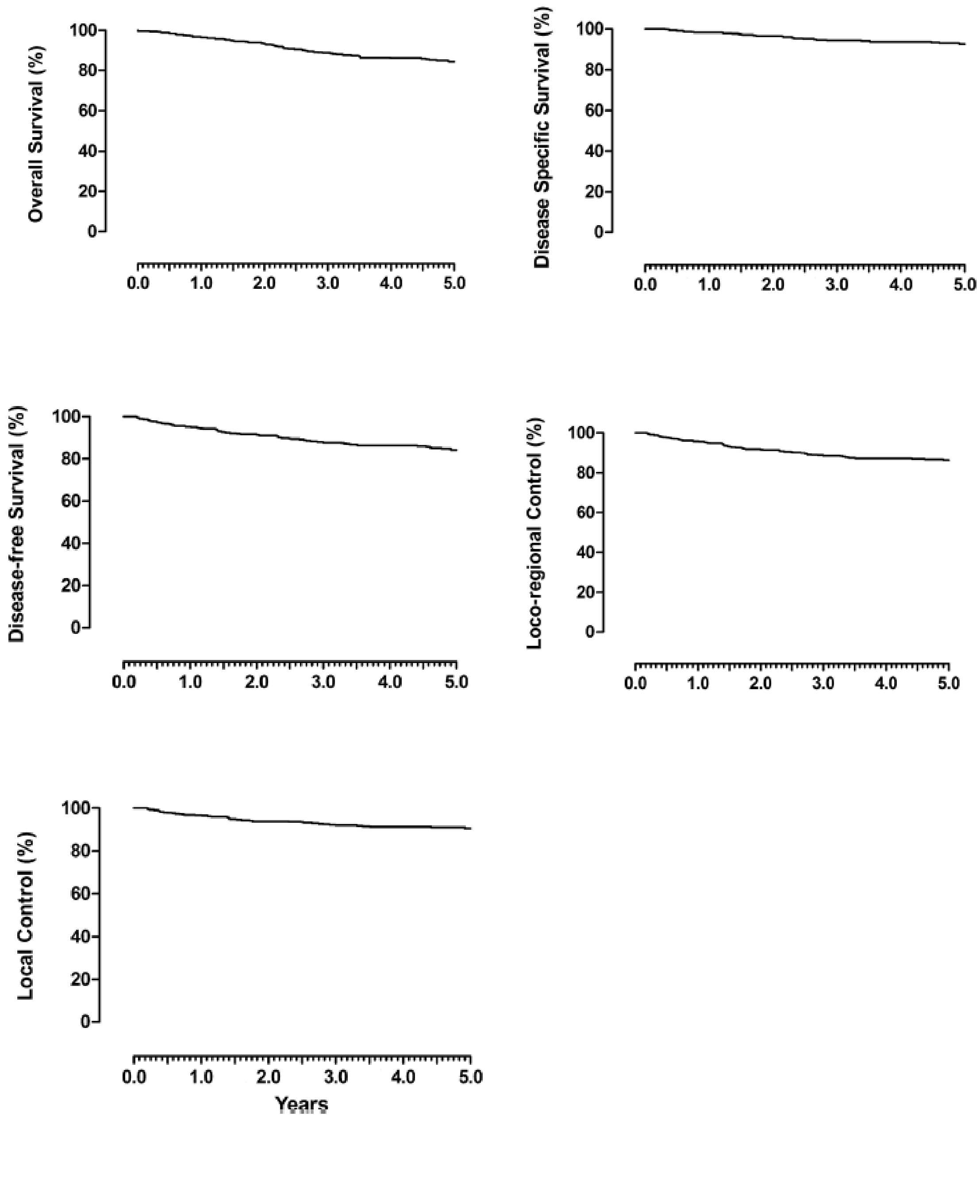


**Figure 2** **Patient cohort stratification for pT classification (left column), pN classification (middle column) and type of surgery (right column) using Kaplan-Meier curves. The endpoints considered were (from top to bottom) overall survival, disease-free survival, locoregional control and local control *p< .05; **p<.01; *** p< .001**

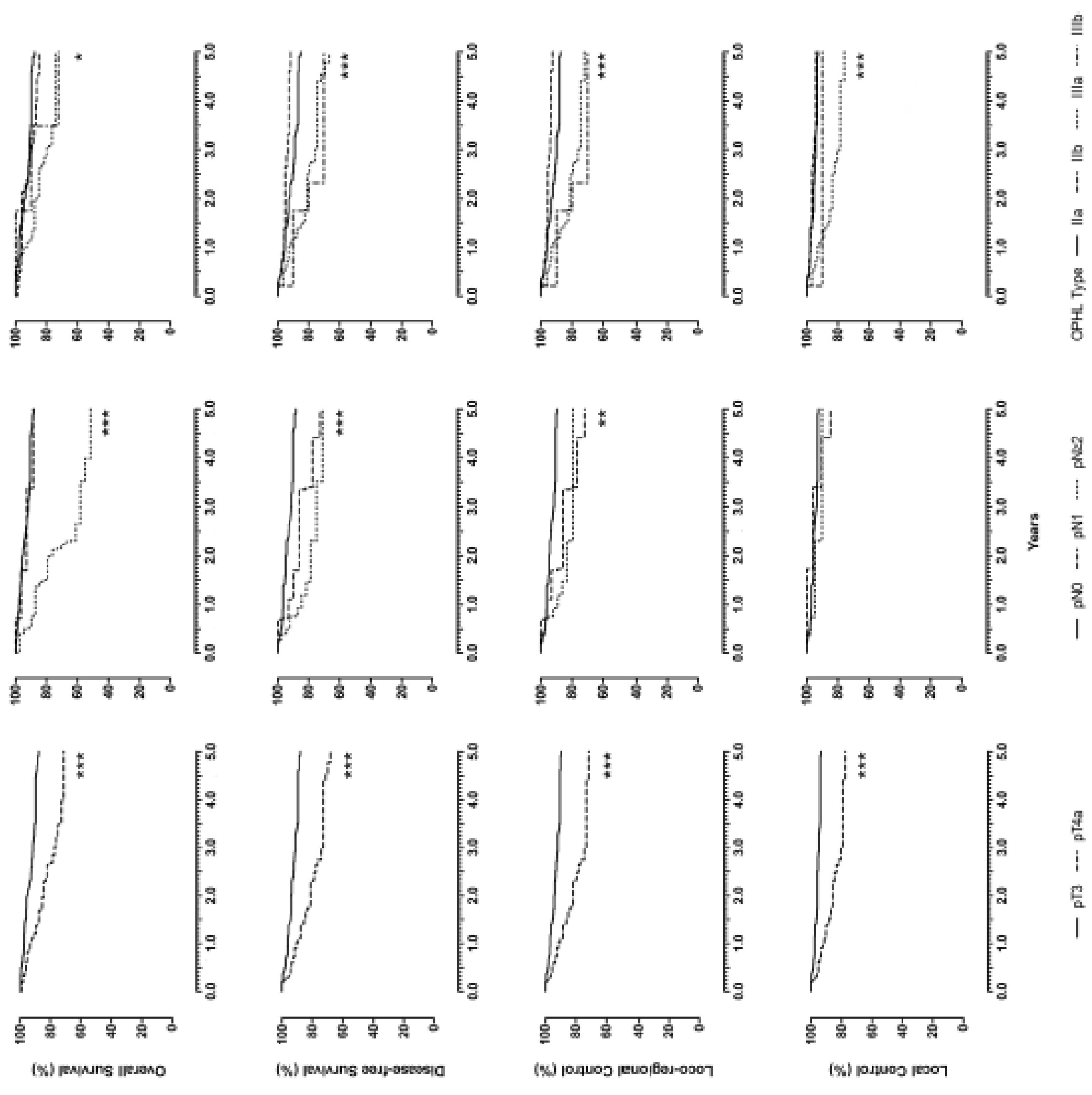


**Figure 3** **Endpoint analysis of laryngeal function preservation and laryngectomy-free survival in the patient cohort using Kaplan-Meier curves**

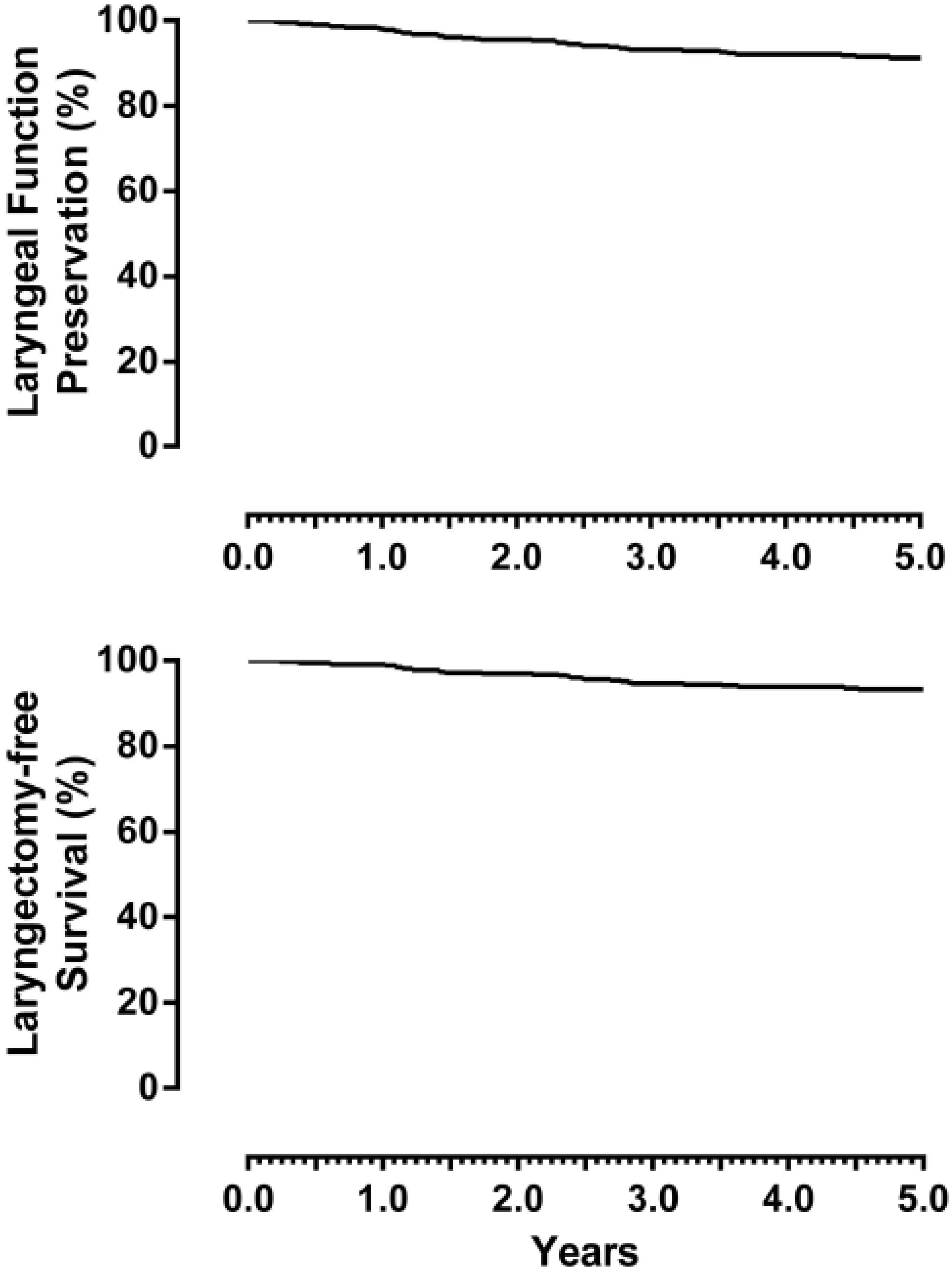
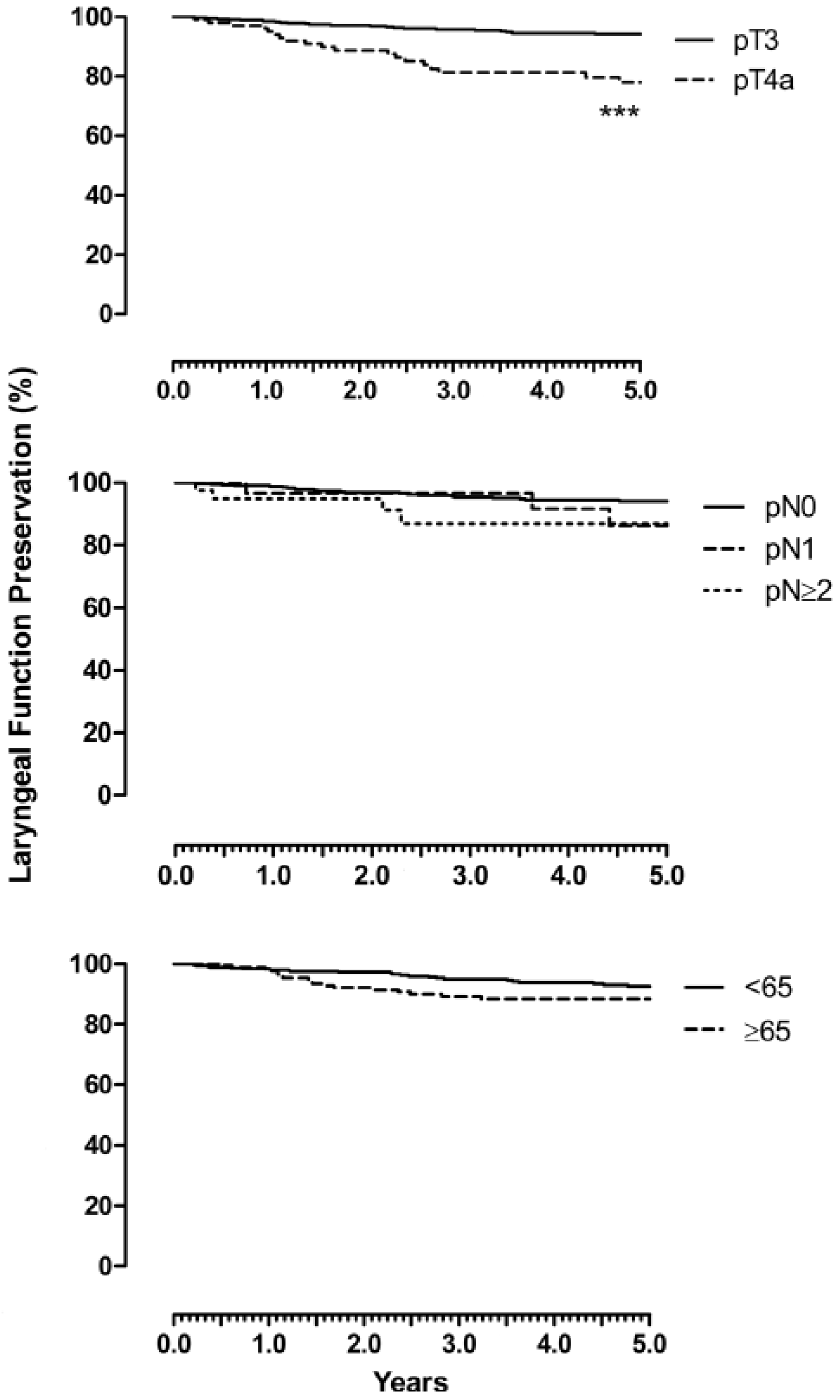


**Figure 4** **Evuluation of laryngeal function preservation in the patient cophort stratified for pT classification (top), pN classification (middle) and age (bottom) using Kaplan-Meier curves *** p< .0001**



# Paper 6

## *Oncologic outcomes of supratracheal laryngectomy: critical analysis*

ABSTRACT:

*Background*. Laryngeal cancer management should pursue function-sparing therapeutic options. Even though demolitive surgery provides better control of disease at intermediate to advanced stages when compared to chemoradiotherapy, it does not preserve laryngeal function. Supratracheal partial laryngectomy has been described as a function-sparing surgical technique for laryngeal cancer with subglottic extension.

*Methods*. In this retrospective study, we analyzed the clinical outcomes of 115 patients who underwent supratracheal partial laryngectomy.

*Results*. At 5 years, overall survival (OS), disease-free survival (DFS), and locoregional control rates were 78.9%, 68.5%, and 69.6%, respectively; DFS and locoregional control prevalences were greatly affected by pT4a classification (49.0% and 51.4%, respectively); and laryngeal function preservation was maintained in 78.3% of patients despite being affected by pT4a classification (59.3%) and age > or = 65 (64.6%).

*Conclusion*. For cases with glottic tumors and with subglottic extension, the choice of supratracheal partial laryngectomy versus chemoradiotherapy can be considered to be effective in terms of prognostic and functional results.

INTRODUCTION

Laryngeal squamous cell carcinoma (SCC) represents 2% to 5% of all diagnosed tumors worldwide with a peak incidence in men aged between 55 and 65 years.1 Therapeutic approaches developed in the 20th century have significantly improved overall survival (OS) from this type of cancer, however, poor prognosis and loss of functionality of the larynx still characterize the disease in its advanced stage.[2–4] Treatment includes surgery alone or in combination with chemotherapy and/or radiotherapy (RT), and management of laryngeal cancer varies depending on localization and staging at diagnosis. Early stages (I and II) are treated with unimodal therapy, which can include surgery or RT, whereas for the advanced stages (III and IV), chemoradiotherapy and demolitive surgery are considered to be the gold standard therapeutic approach.[5–7] A third alternative, although not fully accepted worldwide, is represented by function-sparing surgical protocols with open partial laryngectomy. Despite encouraging oncologic results, the main criticisms of this approach are the criteria for patient selection and functional results, the latter being not easily repeatable.[8–11]

To preserve laryngeal function surgically in intermediate and advanced stages, different types of open partial laryngectomy have been proposed beginning with the first supratracheal open partial laryngectomy described by Serafini [12] in 1972. In 2006, our group reported a modified functional version, in which at least one functioning cricoarytenoid unit was spared (ie half of the posterior cricoid plate, with the corresponding arytenoid and the intact inferior laryngeal nerve on the same side).[13] Currently, supratracheal partial laryngectomy is based on resection of the whole glottic and subglottic sites and of the thyroid cartilage, sparing both or at least one functioning cricoarytenoid unit. Inferiorly, the limit of resection encompasses the cricoid ring sparing the first tracheal ring. The various types of supratracheal partial laryngectomies, also identified by the type of laryngeal resynthesis as supratracheal partial laryngectomy/tracheohyoid epiglottopexy or supratracheal partial laryngectomy/ tracheo-hyoid-pexy, differ in the amount of supraglottis resected and in the lateral extent, if any, to include 1 cricoarytenoid unit. Extending the inferior limit of resection to include a large part of the cricoid cartilage, supratracheal partial laryngectomies expanded the indications with respect to open partial supracricoid laryngectomies. [14,15]

Some “problematic” glottic cT3 (ie, subglottic extension and cricoarytenoid joint invasion) and some supraglottic cT3 (ie, large transglottic extension) result, hence they are manageable with supratracheal partial laryngectomies; these interventions have shown promising oncologic and functional results.[13]

In this study, we present a multicentric retrospective outcome analysis of 115 patients with supraglottic/glottic laryngeal SCC managed by supratracheal partial laryngectomy/tracheo-hyoid epiglottopexy or supratracheal partial laryngectomy/tracheo-hyoid-pexy 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 tumor.[5,7,16]

## MATERIALS AND METHODS

### *Patients*

All patients were from the Hospital of Vittorio Veneto, Treviso, or the Martini Hospital of Turin. Selection was based on the superficial and depth extent of the tumor. During the 3 weeks preceding surgery, all patients underwent: flexible videolaryngoscopy; intraoperative rigid endoscopy with 0_/angled telescopes, and biopsy during microlaryngoscopy; laryngeal and neck CT scan or MRI; bronchoscopy and esophagoscopy to rule out synchronous tumors; chest X-ray or CT scan to exclude lung tumors or distant metastases; assessment of bronchopulmonary function and of comorbidities for at-risk patients; and nutritional evaluation.

Inclusion criteria were histological diagnosis of glottic or supraglottic laryngeal SCC, with Karnofsky index17 higher than 80. Exclusion criteria were severe diabetes mellitus, severe bronchopulmonary chronic obstructive disease, and severe cardiac disease. Advanced age, an important cutoff for relative surgical indication, has not been considered, in itself, as an exclusion criterion.[18]

### *Surgery*

After informed consent had been obtained, 120 patients were selected to undergo supratracheal partial laryngectomies from January 1, 2002, to December 31, 2011. Five cases were excluded from analysis because of the presence of a different pathology: 4 cases of low-grade chondrosarcoma and 1 case of mucoepidermoid carcinoma.

Thirty-six patients (31.3%) included in the present analysis were treated previously for laryngeal carcinoma by chemoradiation therapy (12 of 36; 33.3%), CO2 transoral laser surgery (16 of 36; 44.4%), open partial laryngectomy (4 of 36; 11.1%), or cordectomy (4 of 36; 11.1%). The tumors were glottic in 103 patients and supraglottic in 12 patients. The vocal fold mobility was: 22 cases with normal or impaired vocal cord mobility (8 supraglottic pT4a and 14 glottic pT2), 44 cases with fixed vocal cord and mobile cricoarytenoid joint (1 supraglottic pT3, 3 supraglottic pT4a, 5 transglottic pT3, 16 glottic pT3, and 19 glottic pT4a), and 49 cases with fixed vocal cord and cricoarytenoid joint (29 glottic-subglottic pT3, 19 glottic pT4a, and 1 transglottic pT3).

Resections were classified as follows: supratracheal partial laryngectomy/tracheo-hyoid epiglottopexy = 10 (8.7%), supratracheal partial laryngectomy/tracheo-hyoid epiglottopexy + A = 95 (82.6%), supratracheal partial laryngectomy/tracheo-hyoid-pexy = 4 (3.5%), supratracheal partial laryngectomy/tracheo-hyoid-pexy + A = 6 (5.2%), where "1A" represents the removal of 1 cricoarytenoid unit.

The adopted indications for supratracheal partial laryngectomy interventions were as follows:

(1) glottic T2 tumors with anterior subglottic extension, spreading downward above the conus elasticus and reaching the cricoid ring;

(2) glottic–subglottic T3 tumors spreading within the paraglottic space and controlled by the conus elasticus medially and the perichondrium of the thyroid cartilage laterally (tumor growth is directed downward and laterally, sometimes infiltrating the inferior edge of thyroid cartilage or escaping the larynx between the thyroid and cricoid cartilages through the cricoarytenoid membrane: the so-called early glottic pT4a); typical clinical features are fixed vocal cord, fixed arytenoid, and subglottic swelling;

(3) transglottic T3 tumors spreading superiorly into the deep tissue of the ventricular band under the quadrangular membrane and progressing into the subglottic area, where they invade the internal lamina or the inferior edge of the thyroid cartilage or the superior edge of the cricoid;

(4) T3 glottic tumors with paraglottic space invasion and surface extension toward the posterior commissure (a typical radiological feature is the initial sclerosis of the cricoid hemiplate);

(5) supraglottic T3 of the infrahyoid epiglottis spreading laterally to the petiolus and into the preepiglottic space encompassing the anterior commissure toward the cricoid ring (often escaping the larynx through the thyroid cartilage or cricoarytenoid membrane with fixation or impaired mobility of the anterior vocal cords but without affecting the arytenoid mobility: early supraglottic pT4a).

The contraindications related to locoregional extension were:

(1) glottic-subglottic T3 tumors with massive invasion of the paraglottic space reaching the posterior cricoarytenoid muscle and the pyriform sinus submucosa;

(2) gross glottic–subglottic T4a with massive cricoid invasion or reaching the first tracheal ring;

(3) lymph nodes staged N3.

In all patients, resection margins were examined intraoperatively with frozen sections: when positive, the resection was expanded until the margins were negative. The margins of the surgical specimen were always checked again upon definitive pathology. Neck dissection, graded according to the American Academy of Otolaryngology–Head and Neck Surgery Foundation classification,[19] was performed in 75 patients (65.2%), and was monolateral in 42 (56%) and bilateral in 33 (44%) cases. Neck dissection was elective (neck dissection levels II–IV) in 70 cN0 patients (60.8%), and curative (neck dissection levels II–V1internal jugular vein in 1 case) in 5 cN >0 patients (11.1%). In 55 patients, whole level VI or unilateral paratracheal lymph node clearance was added. No neck dissection was performed in an additional 40 patients (34.8%) with early disease, cN0 disease, or in previously treated necks.

*Postoperative care and adjuvant treatments*

All patients were monitored for early complications (local and general) and late sequelae. Patients underwent the same rehabilitation protocol, apart from those with serious early complications.

The postoperative protocol consisted of: (1) days 1 to 4: insertion of an uncuffed tracheal cannula and beginning of phonation; (2) days 4 to 6: during daytime, intermittent occlusion of the tracheostomy with saline-soaked gauze and starting of feeding without the tracheal cannula in position; (3) day 6 onward: the nasogastric (NG) tube was removed as soon as a good level of swallowing of both solids and liquids was achieved. Grading of postoperative aspiration was performed in accordance with Pearson's scale.4 On the basis of pathological findings (pN1 and/or extracapsular spread, large extralaryngeal extension), 31 patients (26.9%) were subjected to adjuvant RT.

The indications for adjuvant therapy were: 7 N1 (5 level VI N1 and 2 N2b) and 24 cases with gross extralaryngeal extension (8 supraglottic pT4a and 16 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 31 patients also received 100 mg/m2 cisplatin on days 1, 22, and 43 of the course of RT.[20,21]

*Laryngeal functional assessment*

During the 5 postoperative years, Pearson's scale evaluation was repeated and laryngeal functional status was evaluated by the Performance Status Scale.[22]

*Statistical methods*

OS, disease-free survival (DFS), locoregional control, and laryngeal function preservation were estimated at 3 and 5 years using Kaplan–Meier curves. The end points considered were obtained as the length of time from the date of diagnosis to: OS5the date of death; DFS = the date of the first recurrence; locoregional control = the date of the first locoregional recurrence; laryngeal function preservation = the date of total laryngectomy or presence of tracheostomy, NG tube, gastrostomy feeding, or nonintelligible voice.

At the end of the study, the dates of last consultation for patients still alive or free from recurrences or without any laryngeal impairment were used for type-I censoring in the corresponding end point. pT classification, clinical history of previous treatment, and age were evaluated for their correlation with prevalence of OS, DFS, locoregional control, and laryngeal function preservation by log-rank test. The corresponding incidences were evaluated by chi-square tests. All analyses were carried out with GraphPad Prism version 5.00 (GraphPad Software, San Diego, CA), with $p < .05$ as the significant cutoff.

## RESULTS

### *Patients*

One hundred twenty patients undergoing supratracheal partial laryngectomies were initially included in this study. After excluding those treated for non-SCC, a cohort of 115 patients was considered (Table 1). Patients were followed for a mean period of 3.37 years. Current or former smokers made up 91% of the cohort.

### *Pathology*

All patients had a biopsy-proven laryngeal SCC staged between II and IVa, according to the 2002 TNM classification system[23] (Table 1). Furthermore, pathology reports indicated close margins (<2 mm) in 11 cases (9.6%) and in no case were found positive margins at the definitive histopathologic examination. One hundred ten patients (95.6%) had been classified as cN0 by palpation and neck CT scan or MRI. Overall, lymph node metastases were detected in 7 of 115 patients (6.1%), of whom 3 (2.6%) had multiple metastases.

### *Disease control and survival*

The 3-year OS, DFS, and locoregional control were 84.6%, 72.3%, and 73.3%, respectively. At 5 years, they were 78.9%, 68.5%, and 69.6%, respectively (see Figure 1).

### *Correlation of pT category, previous treatment, and age to overall survival, disease-free survival, and locoregional control*

Locally intermediate/advanced laryngeal carcinomas are a heterogeneous group of lesions in terms of superficial and depth extent. As a consequence, they differ greatly in surgical indications and prognosis. Therefore, the analyses were conducted on the basis of pathological staging in order to obtain homogeneous prognostic data. By stratifying the chart data, we evaluated whether they could affect the OS, DFS, and locoregional control in terms of prevalence (see Figure 2). We found that none of the factors affected patients' OS at 5 years. Indeed, the 5-year OS of pT2 tumors was 75.0%, whereas those of pT3 and pT4a SCC were 82.2% and 73.7%, respectively. The 5-year OS of previously treated patients was very similar to that of untreated patients (80.8% and 79.0%, respectively). There was a small but not statistically significant difference in OS between older and younger patients (70.8% and 82.0%, respectively).

DFS and locoregional control prevalence at 5 years were greatly affected by local staging. Despite the fact that pT2 and pT3 carcinomas displayed comparable DFS prevalences of 85.7% and 82.9%, the 5-year DFS of pT4a tumors was only 49.0% ($p < .01$). Likewise, the prevalence of 5-year locoregional control was comparable between pT2 and pT3 tumors (85.7% and 82.9%, respectively), but significantly lower for pT4a SCC (51.4%; $p < .05$). On the other hand, the clinical history of previous treatment did not affect the 5-year prevalence of DFS and locoregional control. In fact, the prevalences of DFS and locoregional control were both 65.1% in pretreated patients, whereas they were 70.1% and 71.7%, respectively, in patients undergoing supratracheal partial laryngectomy as primary surgery. Similarly, age also did not correlate with DFS and locoregional control; older patients had a prevalence of 62.4% for DFS and 65.6% for locoregional control, whereas younger ones had a prevalence of 71.8% for both.

Finally, in terms of incidence, the overall analyses of the end points considered are reported in Table 2.

*Patterns of failure*

Locoregional recurrences affected 28 patients within 5 years from surgery. According to the site of pathology, they were subgrouped as 20 local (71.4%) and 8 regional (28.6%) recurrences.

Local recurrences were observed in 14 (17.7%) untreated and 6 (16.7%) pretreated patients. Among them, 2 patients had subglottic extension and inclusion of a cricoarytenoid joint, 1 patient had surface extension as far as the inferior edge of the cricoid ring, 14 patients had extralaryngeal extension (9 anterior, 5 posterior), and 3 patients 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 or the mucosa at the level of the posterior commissure, 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 metastases at the level of Berry's ligament, or 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 16 patients, and laser surgery in 4 cases. One patient was lost at follow-up, 5 patients died of laryngeal cancer from progression of disease (average 14.0 months; range, 7.4–34.1 months), 3 patients died of other disease, whereas at the last follow-up, 3 patients were alive with the disease and 8 patients were alive and disease-free; overall local control after salvage therapy was achieved in 8 of 20 patients (40.0%), and at 3 years the local control rate was 70.0%.

Recurrence in the neck was observed in 8 cases, 6 of whom were previously classified as cN0 and 2 as cN >0 patients. At the time of primary resection, 5 of these 8 patients received bilateral neck dissection, and 5 of 8 recurrences were observed at the VI level. Five recurrences in the neck were treated with surgery and adjuvant radiation therapy and/or chemotherapy, 3 recurrences with chemotherapy, 1 of whom also received radiation therapy; 3 patients died because of regional recurrences (range, 3.8–21.0 months; mean, 13.7 months), 1 patient died of other disease, whereas at the last follow-up, 1 patient was alive with disease and 3 patients were alive and diseasefree.

*Postoperative course and morbidity*

Overall, acute complications during hospitalization occurred in 7 of 115 patients (6.1%) and there were no perioperative deaths. The mean hospitalization time for patients with acute complications was 3866 days, which was significantly longer than that for patients without acute complications (2465 days; $p < .01$). Late sequelae after discharge were observed in 28 of 115 cases (24.4%; Table 3). All were successfully treated with transoral $CO_2$ laser surgery (23 of 28; 82.1%), injective laryngoplasty using Vox impants, which successfully treated dysphagia (2 of 28; 7.1%), or total laryngectomy (1 of 28; 3.6%).

*Laryngeal function preservation*

At 5 years, laryngeal function preservation was maintained in 90 of 115 patients (78.3%). In addition, we evaluated whether laryngeal function preservation could be affected by local staging, presence of previous treatment, or age > o =65 years (see Figure 3). Patients affected by advanced pT or characterized by older age were statistically significantly more prone to lose laryngeal function ($p < .01$) with respect to intermediate pT or younger patients. In fact, functionality was maintained in all pT2 and in 91.2% of pT3 patients, but only in 59.3% of pT4a patients. Moreover, laryngeal function preservation was maintained in 84.2% of patients <65 years and in only 64.6% of patients _65 years. On the other hand, no statistically significant differences were observed when stratifying patients for previous treatment; laryngeal function was preserved in 79.0% and 75.8% of untreated and treated patients, respectively.

After the first postoperative month, normal swallowing (Pearson's scale grade 0) was achieved in 66 patients (57.4%), grade I and II were observed in 25 patients (21.7%) and 20 patients (17.4%), respectively, whereas aspiration pneumonia (Pearson's grade III) was recorded in 4 patients (3.5%). After the second year, a satisfactory degree of laryngeal function (ie, List's scale: eating in public >50; understandability of speech >50; and normalcy of diet >70) was achieved in 92 of 115 patients without local disease (80.0%). Of the 92 patients evaluated for subjective aspiration by the Pearson's scale, 23 (25.0%) had no aspiration (grade 0), 46 (50.0%) had occasional cough without clinical problems (grade I), and 20 (21.7%) had constant cough that worsened during meals (grade II). Three patients (3.7%) had frequent pulmonary complications (grade III). Nearly all patients (112 of 115; 97.4%) had the NG tube or gastrostomy tube removed. The NG tube remained in place for an average of 21.5 days (range, 12–161 days).

Overall, aspiration pneumonia was observed in 11 of 115 cases (9.6%), 4 cases during hospitalization and 7 cases during follow-up. Because of intense dysphagia and aspiration pneumonia episodes, a temporary gastrostomy was required in 8 patients (7.0%); for 5 of them, it was removed within the first postoperative year. Only in 3 cases the gastrostomy was maintained because of repeated episodes of aspiration pneumonia and severe dysphagia for liquids. In 2 cases, total laryngectomy was proposed for persistent aspiration: 1 patient accepted whereas the second refused, preferring to keep the gastrostomy tube and maintain voice. The third patient was subjected to the endoscopic procedure of injective laryngoplasty using a Vox implant, which successfully resolved the dysphagia, allowing gastrostomy tube removal.

The mean time to intermittent occlusion of the tracheostomy was 26.9 days (range, 4–406 days), and the average time to tracheostomy closure was 86.3 days (range, 29–489 days). In our protocol, progressive closure of the tracheostomy is preferred, and occurs spontaneously in the majority of patients after occlusion. For patients, especially in the first weeks after discharge, this leads to a sensation of greater safety concerning minor episodes of food inhalation, which are relatively frequent. When the tracheostomy has almost closed, minor plastic surgery can then be performed.

## DISCUSSION

The current trend for management of laryngeal cancer indicates that pursuing therapeutic options able to preserve laryngeal functionality provides the best quality of life for patients.[2,7,11,16] To realize this goal, different approaches have been pursued, in terms of chemoradiotherapy [7] or surgical treatment.[3,9,10] The former is able to spare laryngeal function and patient outcome seems satisfactory, nevertheless, locoregional control is compromised during long-term follow-up.[7,24] On the other hand, demolitive surgery provides better control of disease, although incurring a higher percentage of laryngeal function impairment and late sequelae that hamper the patients' quality of life.[5] With the diffusion of supracricoid partial laryngectomies, the advent of supratracheal partial laryngectomies, and the consolidated role of conventional nonsurgical organ sparing protocols and endoscopic procedures, the role of total laryngectomy in the treatment of endolaryngeal neoplasms has decreased considerably. In this study, we have analyzed the outcomes of 115 patients affected by laryngeal SCC undergoing supratracheal partial laryngectomy, a novel laryngeal sparing surgery previously described by our group in 2006.[13]

Glottic tumors with subglottic extension (cT3 with vocal cord and arytenoid fixation) may be a problematic category to manage with supracricoid laryngectomy or chemoradiation, inasmuch as they often result in early pT4a for extralaryngeal extension. Indeed, the selected cohort of patients considered in our study was composed of a higher percentage of pT4a cases, despite the fact that the amount of supraglottic cancers was lower than in previously described trials.

The 5-year OS in the present study was 79%, better than the circa 60% observed for both concomitant chemoradiotherapy or induction chemotherapy and RT.[5,7,25] These data were also confirmed for more advanced pT4a tumors that displayed a 5-year OS of 74%. The DFS observed in our study overlapped with that already demonstrated by The Department of Veterans Affairs Laryngeal Cancer Study Group[5] using the demolitive surgical approach (about 70%). These data show that carefully selected patients can achieve good results even with an “extreme partial” surgical approach. However, the DFS for pT4a cancer (49%) was significantly lower than those for the other classifications considered (83% pT3; 86% pT2), but higher than those obtained by management with RT and/or chemotherapy (ranging from 26% to 38%, respectively).[7,24] As a consequence, the possibility to develop recurrences was reduced. In fact, the 2-year locoregional control was maintained in 79% of patients but decreased to 69% at 5 years. Analyzing these data, we can observe that such a trend was due to pT4a tumors, whose 5-year locoregional control was only 51%. Nevertheless, it is comparable with the locoregional control detected by Forastiere et al[7,24] in concomitant cisplatin/RT management. From this point of view, the total incidence of recurrences after supratracheal partial laryngectomy overlapped with that of total laryngectomy demonstrated by the Department of Veterans Affairs Laryngeal Cancer Study Group.[5]

In the present series, the proportion of patients subjected to total laryngectomy for either functional or oncologic purposes was significantly low (14.8%) and there was no perioperative mortality.

Not surprisingly, the total amount of neck metastases (<10%) was lower than in previously reported statistics for demolitive surgery (17%) and demolitive surgery with concomitant chemoradiotherapy (12% to 22%). These interventions are normally considered in cN0 and cN1 patients, which represent the majority of glottic tumors, even in intermediate/advanced T classification. Finally, the 5-year laryngeal function preservation obtained by supratracheal partial laryngectomy was in line with that achievable with concomitant cisplatin/RT. Maintenance of laryngeal function was critical in patients affected by pT4a cancer (59% at 5 years) and in those older than 65 years (64% at 5 years). Although the function of the remaining larynx is problematic in some cases, both objective and subjective outcomes have demonstrated the quite satisfactory validity of supratracheal partial laryngectomies in sparing laryngeal function, albeit at the obvious expense of a simplified laryngeal framework.

This shows the impressive ability of this organ to recover the essentials of its function after partial surgical mutilation, provided that tissue has been sacrificed and the organ reconstructed according to functional criteria. Based on our experiences, supratracheal partial laryngectomies can be tailored to each patient, depending on the extent of the lesion. This is possible because the larynx tolerates tumor-free margins of only 4 to 5 mm. Therefore, the radicality of surgery should always be routinely checked intraoperatively by frozen sections.

Nevertheless, persistent slight dysphagia and aspiration pneumonia still represent major complications in patients undergoing supratracheal partial laryngectomies, whereas voice was significantly deteriorated, and generally quite hoarse and breathy.[26]

In elderly patients (13 patients aged >70 years), cricoarytenoid joint resection had a clear impact, with worsening swallowing recovery: 5 of 11 cases of aspiration pneumonia occurred in elderly patients, in whom gastrostomy tube was maintained in 1 patient owing to repeated episodes of aspiration pneumonia, and 1 patient was subjected to total laryngectomy. High-grade dysphagia and aspiration pneumonia occurred rarely in patients undergoing supratracheal partial laryngectomies if compared with others type of surgical technique, affecting the physical and emotional condition of these patients.

In conclusion, our results demonstrate that, in the case of glottic tumors with subglottic extension, the choice of supratracheal partial laryngectomy versus chemoradiation protocols can be considered to be viable not only in prognostic terms, but also in terms of functional results, such as a reduction in the number of total laryngectomies. This option must be aimed at carefully selected patients with a strong desire to avoid total laryngectomy and suffering from laryngeal SCC in well-defined intermediate/advanced stages, often early pT4a for extralaryngeal extension. The gold standard indication is glottic cT3 with vocal cord and arytenoid fixation and subglottic extension; the option of a supracricoid partial laryngectomy is very much at risk of leaving positive margins as the section line passes through a cricoarytenoid joint.

Nevertheless, even in these cases, it is possible to obtain good oncologic and functional results, even with an “extreme partial” surgical approach. The selection of patients must be made very carefully because, at the end of the workup, the surgeon should be able to ensure safe margins with sufficient certainty, thus avoiding an upfront total laryngectomy. When the tumor clearly extends beyond the limits of the larynx, both the severity of the intervention and the necessity for adjuvant radiotherapy demand that extreme caution be taken when considering the indications.

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**Table 1** **Characteristics of the 115 patients undergoing supratracheal partial laryngectomy according to age, sex, Karnofsky performance status and pathological grade**

| | No. of patients (%) | |
|---|---|---|
| Age, y | | |
| Mean | 58.3 ± 10.8 | |
| Range | 16–78 | |
| Sex | | |
| Male | 93/115 (80.9) | |
| Female | 22/115 (19.1) | |
| Karnofsky Performance Status | | |
| 100 | 70/115 (60.9) | |
| 90 | 30/115 (26.1) | |
| 80 | 15/115 (13.0) | |
| Pathological grade | Supraglottic | Glottic |
| pT2 | 0/115 (0.0) | 14/115 (12.2) |
| pT3 | 1/115 (0.9) | 49/115 (42.6) |
| pT4a | 11/115 (9.6) | 40/115 (34.8) |
| pN0 | 3/75 (4.0) | 65/75 (86.7) |
| pN1 | | 4/75 (5.3) |
| pN2 | | 3/75 (4.0) |
| Level VI pN+ | | 5/7 (71.4) |

**Table 2 Incidence**

| | No. of patients | OS (%) | DFS (%) | Locoregional control (%) |
|---|---|---|---|---|
| pT status | | | | |
| pT2 | 14/115 | 13/14 (92.9) | 12/14 (85.7) | 12/14 (85.7) |
| pT3 | 50/115 | 43/50 (86.0) | 43/50 (86.0) | 43/50 (86.0) |
| pT4a | 51/115 | 41/51 (80.4) | 31/51 (60.8)* | 32/51 (62.7)† |
| Previous treatment | | | | |
| Untreated | 79/115 | 67/79 (84.8) | 59/79 (74.7) | 60/79 (75.9) |
| Treated | 36/115 | 30/36 (83.3) | 27/36 (75.0) | 27/36 (75.0) |
| Age, y | | | | |
| $<65$ | 81/115 | 70/81 (86.4) | 63/81 (77.8) | 63/81 (77.8) |
| $\geq 65$ | 34/115 | 27/34 (79.4) | 23/34 (67.6) | 24/34 (70.6) |

Abbreviations: OS, overall survival; DFS, disease-free survival.
Chi-square test.
* $p < .01$.
† $p < .05$.

**Table 3** **Acute postoperative complications and late sequelae**

| | No. of patients (%) |
|---|---|
| Acute complications | |
| Cervical bleeding | 2/115 (1.7) |
| Wound infection | 1/115 (0.9) |
| Aspiration pneumonia | 4/115 (3.5) |
| Late sequelae | |
| Laryngeal fibrosis with stenosis | 6/115 (5.2) |
| Laryngeal soft tissue stenosis | 14/115 (12.2) |
| Dyspnea | 1/115 (0.9) |
| Aspiration pneumonia | 7/115 (6.1) |

**Figure 1** **Endpoint analysis (overall survival, disease-free survival and locoregional con of the patient cohort using Kaplan-Meier curves**

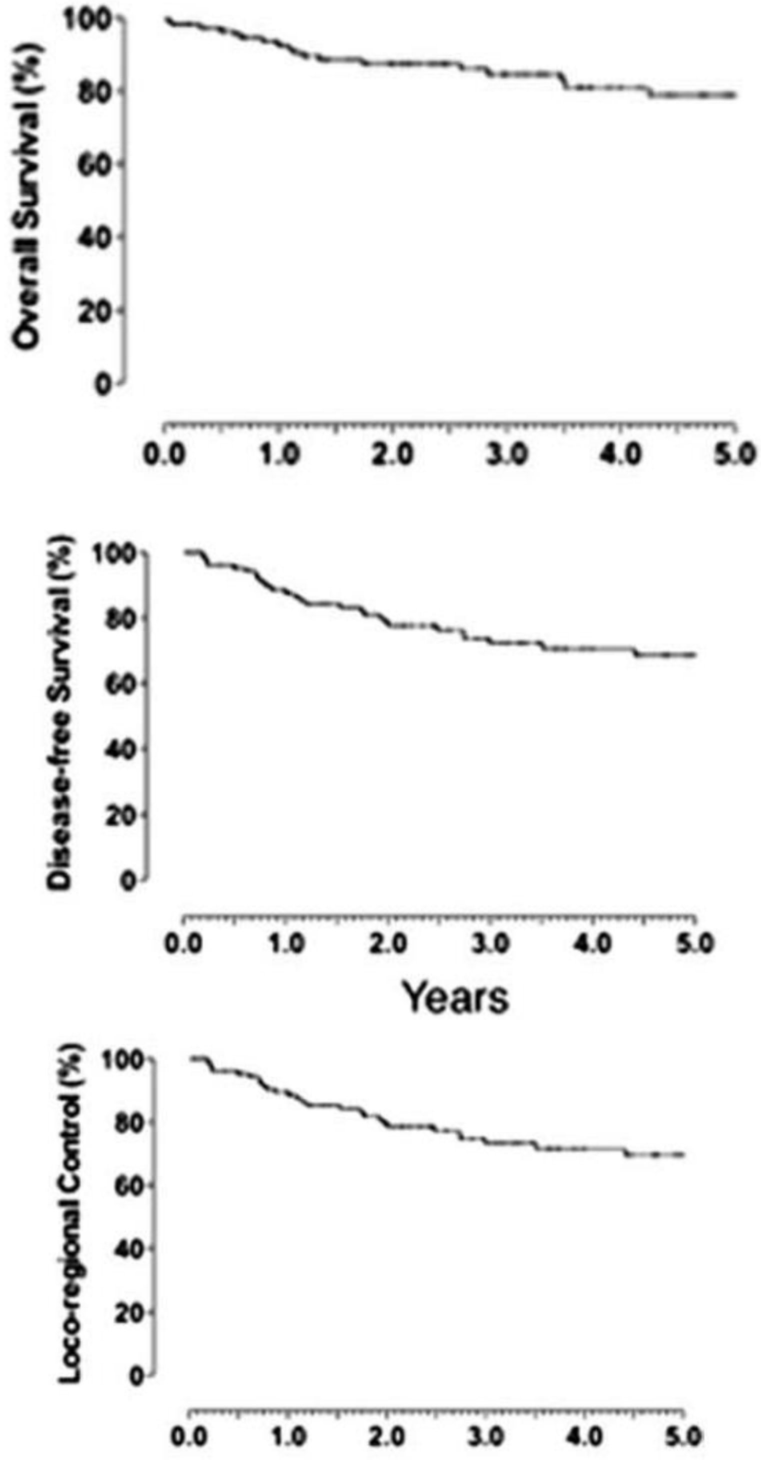


**Figure 2** **Patient chort stratification for lesion classification (left column), previous treatment (middle column) and age (right column) using Kapln-Meier curves. The end points considered were overall survival (top row), disease-free survival (middle row) and locoregional control (bottom row). Statistically significant differences were seen for patients affected by pT4a tumors in terms of both disease-free survival and loco-regional control**
***p < .05; ** p < .01**

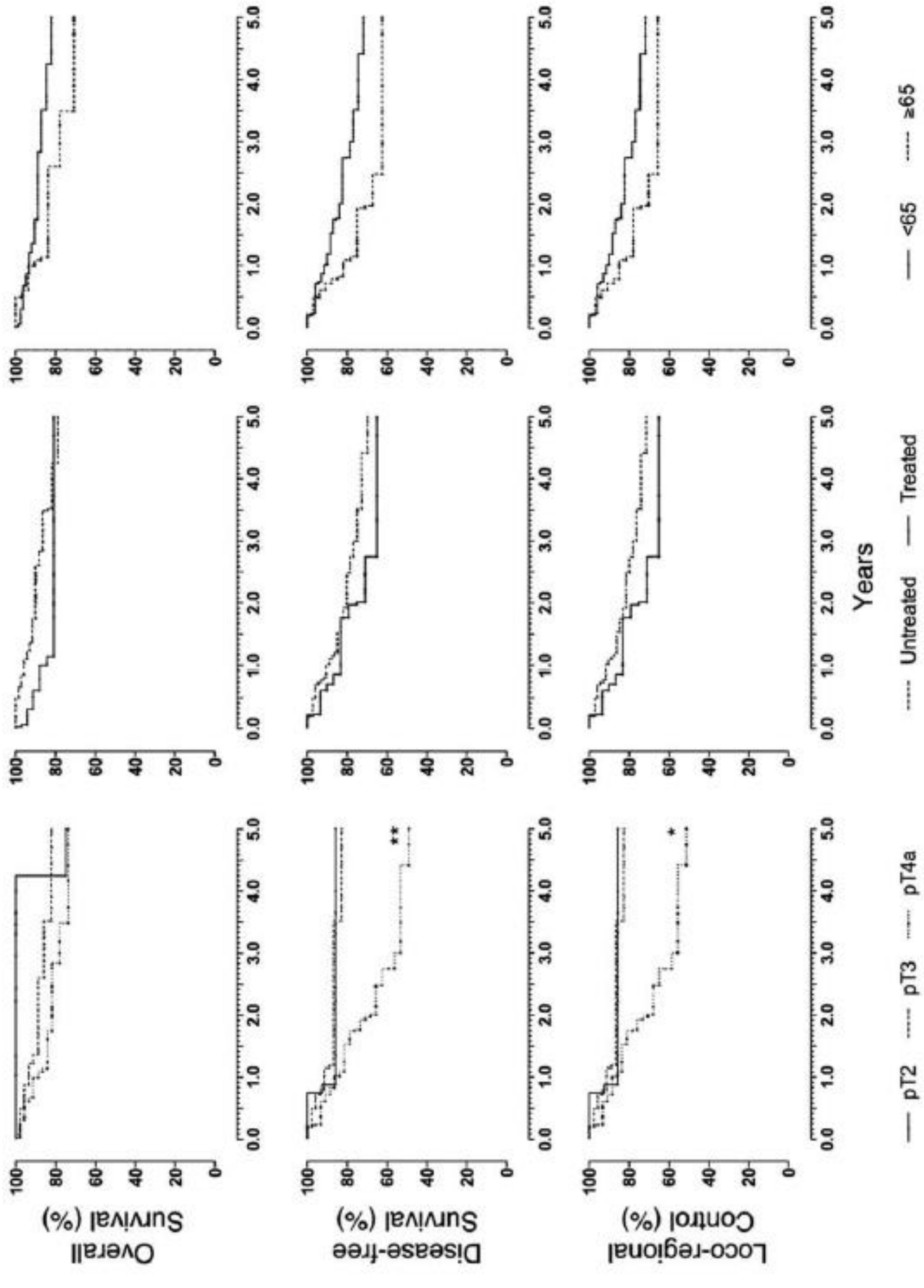
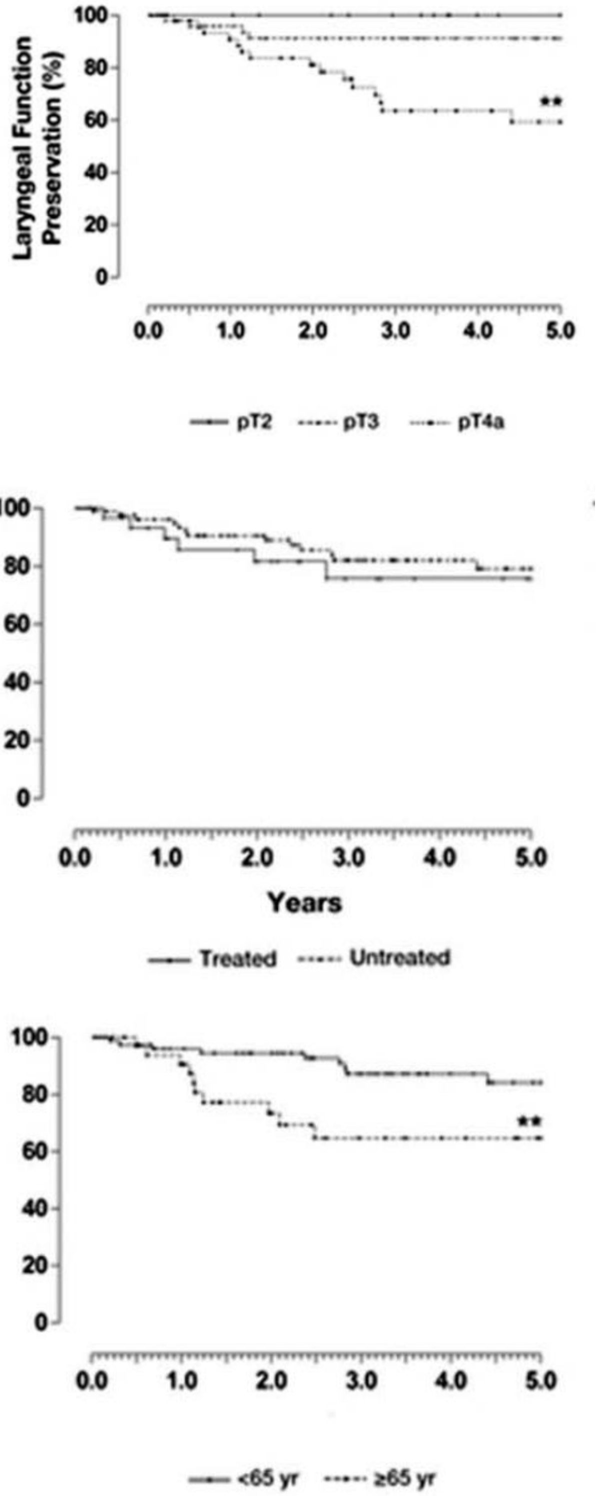


**Figure 3** **Evaluation of laryngeal function preservation in the patient cohort stratified for lesion classification, previous treatment and age using Kapla-Meier curves. Statistically significant impairments were seen in patients affected by pT4a tumors or in those older than 65 years.**
**** p< .01**



## Paper 7

### *Supratracheal laryngectomy: current indications and contraindications*

*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.

### 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, especially when adopting conservative therapeutic protocols such as chemoradiotherapy, transoral laser surgery or open partial laryngectomy [1-3].

In 1972, Italo Serafini[4] 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 resection[7], 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 described [10].

Inclusion criteria were histological diagnosis of intermediate/advanced stage glottic or transglottic laryngeal SCC 8, laryngeal chondrosarcoma 11 or other rare tumours, and a Karnofsky index 12 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 indication 13, 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 elsewhere [9], the preoperative and intraoperative records, and pathological reports were reviewed to allow proper reclassification of these cases according to the 2002 TNM classification system [14].

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 Classification 7, 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 classification [15], 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 scale 16 (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 radiotherapy 17.

*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 locoregional 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 system 14.
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 only 52.7% ($p < 0.05$); the same pattern was also evident or 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 (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 ($p < 0.05$ 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 laser [21], 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 II [27] 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 amenable 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 resection [21], or by OPHL Type II [23], 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 postoperative 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 breathy [9]. 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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**Table 1** **Incidence of disease-specific survival (DSS), disease-free survival (DFS) and locoregional 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%) |

*$\chi^2$-test; $^{*}p < 0.05$.*

**Table 2** **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%) |

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

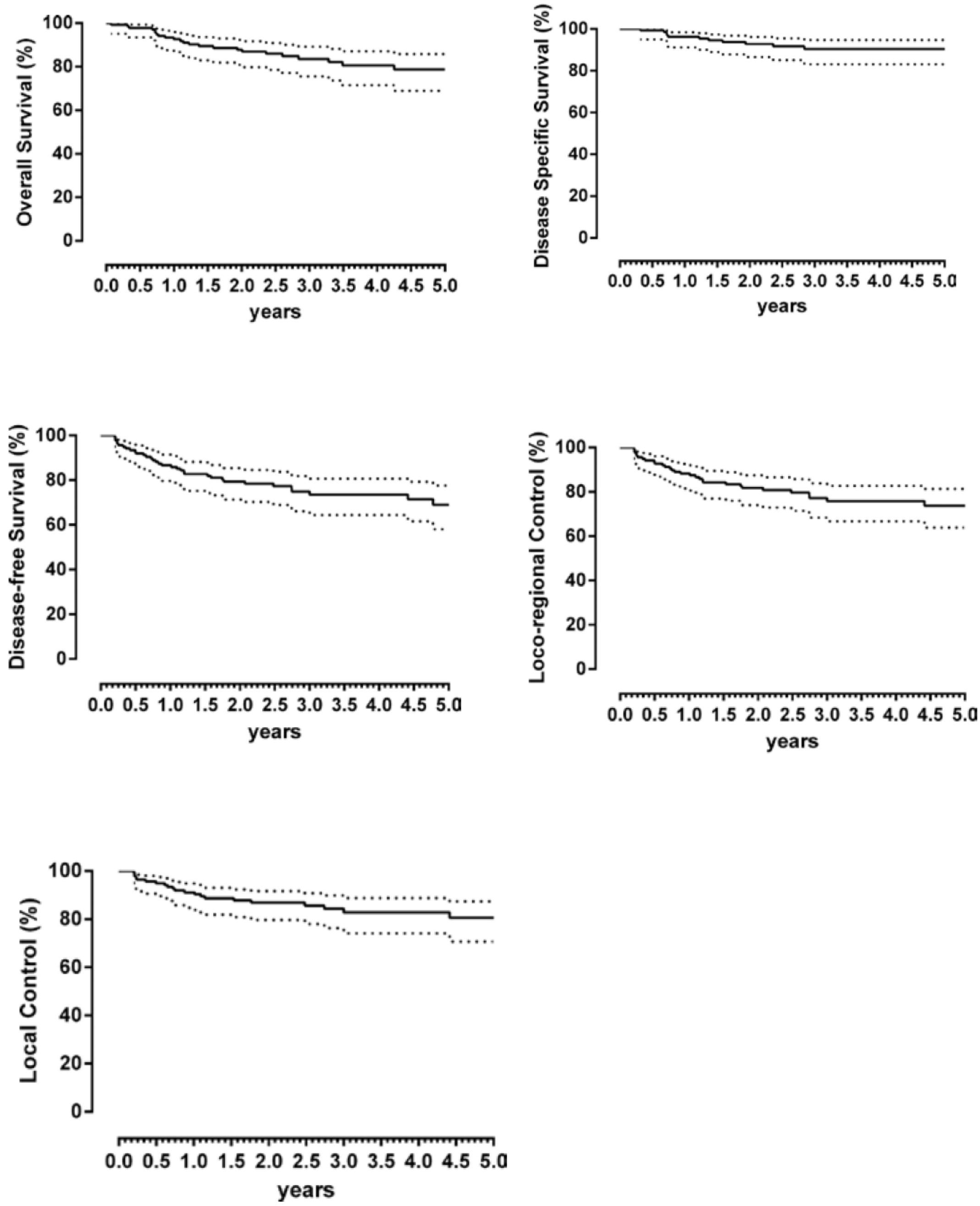


**Figure 2** **Disease-specific survival, disease-free survival and loco-regional control in terms of local staging, previous treatment and age over a 5-year period in 142 patients with laryngeal cancer staged pT2-pT4a who underwent supratracheal laryngectomy**

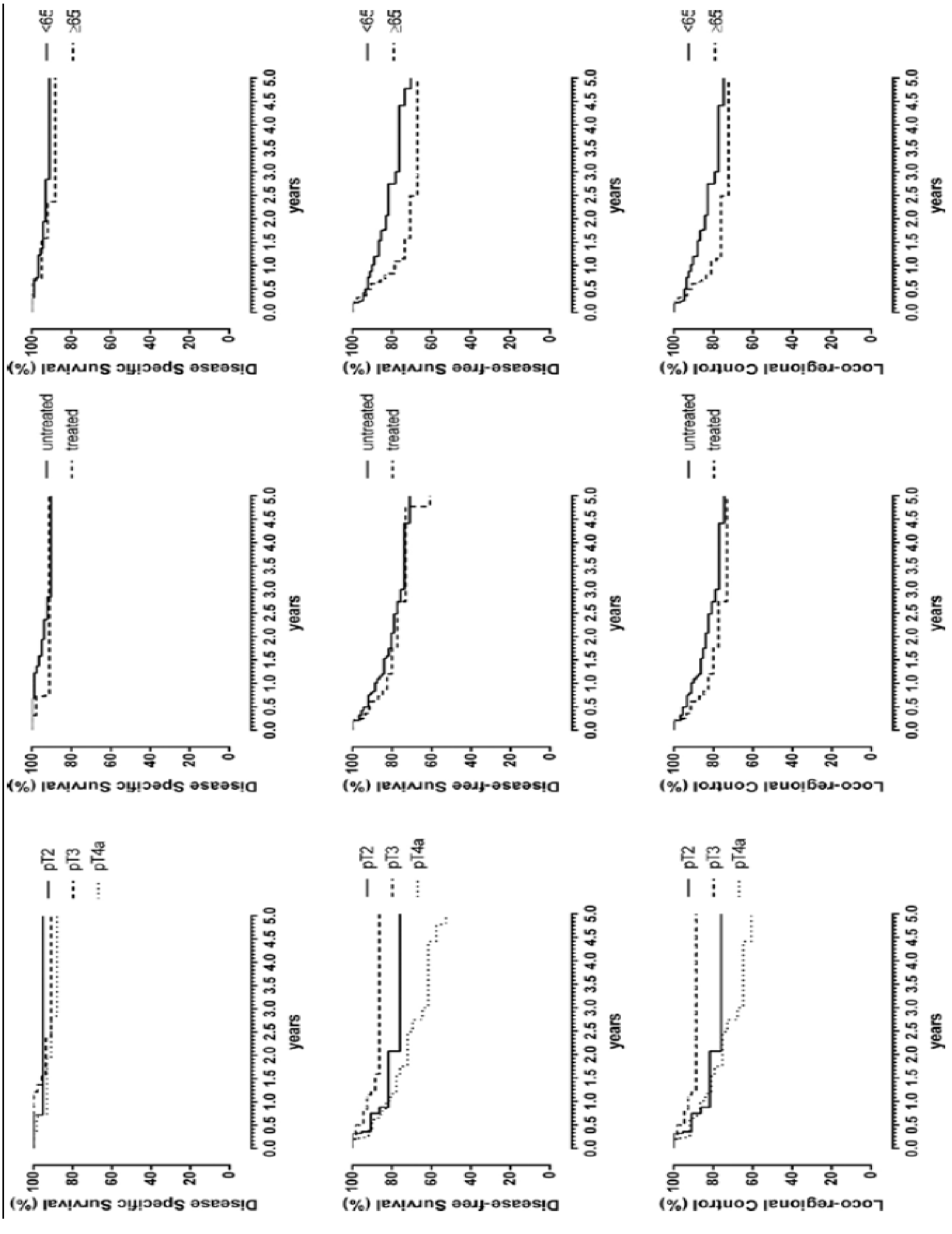
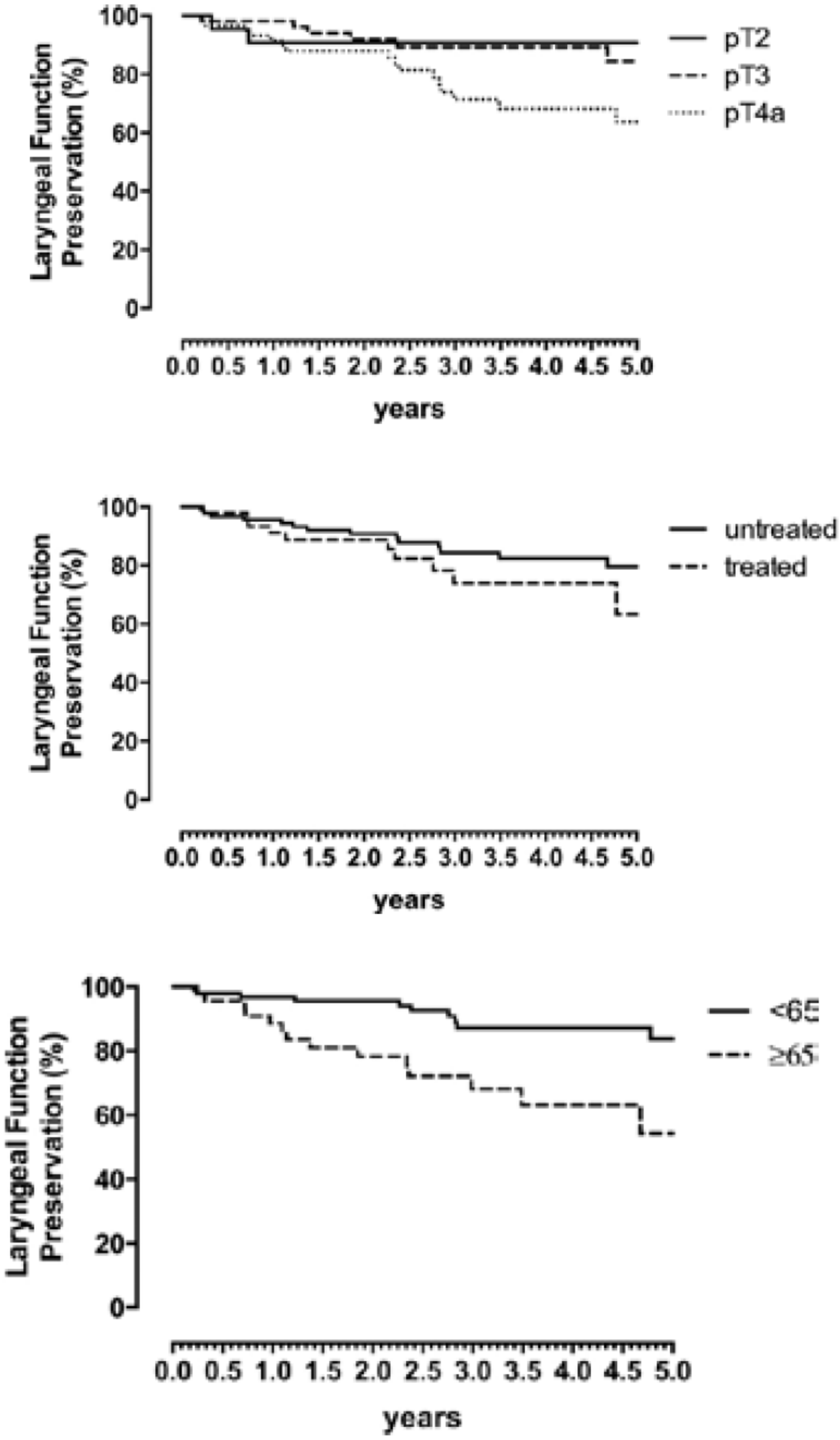


**Figure 3** **Laryngeal function preservation in terms of local staging, previous treatment and age over a 5-year periodi in 142 patients with laryngeal cancer staged pT2-pT4a who underwent supratracheal laryngectomy**



# 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).

• *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. S1.

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.

C. • *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 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 plate 11 (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.

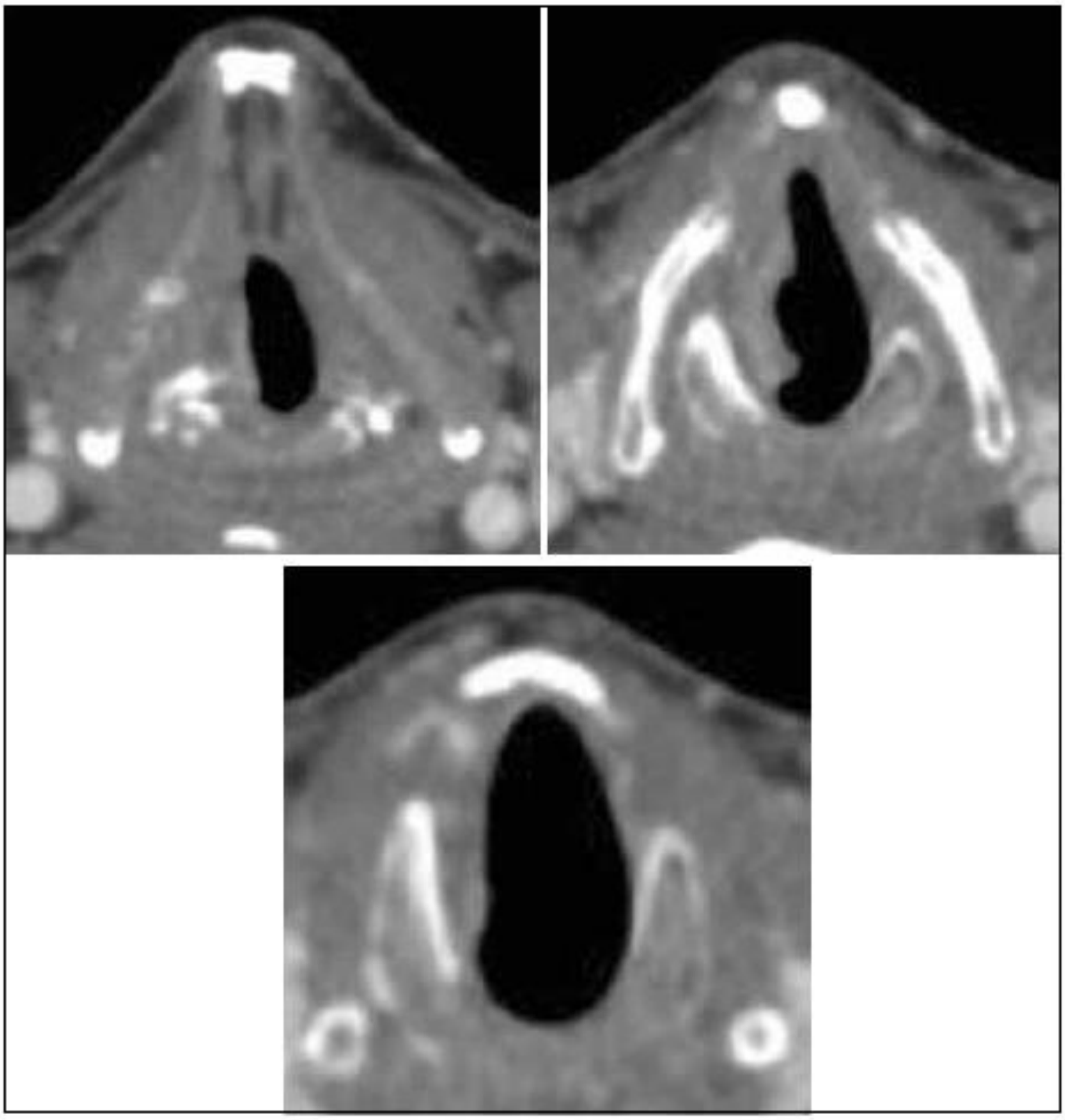


**Fig. S1**. a-b) CT scan in axial view of right recurrent glottic T2 with impaired mobility of the vocal cord, extending superficially to the subglottic site along the elastic cone toward the cricoid cartilage. c) The tumour reaches the cricoid plate and ring.

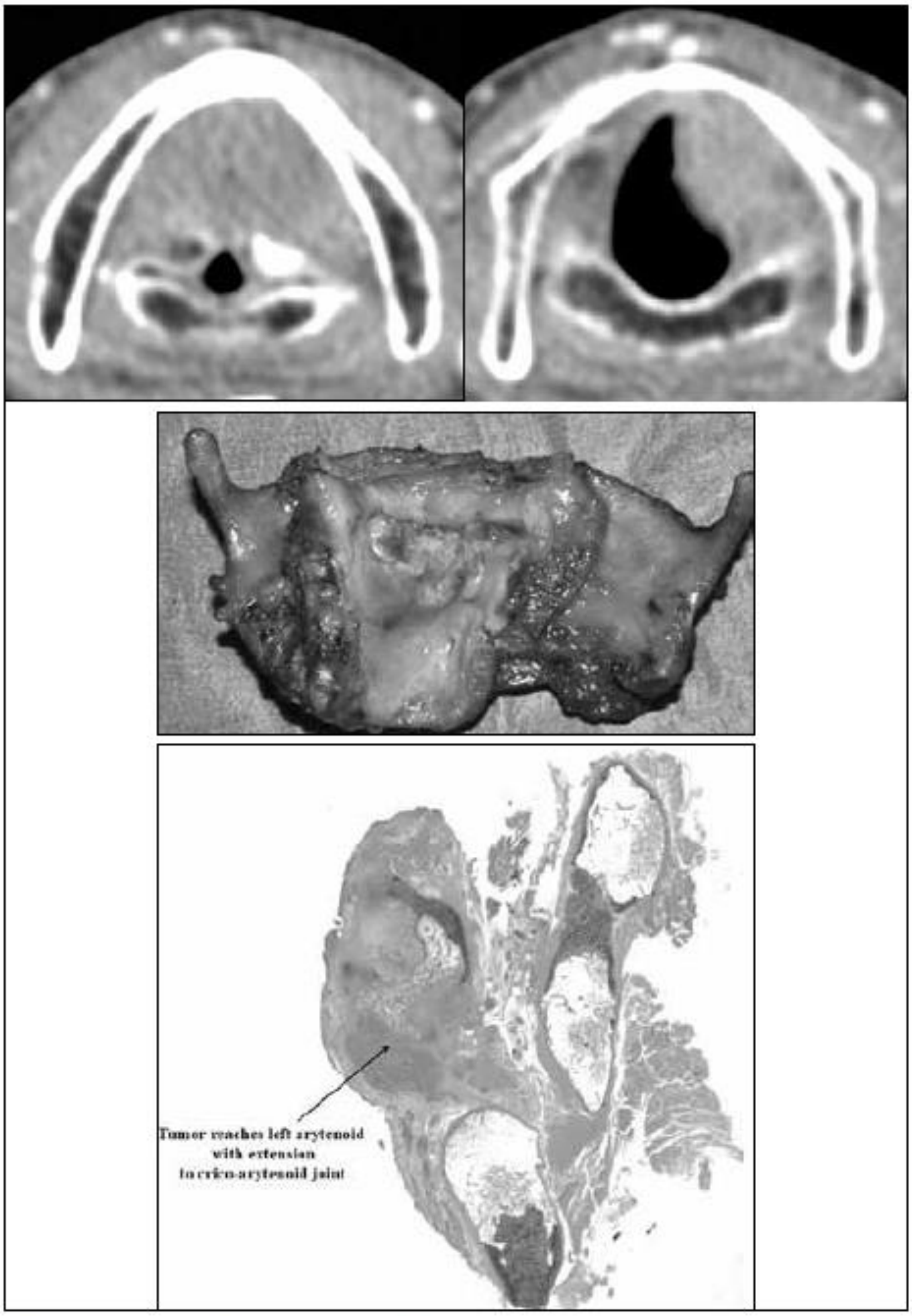



**Fig. S2**. a-b) CT scan in axial view of left glottic T3 with fixed vocal cord and hypomobile arytenoid, extending downward and laterally within inferior paraglottic space. Note the intense sclerosis of the arytenoid without evidence of direct invasion of the cricoid. c) The specimen of OPHL type III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

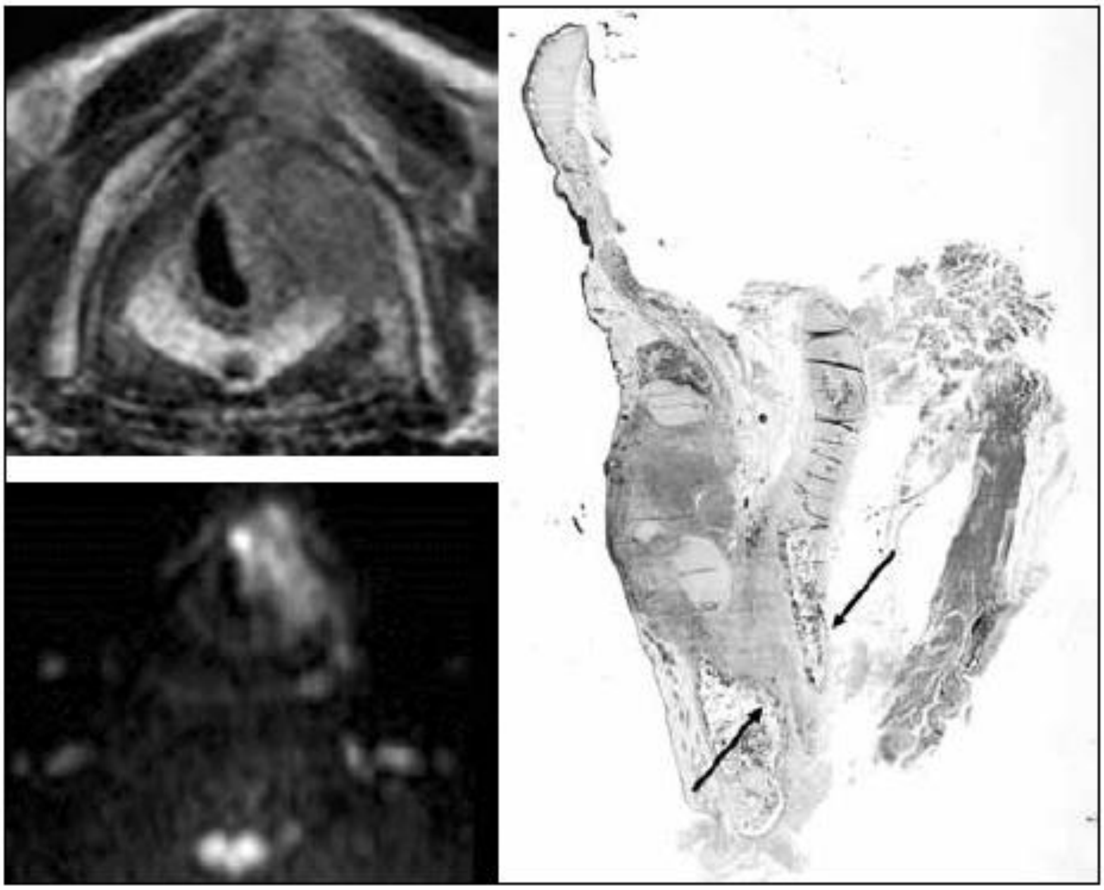


**Fig. S3**. a-b) MRI in axial view of left glottic T3 with fixed vocal cord and arytenoid, extending downward and laterally reaching the crico-thyroid space. Note the intense sclerosis of the cricoid with suspect involvement of thyroid cartilage. c) Macrosection on the specimen of OPHL type III + left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

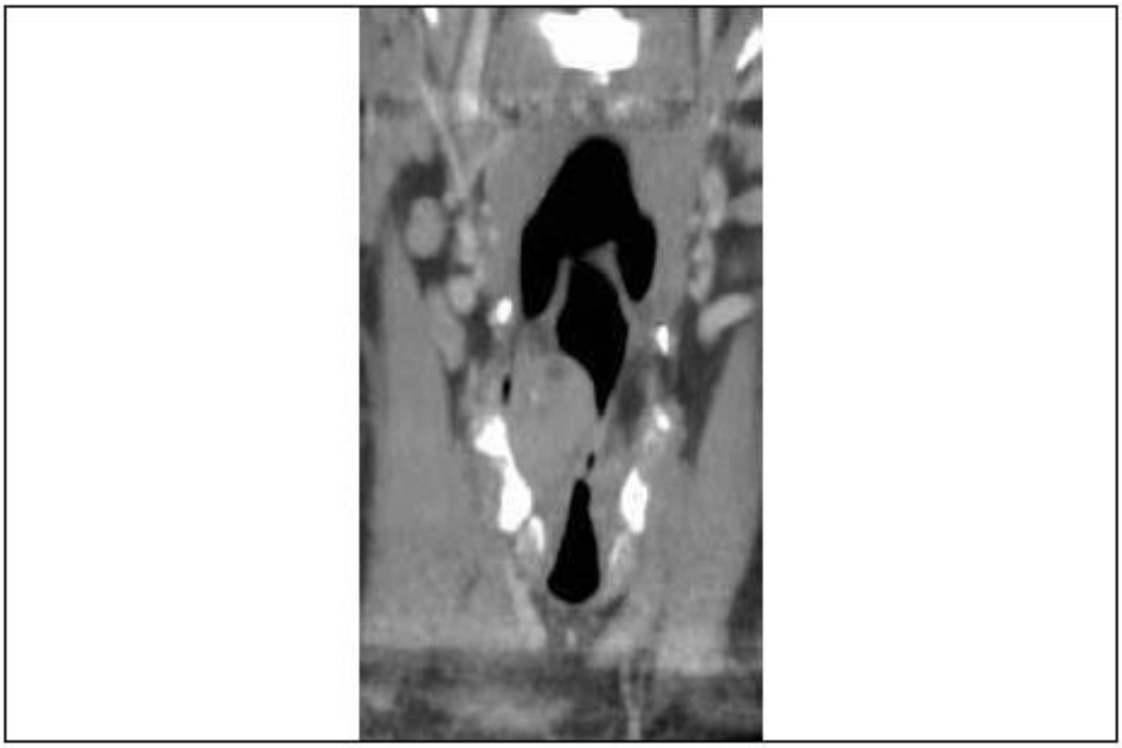


**Fig. S4**. CT scan in coronal view of right transglottic T3 with fixed vocal cord and arytenoid. The tumour clearly invades the superior and inferior paraglottic space with transglottic extension toward the cricoid cartilage.

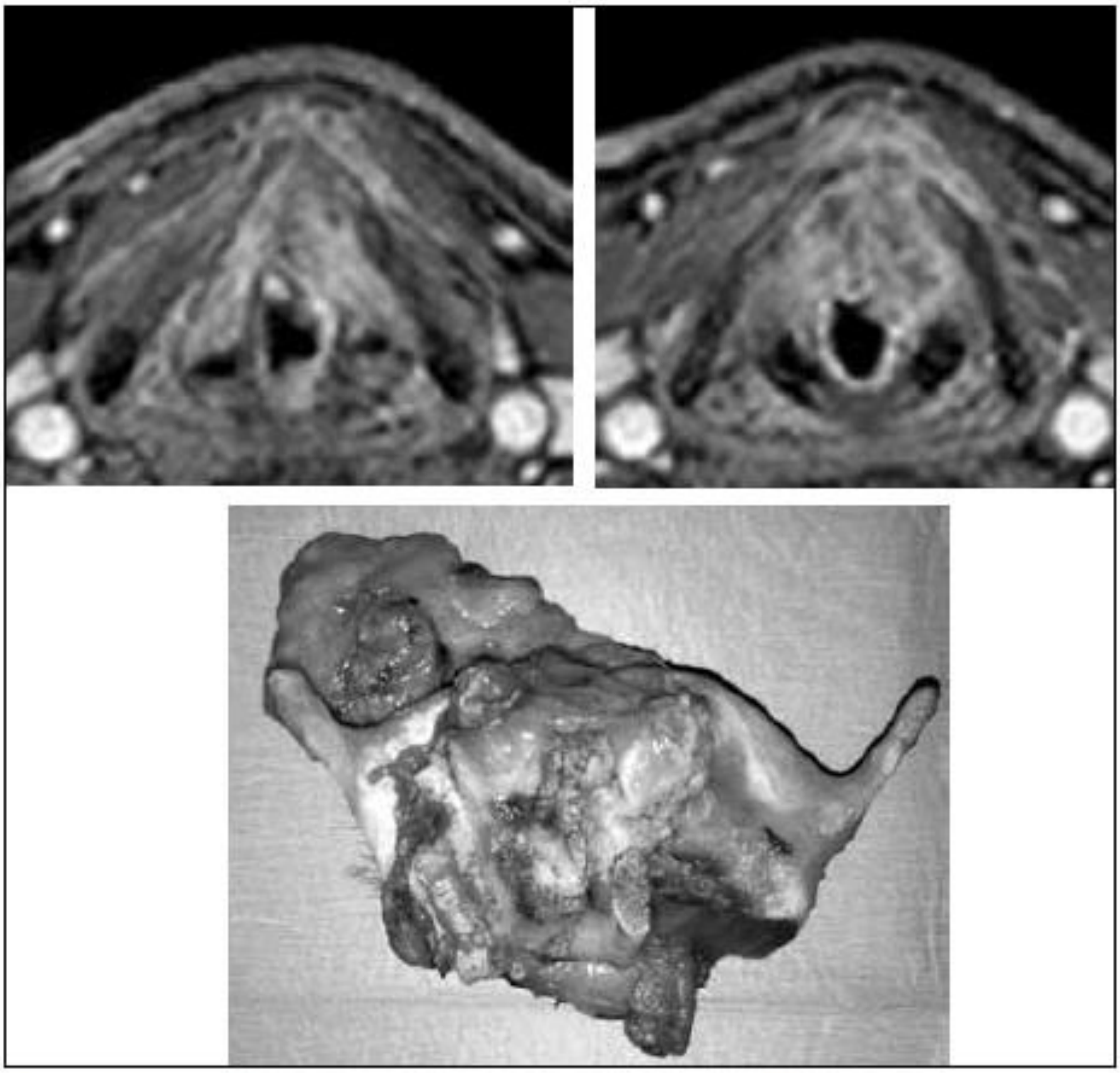


**Fig. S5**. a) MRI in axial view of left glottic T4a with fixed vocal cord and arytenoid, extending downward and laterally within inferior paraglottic space. Note the involvement of the arytenoid and the crico-arytenoid joint without evidence of direct invasion of the cricoid. b) Anterior extralaryngeal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

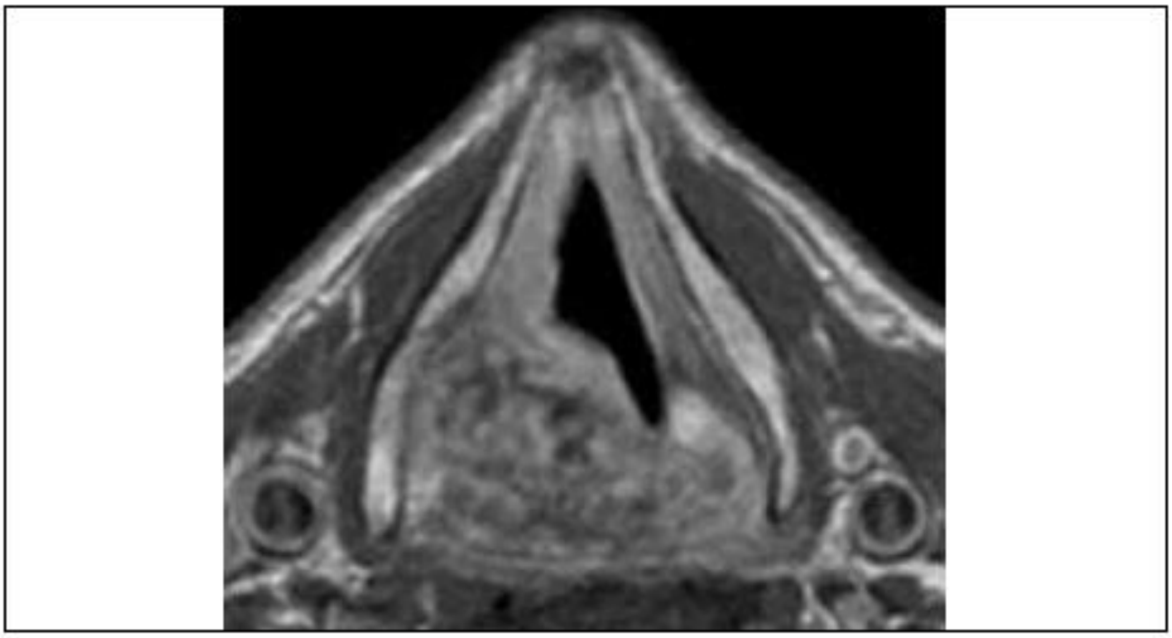


**Fig. S6**. MRI in axial view of right intermediated grade larynx chondrosarcomas without involvement of the whole cricoid plate.

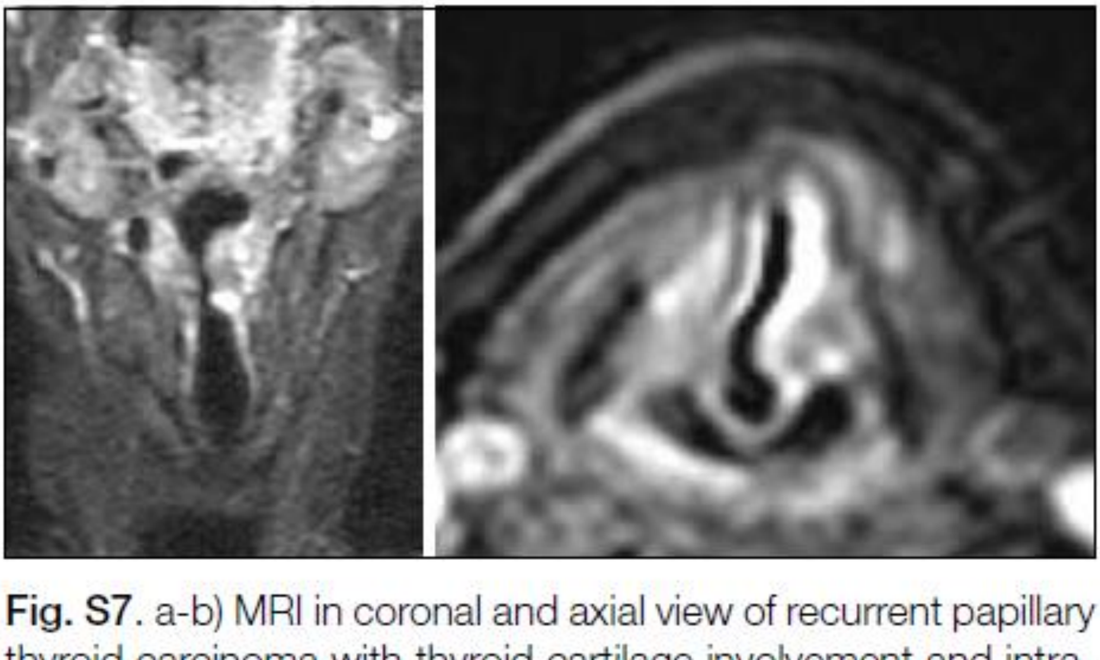


**Fig. S7**. a-b) MRI in coronal and axial view of recurrent papillary thyroid carcinoma with thyroid cartilage involvement and intralaryngeal spread.

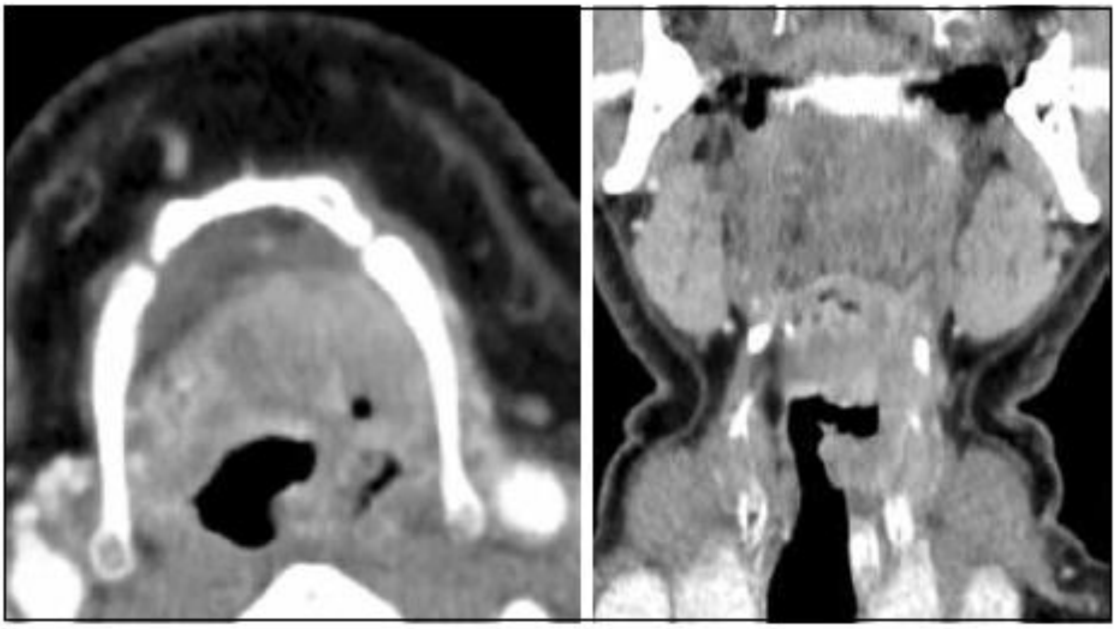


**Fig. S8**. a-b) CT scan of supraglottic T4a tumors reaching the base of the tongue and involving the hyoid bone. a) Axial view. b) Coronal view.

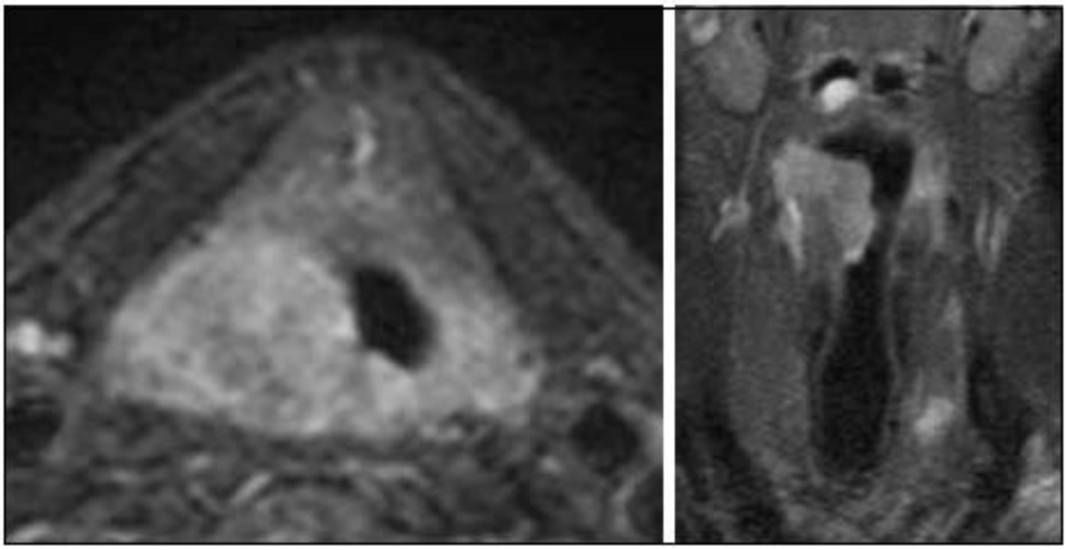


**Fig. S9**. a-b) MRI in axial and coronal view of right glottic T3 with fixed vocal cord and arytenoid, extending posteriorly to the pyriform sinus submucosa and reaching the posterior commissure and posterior crico-arytenoid muscles.

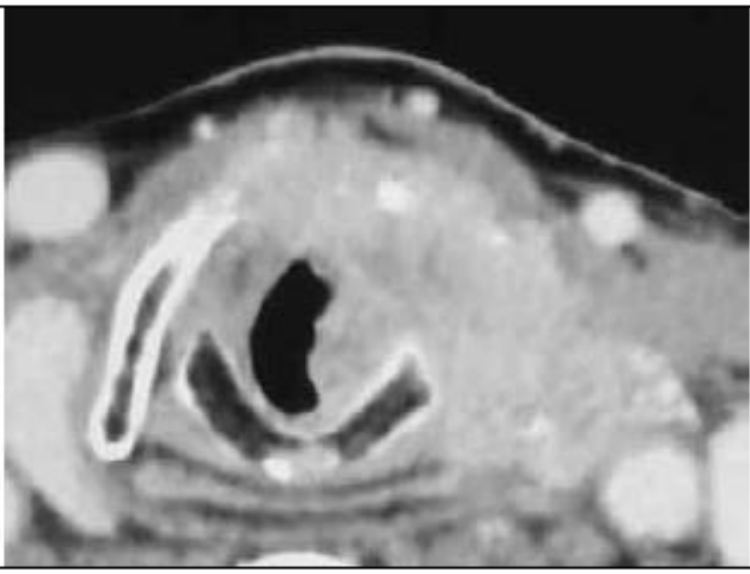


**Fig. S10**. CT scan of large glottic-subglottic T4a with massive cricoid invasion and extralaryngeal spread.

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

# SECOND CHAPTER

# Paper 1

## *Swallowing, voice, and quality of life after supratracheal laryngectomy: Preliminary long-term results*

ABSTRACT: Background. The purpose of this study was to report preliminary long-term outcomes after supratracheal laryngectomy (STL). Methods. Twenty-two male patients who underwent STL were involved in this study. Swallowing skills, neoglottis motility, and vibrations were videoendoscopically assessed. Aerodynamic measures, spectrogram analysis, aspiration pneumonia, body weight variations, and voice perceptual assessment were performed. Generic, voice-related, and swallowing-related quality of life (QOL) were assessed. Results. Aspiration was found in 10, 2, and 5 patients, respectively, for liquids, semisolids, and solids. Neoglottis motility was generally preserved, whereas vibration was impaired. Aerodynamic measures showed a poor performance. Perceptual assessment revealed highly dysphonic voices. In only 8 patients, a harmonic structure was visible in the spectrograms. Aspiration pneumonia occurred in 2 patients. Preoperative weight was maintained in 16 patients. Generic, voice-related, and swallowing-related QOL revealed satisfied patients. Conclusion. After STL, swallowing was sufficiently restored and QOL was satisfactory, whereas the voice was severely impaired even if oral communication was well preserved.

INTRODUCTION

Supratracheal laryngectomies (STLs) are a recently introduced type of horizontal partial laryngectomy indicated in the treatment for selected laryngeal tumors of locally intermediate/advanced stage with subglottic extension. STLs maintain at least 1 functioning cricoarytenoid unit (ie, half of the posterior cricoid plate), with the corresponding arytenoid and the intact inferior laryngeal nerve of the same side; therefore, STLs allow the preservation of the main laryngeal functions (respiration, phonation, and swallowing) and a permanent tracheostoma is not required.

The surgical technique is analog to the partial supracricoid laryngectomies (SCLs) extending toward the cricoid, which allows the treatment of: (1) glottic tumors with subglottic extension, reaching the cricoid ring (T2–T3); (2) laryngeal tumors with involvement of 1 cricoarytenoid joint, characterized by arytenoid fixation (T3); and (3) locally advanced laryngeal tumors with anterior extension through the thyroid cartilage (T4a).

Two variations of STL have been described: (1) tracheohyoidopexy (THP) consisting in the subtotal removal of the larynx maintaining both (STL-THP) or 1 (STLTHP+A) cricoarytenoid unit and subsequent tracheohyoidopexy; (2) tracheohyoidoepiglottopexy (THEP) in which resection foresees preservation of the suprahyoid epiglottis maintaining both (STL-THEP) or 1 (STL-THEP+A) cricoarytenoid unit and further suspension of the tracheal stump at the epiglottis and hyoid bone.[1] Local contraindications are T3 tumors reaching both arytenoid and posterior commissure and T4 tumors reaching the base of the tongue and/or hypopharynx and/or trachea. The presence of lymph node metastases does not represent an absolute contraindication.

Overall survival has been shown to be good for patients treated with STL and, at 5 years, SCL and STL were demonstrated to provide similar rates of local control.[2] Moreover, it was found that STL can be used as salvage surgery, even after organ-sparing protocols.[2] A previous study on immediate postoperative functional results showed that 1 month after surgery all the patients were able to tolerate a soft diet, allowing nasogastric tube or percutaneous gastrostomy removal before the 40th postoperative day, whereas 6 months after surgery, phonatory results were comparable to those obtained with SCL.[1] The sphincteric action of the neoglottis is achieved through the approximation of the arytenoid cartilage/cartilages and the base tongue, together with the epiglottis in STL-THEP, providing a mucosal source of vibration for phonation during the airflow passage. As in SCLs, an anatomic continuity is preserved between the oropharynx and the lower airways. Because of the large laryngeal resection resulting in a “simplified” laryngeal framework, it is reasonable to suggest that patients undergoing STL could experience dysphonia and some degree of dysphagia with aspiration. In the literature, different studies reported long-term functional outcomes after SCL, showing satisfactory functional results, but with inevitable significant alterations of both swallowing and voice, requiring several months to restore these functions.[3–13] In a previous study, at the end of the second year after surgery, the rate of laryngeal function preservation was shown to be slightly worse for STL compared to SCL.[2] However, no previous study carried out a detailed assessment of functional outcomes in patients who underwent STLs. The purpose of this study was to report preliminary long-term results of swallowing, voice, and quality of life (QOL) after STL-THP and STL-THEP. Knowledge on long-term functional and QOL outcomes will give insight on the impact of STLs on daily activities and social participation of the patients who underwent this type of surgery. Furthermore, these data could guide clinicians in the preoperative and postoperative counseling on longterm outcomes of STLs.

## MATERIALS AND METHODS

This cross-sectional outcome study was carried out according to the Declaration of Helsinki and was previously approved by the institutional review board. All patients enrolled in the study gave their written informed consent; all data were collected prospectively.

### *Patients*

A total of 22 male patients with a laryngeal tumor who underwent STL at least 6 months before the study were recruited (Table 1). Selection criteria were: no evidence of disease at the last follow-up, preservation of respiration and speech, non-enteral feeding (percutaneous gastrostomy or nasogastric tube), absence of the tracheostoma, no salvage total laryngectomy performed, and over 6 months after surgery. The mean age was 60.5612.6 years (range, 23–84 years). Patients underwent the following operations: 3 STL-THEP; 16 STL-THEP1A; and 3 STL-THP1A. The mean distance from surgery was 42.8627.8 months (range, 7–94 months).

### *Swallowing assessment*

Swallowing was assessed through the fiber-optic endoscopic evaluation of swallowing (FEES).[14] The study was conducted using an Olympus Evis Exera II 18 endoscopy system and an Olympus ENF VQ transnasal flexible endoscope (Olympus Corporation, Tokyo, Japan); each FEES was video-recorded. Swallowing of liquids, semisolids, and solids was assessed using room temperature blue-dyed water, pudding, and crackers. A 5-cc bolus was given to each participant 3 times for each consistency. Premature spillage and piecemeal deglutition were scored as present or absent. Spillage was defined as bolus falling over the base of the tongue or lower before whiteout; piecemeal deglutition was defined as division of the bolus into 2 or more swallows successively rather than swallowing the entire bolus in

1 swallow. Laryngeal penetration and aspiration and the ability to cough or clear aspirated substances were assessed through the 8-point Penetration-Aspiration Scale (PAS); a score of 1 is associated with no materials entering the airway, whereas a score of 8 means aspiration without any effort to reject materials.[15,16] Retention of the bolus was evaluated using the Pooling Score.[17] The Pooling Score, ranging between 4 and 11, is assigned on the basis of the site (from 1–4), the amount (from 1–3), and the management of the pooling (from 2–4); the higher the score, the lower the pooling's site, the greater its amount, and the lower the ability to clean it.

The Dysphagia Outcome and Severity Scale (DOSS), a validated and reliable 7-point scale, was used to rate functional severity of dysphagia.18 The DOSS level, ranging between 7 ("normal in all situations") and 1 ("severe dysphagia, non–per-oral nutrition, unable to tolerate any per oral nutrition safely"), is defined on the basis of the objective assessment, of the necessity of diet modifications, of the independence level, and of the type of nutrition required.

The onset of aspiration pneumonia after surgery was recorded. The difference between presurgery and postsurgery weight was calculated.

*Voice and speech assessment*

A videolaryngoscopic examination of each patient was made using an Olympus Evis Exera II 18 endoscopy system and an Olympus ENF VQ transnasal flexible endoscope (Olympus Corporation, Tokyo, Japan). The patients were asked to produce the following tasks in order: a sustained /i/, a low-pitched /i/, a high-pitched /i/, a low-intensity /i/, and a high-intensity /i/. The following variables were assessed: (1) vibratory characteristics of the neoglottis; (2) degree of arytenoids motion; and (3) sphincteric closure of the larynx. Each variable was scored on a 5-point rating scale from 1 (poor performance) to 5 (excellent ability), as suggested by Zacharek et al.[8]

The maximum phonation time (MPT) was measured on the production of 3 sustained /a/. The longest phonation time was recorded. Diadochokinesis was assessed by asking each patient to utter the syllable /pa/ and the trisyllable /pataka/ as fast as possible. The Computerized Speech Laboratory program (version 5.05) with a 4300 external module of

Kay Elemetrics Corporation (Kay Elemetrics, Lincoln Park, NJ) was used. Syllable and trisyllable diadochokinesis were rated, respectively, in syll/sec and trisyll/sec.

The patients were asked to read a 56-word and 99-syllable passage19 and they were audio recorded with a microphone Samson Go Mic (Samson Technologies, Hauppauge, NY) and the Apple Soundtrack Pro software version 3.0.1 using a 50 kHz sample rate (Apple, Cupertino, CA). The time needed to read the passage as well as the syll/sec speed in reading were calculated. Both the grade, instability, roughness, breathiness, asthenia, and strain (GIRBAS) scale20 and the impression, noise, fluency and voicing (INFVo) rating scale [21,22] were used for the perceptual assessment of voice, on the basis of the reading passage's audio recordings. The GIRBAS scale is a widely used scale that specifically assesses different parameters of voice quality: grade, instability, roughness, breathiness, asthenia, and strain; the score ranges from 0 (normal voice) to 3 (severe dysphonia).

The INFVo rating scale is a perceptual scale specifically developed for substitution voice; it assesses: overall quality impression and intelligibility, additive and unnecessary noise, speech fluency, and presence of voiced segments. Each parameter is scored on a visual analog scale from 0 (minimally deviant) to 10 (maximally deviant substitution voicing).

The Computerized Speech Laboratory program version 5.05 with a 4300 external module of Kay Elemetrics Corporation was used to perform the spectrographic analysis of voice. All voices were recorded with a microphone placed approximately 15 cm from the voice source. A spectrograph of the sustained vowels /a/ and /i/ at FFT-1024 points ranging between 0 and 8 kHz was performed; the sample frequency was 20000 Hz. Patients' voices were classified into 4 categories on the basis of the spectrogram analysis, according to the recently proposed modification of Titze's classification.23 The following categories were used: (1) type 1 voices, periodic without strong modulations or subharmonics; (2) type 2 voices, with strong modulations, bifurcations, or subharmonics; (3) type 3 voices, smearing of energy across harmonics with visible fundamental frequency and 1 or 2 harmonics; and (4) type 4 voices, aperiodic.

Perceptual assessment of video and audio recordings FEES, videolaryngoscopies, and voice recordings were assessed independently by 2 raters blinded to the study, speech and language pathologists, who underwent a specific training. In case of disagreement between the raters, they jointly reassessed the parameter until a consensus was reached.

*Quality of life*

The Italian Short Form 36 Items Health Survey (SF-36) questionnaire was completed by each participant to assess QOL, functional health, and well-being.[24,25] The Italian SF-36 is a valid and reliable short-form health survey. It is divided into 8 scales: Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, and Mental Health. Each subscale is scored from 0 (worst possible health status) to 100 (best possible health status).

Dysphagia-related disability was investigated through the Italian MD Anderson Dysphagia Inventory (MDADI).[26,27] The Italian MDADI is a reliable and clinically valid dysphagia-specific QOL questionnaire for Italian-speaking patients with head and neck cancer, divided into a global, an emotional, a physical, and a functional subscale. The total score and each subscale's score ranged from 20 (extremely low functioning) to 100 (high functioning).

Each patient completed the Italian version of the Voice Handicap Index (VHI)[28,29] and the Italian version of the Self-Evaluation of Communication Experiences after Laryngeal Cancer (I-SECEL).[30,31] The VHI assesses patients' perception of disability related to voice dysfunction. It is made up of 3 subscales: emotional, physical, and functional. A total score (possible range, 0–120 points) and subscales' scores (possible range, 0–40) are given; the higher the score, the greater the voice handicap.

The I-SECEL questionnaire specifically assesses communication dysfunction in patients with laryngectomy and their effects on patients' daily living activities. The questionnaire is made up of 34 items divided into 3 subscales: General (5 items), Environmental (14 items), and Attitudinal (15 items). Scores range from 0 to 102 for the total score, from 0 to 15 for the general subscale, from 0 to 42 for the environmental subscale, and from 0 to 45 for the attitudinal subscale. The higher the score, the greater the perception of communication dysfunction. A cutoff of 60 for the total score was established to identify patients in need of a specific counseling. Results are reported as arithmetic mean ±SD and range of the variable.

## RESULTS

*Swallowing assessment*

Results of the swallowing study with FEES are reported in Table 2. Premature spillage was present in 8 patients with liquid boluses, in 5 patients with semisolid boluses, and in 7

patients with solid boluses. Piecemeal deglutition was recorded as present in 1 patient with liquids, in 1 patient with semisolids, and in 1 patient with solids. Aspiration (PAS > or =6) occurred in 10 patients with the liquid bolus, in 2 patients with the semisolid bolus, and in 5 patients with the solid bolus. Penetration was recorded only in 1 patient with liquids, whereas it was present in 3 patients with semisolids and in 9 patients with solids. A Pooling Score of 10 or 11, corresponding to severe dysphagia, was assigned only to 2 patients with the solid bolus.17 The DOSS scores showed that 5 patients were able to tolerate a full-per-oral nutrition with normal diet (DOSS > or = 6), 15 patient could tolerate a full-per-oral nutrition but with the necessity of a modified diet and/or independence (DOSS score between 5 and 3), whereas 2 patients presented severe dysphagia (DOSS < or = 2).
Aspiration pneumonia after surgery occurred in 2 patients (patient #12 and #18). The mean difference between presurgery and postsurgery weight was 2.6±6.8 kg (range, -5 to 19 kg).

*Voice assessment*

Table 3 shows the results of vocal behavior assessment through videolaryngoscopic examination. In most of the patients, arytenoid motion and sphincteric closure were well preserved, whereas vibratory characteristics of the neoglottis were sometimes impaired.
Data on different aerodynamic measures are reported in Table 4. MPT was <10 seconds for all the patients, except one. The reading time and rapidity data were not available for 1 illiterate patient. Mean MPT was 5.3±3 seconds (range, 1.4–15.4 seconds); mean syllable diadochokinesis was 2.8±0.5 syll/sec (range, 1.5–3.8 syll/sec) for the syllable /pa/ and 1±0.3 trisyll/sec (range, 0.4–2 trisyll/sec) for the trisyllable /pataka/. The mean time needed for reading the 99-syllable passage was 29.4±5.5 seconds (range, 22.4–44.2 seconds), with a mean speed of 3.5±0.5 syll/sec (range, 2.4–4.4 syll/sec).
Perceptual and acoustical analysis' results are reported in Table 5. Scores on the INFVo rating scale showed a preserved fluency and the absence of additive and unnecessary noise in many patients; the Vo parameter was altered in only 3 patients. At the GIRBAS scale, 18 patients were classified as G3 and 4 patients as G2. Instability was present in only 4 patients. Fifteen patients were assessed as R2 or R3 and 10 patients as B2 or B3. On the basis of the spectrogram analysis, a harmonic structure of the voice signal was clearly visible in 8

patients; 3 patients' voices were classified as type 1, 5 as type 2, 11 as type 3, and 3 as type 4.

*Quality of life*

Data on QOL assessment using the Italian SF-36 questionnaire are reported in Table 6, whereas results of the self-assessment measurement for both voice and swallowing are reported in Table 7. In the SF-36 questionnaire, the physical functioning's scale had the higher mean score, whereas the role-physical's scale had the lower mean score. In the Italian MDADI, mean values were >75 for both the total score and each subscale's score.

The I-SECEL total score was >48 in 3 patients, whereas it was >60 for none of the patients. Mean values of the Italian VHI were 36.4±19.3 (range, 7–91) for the total score.

## DISCUSSION

Swallowing, voice, and QOL were assessed in a group of 22 male patients who underwent STL. At the present time, no data on long-term functional results after STL exist in literature. Considering the important anatomic demolition consequent to the surgical procedure, swallowing restoration was achieved after STL in most of the patients, whereas postoperative voice was found to be highly dysphonic; patients reported only little impact on QOL. A certain variability of swallowing and voice performance was found in the results. The reason for the variability is not known, but it could be due to the heterogeneity of the population included in the present study (reconstruction type, neck dissection, combined chemotherapy and/or radiation therapy, rehabilitation, and time from surgery). Although the small number of patients cannot lead to definitive considerations, the present results did not show large differences between STLTHP and STL-THEP or between patients who spared both or 1 cricoarytenoid unit.

Swallowing was assessed through the FEES. Aspiration occurred in just a few patients with solid and semisolid boluses, showing a generally good sphincteric action of the neoglottis to separate the lower airways from the oropharynx during swallowing. A poorer performance was recorded with liquids as a spiration was found in nearly half of the patients. Similar results were reported for SCL.[8,32] Retention of the bolus is associated with the risk of postdeglutitive aspiration. The majority of the patients were scored as lower than 7 (corresponding to mild dysphagia) in the Pooling Score with all the consistencies, revealing a low risk of aspiration because of pooled bolus after swallow. Comparable results were found by Simonelli et al[13] and by Zacharek et al[8] for SCL, whereas other studies report a higher presence of pooling after SCL.[11,32] On the basis of the DOSS score, 20 of 22 patients were judged as able to tolerate a full-per-oral nutrition, although a diet modification was necessary in the majority of the patients. Therefore, it seems that in the long term, enteral feeding can be avoided in most of the patients who underwent STL. The present findings are comparable to data from literature on swallowing restoration after SCL.[8,33,34] Furthermore, the full-per-oral nutrition was found to be sufficient to give an adequate nutritional supply to the patients, as, at the time of the study, the preoperative weight was unvaried in the majority of the patients. Aspiration pneumonia occurred in 2 patients after surgery, although aspiration was found in more patients. This could be due to the fact that the 2 patients with pulmonary complications had undergone STL-THEP1A and were the only to be aged >70 years at the time of surgery. Benito et al[34] demonstrated that the statistical risk of aspiration and of pulmonary complications significantly increases when a partial or total arytenoid resection is performed in patients >70 years of age. According to Simonelli et al [(13)], some patients with dysphagia are able to tolerate a certain degree of chronic aspiration without developing pneumonia because of an efficient tracheopulmonary mucociliary action and strong cough or of a general good condition of the patient. Of the 2 patients with pulmonary complication, 1 underwent radiation therapy before surgery (pT4a), whereas the second underwent a postoperative chemotherapy (lung metastases) and both patients underwent selective neck dissection. Schindler et al[35] reported a moderate to severe laryngeal adductor reflex in patients with additional neck dissection and radiation therapy because of reduced laryngeal sensitivity that can be a complication of radiation therapy or can depend on nerve injury during lateral neck dissection. Therefore, it is possible to speculate that other factors besides STL significantly contributed to the development of aspiration pneumonia in these 2 patients of our population.

V ideolaryngoscopic examination showed a poor to moderate vibration of the neoglottis, whereas the anteroposterior valving of the arytenoid/epiglottal/ventricular band complex and arytenoids mobility were generally preserved; similar results have been reported by Zacharek et al[8] and by Schindler et al[11] for SCL.

The measurement of MPT is reported to imply adequacy of air support for speech. MPT resulted to be highly reduced after STL, caused by the loss of air from an incompetent neoglottis. Data from literature show that MPT is reduced after SCL, horizontal glottectomy, and total laryngectomy. MPT after STL is comparable to the MPT after SCL, as reported by So et al[36] and Makeieff et al,[10] whereas it is shorter than the MPT reported by other authors after SCL and after horizontal glottectomy and total laryngectomy.[4,8,11,36–38] Results on all the other aerodynamic measures are similar to those obtained after SCL, horizontal glottectomy, and total laryngectomy, except for the reading speed that was found to be generally better than the reading speed after total laryngectomy. [11,36–38] Diadochokinesis' performance after STL was found to be fair.[19]

For the perceptual evaluation of the voice, both the GIRBAS scale and the INFVo rating scale were used. Present results on the GIRBAS scale showed values similar to those of literature on SCL, horizontal glottectomy, and total laryngectomy.[11,37] Postoperative voice was found to be significantly worsened after STL, with moderate to severe roughness component and slight to severe breathiness. The high-grade of dysphonia and the presence of the breathiness component are consistent with the spectrogram analysis, as more than half of the patients were classified as Titze's type 3 or type 4, corresponding to aperiodic signal.[23] Results on the INFVo rating scale confirm the deterioration of vocal quality after STL.
However, the low scores of the unnecessary noise, fluency, and voice parameters reveal that fluency and voicing are usually not compromised after STL and no unintended additive noises accompany voice production. The fact that fluency was found to have low values in almost all patients reveals that, although the MPT was significantly reduced after STL, it is sufficient to allow a normal spontaneous speech. Because swallowing and voice are abilities that impact on everyday social activities, such as eating and communication, both general and specific self-assessment instruments were included in the present study. Results of the swallowing self-assessment after STL, conducted through the use of the Italian MDADI questionnaire, reveals that patients were, on average, little disabled in eating, suggesting that, from the patients' perspective, swallowing ability is sufficiently restored in the long term. Uniform results were found on the Italian MDADI subscales, meaning that individual affective response to swallowing disorders, its impact on daily activities, and selfperception of bolus transit play a similar role in QOL after STL. Comparable data on dysphagia-specific

QOL were found by Schindler et al11 after SCL. Similarly, low VHI results revealed that perceived disability related to voice disorders after STL is only moderate. Therefore, although postoperative voice resulted to be significantly deteriorated, patients reported to be relatively satisfied speakers on emotional, physical, and functional levels, suggesting that oral communication is not significantly limited after STL. A possible explanation for the discordance between the voice assessment, through the perceptual evaluation and the aerodynamic measures, and the perceived voice handicap can be that voice impairment is considered an inevitable consequence after laryngeal cancer surgery. Therefore, vocal impairment is regarded as less important and consequently scored as having less impact on life. Moreover, it should be taken into account that many patients included in the present study, being over 60 years of age, were retired at the time of the assessment, therefore, they do not have occupational communication needs. VHI results were confirmed by those of the I-SECEL, in which almost all patients showed a good attitude toward their communication dysfunction.

Present VHI results are comparable to those reported by Schindler et al[11,37,38] on SCL, horizontal glottectomy, and total laryngectomy, whereas a worse voice disorder's perception was found by Zacharek et a[l8] after SCL and by So et al[36] after SCL and total laryngectomy. This can be due to the fact that QOL brings many factors into play, including client's psychosocial traits and cultural and ethnic backgrounds. General QOL was found to be satisfactory after STL. Indeed, SF-36 results reported in the present study are comparable to those of the Italian general population, except for the RP subscale (concerning problems with work or other daily activities as a result of physical health), revealing that QOL is only slightly compromised after STL.[39] The positive data on general perceived QOL and self-assessment of voice and swallowing after STL reported in the present study represent an essential point to be addressed in the preoperative consultation.

SF-36 results after STL are lower than those reported by Weinstein et al40 after SCL, but higher than those reported by the same authors after total laryngectomy.

This is in accordance with the study of Mosconi et al,[41] who found that conservative treatments of laryngeal cancer have a positive impact on subjective health status when compared to total laryngectomy, although the latter causes less swallowing impairment. This is mostly because of the fact that conservative laryngectomies, including STL, avoid the potential limitation and emotional problems associated with a permanent tracheostoma, which causes cosmetic disability and, therefore, has a profound effect on the sense of social acceptability of the patient.[42]

Limitations of our study were: the small number of patients; the population selection bias related to the inclusion criteria used (no evidence of disease, no salvage total laryngectomy, functional preservation); and the heterogeneity of the study population for age, length of rehabilitation, and time from surgery. These limitations do not allow the generalization of our preliminary results to all patients who undergo STL. Further studies should be conducted including a larger population and investigating whether the anatomic differences because of the use of STL-THP or STL-THEP and the number of arytenoids spared correspond to significantly different functional outcomes.

Moreover, the study of factors, such as age, that can influence functional outcomes, will allow a more accurate selection of patient candidates for STL in order to achieve not only oncologic safety, but also better longterm outcomes.

In conclusion, long-term voice and swallowing results after STL showed that swallowing was found to be sufficiently restored, often allowing a full-per-oral nutrition, whereas voice resulted to be significantly worsened, generally quite hoarse and breathy. Patients reported a good perception of disability related to voice disorders, suggesting that oral communication was not significantly limited. General QOL after STL was generally satisfactory.

Therefore, STL seems to have reduced the impact on QOL, avoiding the social disability associated with a permanent tracheostomy. However, the risk of aspiration and the vocal impairment are inevitable consequences of the anatomic modifications after STL, stressing the need of a meticulous preoperative selection of the patients in order to decrease functional sequelae and to achieve better functional outcomes and of a careful postsurgical swallowing assessment before oral nutrition restoring.

The preliminary outcome data make it necessary, after these “extreme” function-sparing procedures, to be prepared for subsequent endoscopic surgery, laser surgery, or injective laryngoplasty, in order to correct the anatomic and functional results and to achieve the best laryngeal function as possible. Future studies, including a larger population, are necessary to confirm present data.

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**Table 1 Study population characteristics**

| Patient no. | Age, y | Educational degree | Job | Marital status | Months since surgery | Type of surgery | ND | RT | CT | Rehabilitation | TNM classification |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 65 | Degree | Retired | Married | 7 | STL-THEP+A | l-SND (II–IV + VI) | – | – | 1 mo | T3N0M0 |
| 2 | 41 | Middle school | Hydraulic | Single | 7 | STL-THEP+A | l-SND (II–IV + VI) | – | – | 6 mo | T2N0M0 |
| 3 | 65 | High school | Retired | Married | 7 | STL-THEP | – | – | – | – | T2N0M0 |
| 4 | 70 | Middle school | Retired | Married | 14 | STL-THEP | – | – | – | – | T3N/M0 |
| 5 | 55 | High school | Self employed | Married | 15 | STL-THP+A | r-SND (II-III) | Post | Post | – | T4N0M0 |
| 6 | 49 | Middle school | Pizza maker | Divorced | 16 | STL-THP+A | r-LND (VI) | – | – | 1 mo | T3N0M0 |
| 7 | 61 | Degree | Employee | Married | 19 | STL-THEP+A | – | – | – | 3 mo | T3N/M0 |
| 8 | 63 | High school | Retired | Married | 26 | STL-THEP+A | r-SND (II–IV) | – | – | – | T3N0M0 |
| 9 | 67 | Elementary | Retired | Single | 33 | STL-THEP+A | – | – | – | – | T3N/M0 |
| 10 | 53 | Middle school | Employee | Married | 39 | STL-THEP+A | r-SND (II–IV, VI) | – | – | – | T3N0M0 |
| 11 | 69 | Degree | Self employed | Married | 40 | STL-THEP | – | – | – | 2 mo | T1bN0M0 |
| 12 | 77 | Degree | Retired | Widower | 42 | STL-THEP+A | bil-SND (II–IV+VI) | – | Post | 2 mo | T3N0M0 |
| 13 | 50 | Middle school | Employee | Married | 43 | STL-THEP+A | r-SND (II–IV+VI) | – | – | – | T2N0M0 |
| 14 | 69 | Elementary | Retired | Widower | 52 | STL-THEP+A | l-SND (II–VI) | – | – | – | T3N0M0 |
| 15 | 56 | Middle school | Unemployed | Married | 52 | STL-THEP+A | r-SND (II–IV+VI) | – | – | 1 mo | T3N0M0 |
| 16 | 60 | Middle school | Barman | Married | 55 | STL-THEP+A | r-SND (II–IV) | – | – | – | T3N0M0 |
| 17 | 62 | High school | Self employed | Divorced | 71 | STL-THEP+A | r-SND (II–IV+VI) | – | – | – | T4N0M0 |
| 18 | 84 | Elementary | Retired | Married | 74 | STL-THEP+A | l-SND (II–IV) | Pre | – | 1 mo | T3N0M0 |
| 19 | 23 | High school | Unemployed | Single | 74 | STL-THEP+A | r-SND (II–IV+VI) | – | – | 2 mo | T3N0M0 |
| 20 | 60 | Elementary | Laborer | Married | 80 | STL-THEP+A | l-SND (II–IV + VI) | – | – | – | T2N0M0 |
| 21 | 63 | High school | Employee | Single | 85 | STL-THEP+A | – | Pre | – | – | T2N/M0 |
| 22 | 68 | Middle school | Retired | Widower | 94 | STL-THP+A | r-SND (II–IV) | – | – | – | T3N0M0 |

Abbreviations: ND, neck dissection; RT, radiotherapy; CT, chemotherapy; STL-THEP+A, supratracheal laryngectomy-tracheohyoidoepiglottopexy + one cricoarytenoid unit resected; l-SND, left selective neck dissection; STL-THEP, supratracheal laryngectomy-tracheohyoidoepiglottopexy; STL-THP+A, supratracheal laryngectomy-tracheohyoidopexy + one cricoarytenoid unit resected; r-SND, right selective neck dissection; r-LND, right limited neck dissection; bil-SND, bilateral selective neck dissection.

**Table 2 Outcome of swalloeing study with fiberoptic endoscopic evaluation of swallowing**

| Patient no. | Spillage | | | Piecemeal deglutition | | | PAS | | | Pooling score | | | DOSS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Liquid | Semisolid | Solid | Liquid | Semisolid | Solid | Liquid | Semisolid | Solid | Liquid | Semisolid | Solid | |
| 1 | + | − | − | − | − | − | 1 | 2 | 3 | 4 | 8 | 8 | 5 |
| 2 | + | − | − | − | − | − | 1 | 1 | 2 | 4 | 8 | 7 | 5 |
| 3 | + | − | − | − | − | − | 8 | 1 | 2 | 7 | 4 | 6 | 4 |
| 4 | + | + | + | − | − | − | 1 | 1 | 1 | 5 | 5 | 6 | 6 |
| 5 | − | − | − | − | − | − | 6 | 1 | 7 | 7 | 5 | 9 | 3 |
| 6 | − | − | + | − | − | − | 1 | 1 | 1 | 6 | 4 | 5 | 6 |
| 7 | − | − | + | − | − | − | 1 | 1 | 1 | 4 | 4 | 5 | 6 |
| 8 | − | − | − | − | − | − | 1 | 1 | 8 | 4 | 5 | 7 | 3 |
| 9 | − | − | − | − | − | − | 7 | 7 | 2 | 9 | 9 | 6 | 2 |
| 10 | + | − | − | − | − | − | 8 | 1 | 8 | 7 | 5 | 10 | 3 |
| 11 | − | + | − | − | − | − | 1 | 1 | 1 | 6 | 4 | 5 | 5 |
| 12 | + | − | − | − | − | − | 7 | 8 | 8 | 9 | 9 | 9 | 2 |
| 13 | − | − | − | − | − | − | 1 | 2 | 2 | 4 | 6 | 8 | 5 |
| 14 | − | + | + | − | + | − | 1 | 1 | 3 | 5 | 6 | 8 | 5 |
| 15 | − | + | + | − | − | − | 1 | 1 | 1 | 5 | 4 | 4 | 6 |
| 16 | − | − | − | − | − | − | 8 | 2 | 2 | 8 | 4 | 7 | 5 |
| 17 | − | + | + | − | − | − | 7 | 1 | 3 | 7 | 5 | 8 | 4 |
| 18 | − | − | − | − | − | − | 5 | 1 | 1 | 7 | 4 | 8 | 4 |
| 19 | − | − | − | − | − | − | 8 | 1 | 1 | 7 | 5 | 4 | 4 |
| 20 | + | − | + | + | − | + | 8 | 1 | 8 | 9 | 5 | 10 | 3 |
| 21 | − | − | − | − | − | − | 7 | 1 | 3 | 9 | 6 | 7 | 4 |
| 22 | + | − | − | − | − | − | 1 | 1 | 1 | 4 | 4 | 4 | 6 |
| Average | | | | | | | 4.1 | 1.7 | 3.1 | 6.2 | 5.4 | 6.9 | 4.4 |
| SD | | | | | | | 3.2 | 1.9 | 2.7 | 1.8 | 1.7 | 1.9 | 1.3 |

Abbreviations: PAS, Penetration-Aspiration Scale; DOSS, Dysphagia Outcome and Severity Scale.

**Table 3 Vocal behaviourassessed endoscopically**

| Patient no. | Vibratory characteristics of the neoglottis | Degree of arytenoids motion | Sphincteric closure of the larynx |
|---|---|---|---|
| 1 | 2 | 2 | 2 |
| 2 | 2 | 4 | 4 |
| 3 | 2 | 4 | 3 |
| 4 | 1 | 5 | 4 |
| 5 | 2 | 2 | 3 |
| 6 | 3 | 2 | 5 |
| 7 | 2 | 3 | 3 |
| 8 | 4 | 3 | 5 |
| 9 | 3 | 4 | 3 |
| 10 | 2 | 2 | 1 |
| 11 | 3 | 1 | 5 |
| 12 | 4 | 5 | 4 |
| 13 | 2 | 4 | 2 |
| 14 | 5 | 3 | 3 |
| 15 | 2 | 2 | 3 |
| 16 | 4 | 3 | 3 |
| 17 | 3 | 4 | 4 |
| 18 | 3 | 3 | 3 |
| 19 | 1 | 2 | 2 |
| 20 | 5 | 4 | 4 |
| 21 | 2 | 2 | 5 |
| 22 | 4 | 2 | 5 |
| Average | 2.8 | 3.0 | 3.5 |
| SD | 1.2 | 1.1 | 1.1 |

**Table 4** **Aerodynamic measures**

| Patient no. | MPT | Diadochokinesis /pa/ | Diadochokinesis /pataka/ | Reading time, s | Reading rapidity, syll/sec |
|---|---|---|---|---|---|
| 1 | 1.4 | 2.3 | 0.9 | 40.7 | 2.43 |
| 2 | 5.2 | 2.8 | 1 | 23 | 4.30 |
| 3 | 2.4 | 3 | 1.2 | 24.9 | 3.98 |
| 4 | 15.4 | 3.2 | 0.9 | 29.1 | 3.40 |
| 5 | 2.9 | 2 | 0.8 | 24.9 | 3.98 |
| 6 | 7.8 | 3 | 1 | 44.2 | 2.38 |
| 7 | 3.9 | 3.8 | 2 | 29.1 | 3.47 |
| 8 | 6.7 | 2.8 | 0.9 | 29.5 | 3.36 |
| 9 | 5.6 | 2.2 | 0.5 | 36.4 | 2.72 |
| 10 | 2.2 | 2.9 | 1.4 | 27.4 | 3.61 |
| 11 | 5.8 | 2.9 | 0.8 | 25 | 3.96 |
| 12 | 2.5 | 2.4 | 0.8 | 32.8 | 3.17 |
| 13 | 6 | 3.7 | 1.1 | 28.1 | 3.52 |
| 14 | 4.2 | 2.1 | 0.8 | 30.2 | 3.28 |
| 15 | 8.4 | 2.9 | 0.9 | 22.4 | 4.42 |
| 16 | 6.3 | 2.8 | 1 | 28.2 | 3.51 |
| 17 | 7.7 | 3.1 | 1.3 | 29.2 | 3.39 |
| 18 | 2.5 | 1.5 | 0.4 | N/A | N/A |
| 19 | 6.9 | 2.8 | 0.8 | 25 | 3.96 |
| 20 | 3.3 | 3 | 0.9 | 32.4 | 3.09 |
| 21 | 4.9 | 2.9 | 1 | 27.3 | 3.63 |
| 22 | 5.1 | 3.2 | 1.1 | 27.5 | 3.60 |
| Average | 5.3 | 2.8 | 1.0 | 29.4 | 3.5 |
| SD | 3.0 | 0.5 | 0.3 | 5.5 | 0.5 |

Abbreviation: MPT, maximum phonation time.

**Table 5 Perceptual and acoustic voice analysis**

| Patient no. | INFVo | | | | GIRBAS | | | | | | Titze classification |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | I | N | F | Vo | G | I | R | B | A | S | |
| 1 | 9.7 | 1.9 | 10 | 10 | 3 | 0 | 0 | 3 | 3 | 0 | 3 |
| 2 | 3.2 | 0 | 0 | 0 | 3 | 0 | 3 | 0 | 0 | 0 | 1 |
| 3 | 4.3 | 0 | 2.7 | 0 | 3 | 0 | 3 | 2 | 1 | 2 | 4 |
| 4 | 7.3 | 0 | 0 | 0 | 3 | 0 | 1 | 2 | 0 | 3 | 2 |
| 5 | 6.2 | 0 | 0 | 8.5 | 3 | 3 | 3 | 3 | 2 | 0 | 4 |
| 6 | 5.5 | 2.3 | 0 | 0 | 3 | 0 | 3 | 0 | 0 | 0 | 3 |
| 7 | 6.7 | 0 | 0.9 | 0 | 3 | 0 | 0 | 3 | 2 | 1 | 2 |
| 8 | 5.9 | 1 | 1.3 | 0 | 3 | 0 | 3 | 0 | 0 | 1 | 3 |
| 9 | 8.5 | 3.4 | 0.9 | 0 | 3 | 0 | 3 | 0 | 1 | 1 | 4 |
| 10 | 9.3 | 1.1 | 4.1 | 10 | 3 | 0 | 0 | 3 | 3 | 0 | 3 |
| 11 | 2.7 | 1.3 | 0.7 | 2.5 | 3 | 0 | 2 | 3 | 1 | 2 | 3 |
| 12 | 1.8 | 1.3 | 2.9 | 0 | 2 | 0 | 3 | 0 | 0 | 0 | 2 |
| 13 | 2.9 | 0 | 0 | 0 | 3 | 0 | 3 | 0 | 0 | 0 | 2 |
| 14 | 6.8 | 6.4 | 7.2 | 0 | 3 | 0 | 3 | 0 | 0 | 0 | 3 |
| 15 | 9 | 0 | 0 | 0 | 3 | 0 | 1 | 3 | 1 | 1 | 3 |
| 16 | 4.6 | 0 | 0.9 | 0 | 2 | 0 | 2 | 0 | 0 | 0 | 1 |
| 17 | 4.5 | 2.6 | 2.8 | 0 | 3 | 0 | 2 | 1 | 1 | 1 | 2 |
| 18 | 7.9 | 0 | 2.4 | 0 | 3 | 1 | 2 | 2 | 1 | 3 | 3 |
| 19 | 3.5 | 0 | 0.7 | 0 | 2 | 0 | 1 | 0 | 0 | 0 | 1 |
| 20 | 6.6 | 4.2 | 1.3 | 0 | 3 | 0 | 3 | 0 | 0 | 0 | 3 |
| 21 | 1.4 | 0 | 0 | 0 | 2 | 0 | 1 | 2 | 3 | 0 | 3 |
| 22 | 6.6 | 1 | 5.1 | 0 | 3 | 0 | 3 | 0 | 0 | 1 | 3 |
| Average | 5.7 | 1.2 | 2.0 | 1.4 | 2.8 | 0.2 | 2.1 | 1.2 | 0.9 | 0.7 | |
| SD | 2.4 | 1.7 | 2.6 | 3.3 | 0.4 | 0.7 | 1.1 | 1.3 | 1.1 | 1.0 | |

Abbreviations: INFVo, I, overall quality impression and intelligibility; N, additive and unnecessary noise; F, speech fluency; Vo, presence of voiced segments; GIRBAS, G, grade; I, instability; R, roughness; B, breathiness; A, asthenia; S, strain.

**Table 6 Quality of life assessment through the Italian Short Form-36 questionnaire**

| Patient no. | Short Form-36 | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | PF | RP | BP | GH | VT | SF | RE | MH |
| 1 | 85 | 25 | 74 | 56 | 45 | 37 | 0 | 56 |
| 2 | 95 | 75 | 100 | 92 | 80 | 87 | 100 | 100 |
| 3 | 100 | 100 | 100 | 61 | 80 | 100 | 100 | 92 |
| 4 | 95 | 75 | 100 | 82 | 70 | 87 | 66 | 80 |
| 5 | 90 | 25 | 74 | 52 | 40 | 37 | 0 | 36 |
| 6 | 95 | 100 | 80 | 92 | 80 | 75 | 100 | 84 |
| 7 | 100 | 50 | 100 | 76 | 70 | 87 | 100 | 72 |
| 8 | 15 | 0 | 41 | 56 | 35 | 37 | 0 | 36 |
| 9 | 45 | 25 | 41 | 45 | 15 | 62 | 33 | 52 |
| 10 | 85 | 50 | 74 | 67 | 70 | 62 | 66 | 80 |
| 11 | 100 | 100 | 84 | 72 | 85 | 87 | 100 | 80 |
| 12 | 85 | 0 | 74 | 45 | 40 | 50 | 0 | 24 |
| 13 | 90 | 75 | 12 | 52 | 80 | 75 | 100 | 80 |
| 14 | 100 | 100 | 61 | 76 | 90 | 100 | 100 | 88 |
| 15 | 80 | 0 | 100 | 86 | 85 | 100 | 100 | 96 |
| 16 | 75 | 75 | 41 | 76 | 75 | 75 | 100 | 60 |
| 17 | 95 | 100 | 100 | 82 | 65 | 100 | 100 | 80 |
| 18 | 60 | 0 | 100 | 82 | 35 | 75 | 100 | 88 |
| 19 | 100 | 100 | 100 | 97 | 75 | 87 | 100 | 76 |
| 20 | 80 | 50 | 52 | 67 | 40 | 25 | 66 | 40 |
| 21 | 100 | 100 | 100 | 67 | 65 | 87 | 100 | 60 |
| 22 | 45 | 25 | 70 | 67 | 55 | 75 | 0 | 56 |
| Average | 82.5 | 56.8 | 76.3 | 70.4 | 62.5 | 73.1 | 69.6 | 68.9 |
| SD | 22.4 | 38.7 | 25.7 | 15.3 | 20.9 | 23.0 | 42.3 | 21.5 |

Abbreviations: PF, physical functioning; RP, role-physical; BP, bodily pain; GH, general health; VT, vitality; SF, social functioning; RE, role-emotional; MH, mental health.

**Table 7** **Self-assessment of voice and swallowing through the Italian MD Anderson Dysphagya Inventory, the Voice Handicap Index and the Italian Self-Evaluation of Communication Experiencea after Laryngeal cancer**

| | MDADI | | | | | VHI | | | | I-SECEL | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Patient no. | T | P | F | E | G | T | P | E | F | T | G | E | A |
| 1 | 62 | 55 | 64 | 67 | 80 | 62 | 17 | 15 | 30 | 59 | 9 | 30 | 20 |
| 2 | 85 | 80 | 96 | 83 | 80 | 21 | 10 | 3 | 8 | 25 | 10 | 14 | 1 |
| 3 | 78 | 75 | 84 | 77 | 80 | 40 | 19 | 6 | 15 | 40 | 12 | 21 | 7 |
| 4 | 96 | 90 | 100 | 100 | 100 | 11 | 7 | 0 | 4 | 19 | 10 | 7 | 2 |
| 5 | 66 | 65 | 68 | 70 | 40 | 42 | 18 | 8 | 16 | 45 | 11 | 23 | 11 |
| 6 | 93 | 95 | 100 | 87 | 80 | 18 | 11 | 0 | 7 | 34 | 13 | 18 | 3 |
| 7 | 80 | 68 | 100 | 80 | 80 | 24 | 14 | 0 | 10 | 46 | 13 | 26 | 7 |
| 8 | 93 | 90 | 100 | 93 | 80 | 64 | 20 | 17 | 27 | 48 | 11 | 22 | 15 |
| 9 | 63 | 58 | 64 | 73 | 40 | 40 | 13 | 8 | 19 | 38 | 10 | 21 | 7 |
| 10 | 72 | 70 | 72 | 73 | 80 | 49 | 16 | 13 | 20 | 44 | 10 | 23 | 11 |
| 11 | 96 | 100 | 84 | 100 | 100 | 25 | 5 | 4 | 16 | 28 | 10 | 14 | 4 |
| 12 | 55 | 70 | 44 | 50 | 20 | 36 | 17 | 5 | 14 | 36 | 11 | 16 | 9 |
| 13 | 71 | 63 | 80 | 73 | 80 | 44 | 16 | 10 | 18 | 51 | 11 | 27 | 13 |
| 14 | 96 | 98 | 100 | 90 | 100 | 7 | 5 | 0 | 2 | 13 | 9 | 3 | 1 |
| 15 | 100 | 100 | 100 | 100 | 100 | 18 | 10 | 0 | 8 | 28 | 15 | 11 | 2 |
| 16 | 91 | 88 | 100 | 87 | 100 | 49 | 16 | 13 | 20 | 47 | 7 | 28 | 12 |
| 17 | 74 | 68 | 80 | 77 | 80 | 29 | 10 | 5 | 14 | 33 | 12 | 17 | 4 |
| 19 | 88 | 88 | 92 | 87 | 80 | 39 | 21 | 9 | 9 | 32 | 8 | 14 | 10 |
| 18 | 53 | 45 | 60 | 53 | 80 | 38 | 20 | 7 | 11 | 23 | 7 | 8 | 8 |
| 20 | 52 | 43 | 76 | 50 | 20 | 91 | 27 | 34 | 30 | 59 | 9 | 29 | 21 |
| 21 | 89 | 88 | 96 | 83 | 100 | 21 | 10 | 0 | 11 | 26 | 8 | 17 | 1 |
| 22 | 74 | 75 | 72 | 77 | 60 | 33 | 14 | 6 | 13 | 37 | 11 | 16 | 10 |
| Average | 78.5 | 76.0 | 83.3 | 78.6 | 75.5 | 36.4 | 14.4 | 7.4 | 14.6 | 36.9 | 10.3 | 18.4 | 8.1 |
| SD | 15.3 | 17.1 | 16.5 | 14.7 | 24.6 | 19.3 | 5.5 | 7.9 | 7.6 | 12.3 | 2.0 | 7.4 | 5.8 |

Abbreviations: MDADI, MD Anderson Dysphagia Inventory; T, total score; P, physical subscale; F, functional subscale; E, emotional subscale; G, global subscale; VHI, Voice Handicap Index; T, total score; P, physical subscale; F, functional subscale; E, emotional subscale; I-SECEL, Italian-Self-Evaluation of Communication Experiences after Laryngeal Cancer; T, total score; G, general subscale; E, environmental subscale; A, attitudinal subscale.

# Paper 2

## *Functional outcomes after supracricoid laryngectomy: what do we not know and what do we need to know?*

*Abstract* Supracricoid laryngectomies (SCLs) are conservative organ-sparing surgical techniques for the treatment of selected T2–T4 laryngeal carcinomas. Although these procedures allow preserving the larynx and its functions, in several countries SCLs are not adopted in oncological protocols. One of the possible reasons to account for this choice is the complexity of post-surgical in-hospital management and the variability in functional results. The aim of this review is to analyse the literature on functional results after SCLs as knowledge on functional results will help in focusing on what is needed in the future to reach more standardized post-surgical procedures and homogeneous outcomes. The analysis of the length of hospital stay, feeding-tube removal time and time to eventual tracheotomy decannulation showed a marked variability across authors and centres. Several factors may come into play, including health-system organizations in different countries. In most studies in-depth description of the criteria applied for discharge, tracheotomy tube removal and commencement of oral feeding were not reported. Moreover, -. Therefore, there is a need for clearer clinical recommendations on early post-surgical management, tracheal-cannula and feedingtube removal criteria, voice- and swallowing-assessment protocol, rehabilitation need and timing.

*Introduction*

Supracricoid laryngectomies (SCLs) are conservative surgical techniques for the treatment of selected laryngeal carcinomas, classified as T2–T4. SCLs are a group of open partial horizontal laryngectomies characterized by the resection of the entire thyroid cartilage, with the inferior limit represented by the upper edge of the cricoid ring. The differences between the various subtypes of SCLs are related to the amount of supraglottis removed and their extension, if any, to include one arytenoid [1]. In SCL with cricohyoidoepiglottopexy (CHEP) the thyrohyoid membrane is entered horizontally from above and the preepiglottic space and epiglottic cartilage are transected so that the suprahyoid part of the epiglottis is spared. On both sides, the inferior constrictor muscles are incised, the piriform sinuses dissected, the inferior horns of thyroid cartilage cut, and the ventricular and vocal folds divided down to the lower limit of resection in the subglottic region. The trachea is mobilized by blunt dissection along the anterior tracheal wall and a cervico-mediastinal release of the trachea is performed; it is therefore allowed to pull the cricoid up to the level of the hyoid bone so that laryngeal reconstruction is achieved by CHEP. In SCL with cricohyoidopexys (CHP), superiorly, the thyrohyoid membrane is horizontally divided along the lower border of the hyoid bone. The posterior aspect of the hyoid is dissected, and the valleculae and the entire epiglottis are included in the surgical specimen. Laterally and inferiorly the procedure is carried out as SCL with CHEP. The entire supraglottis and the pre-epiglottic space are removed [2–5].

Previous studies demonstrated a similar local control and survival rates of SCLs and total laryngectomy (TL), the standard technique for advanced-stage laryngeal carcinoma (70–89 % survival rates for T3 cancers and 49–60 % survival rates for T4a cancers) [6–12]. In particular, Wang et al. [13] reported that the 5-year local recurrence rate was 5.77 %, the 5-year disease-specific survival rate was 82.7 % and the 5-year overall survival rate was 84.1 %, in a group of T1b–T4 patients with glottic and supraglottic cancer. In addition, SCLs have also been shown to be an acceptable salvage surgical technique [14].

On the other hand, current literature reports somewhat confusing data on the functional results after TL and SCLs [15]. In particular, Weinstein et al. [16] demonstrated that subjects treated with SCL had significant higher domain scores than TL patients when general quality of life (QOL) was analysed through SF-36. Furthermore, Torrejano et al. [17] found that TL patients scored significantly better than SCL patients did in voice-related QOL (VR-QOL) measures, while So et al. [18] reported no differences between voice characteristics of TL and SCL patients. Nonetheless, since permanent tracheostoma is usually not required and at least one arytenoid is spared (thus preserving both voice and swallowing), SCLs have to be considered an important organ sparing treatment option. The alternative organpreserving treatment for laryngeal carcinoma is (chemo)radiotherapy. This latter modality demonstrates similar cure rates to those of TL in T2–T4 patients, with an overall survival rate of 75 % at 2 years and a metastasis free rates of 91, 92 and 84 % at 2 years in patients who had received induction cisplatin and 5-fluorouracil (5-FU) followed by radiotherapy, radiotherapy with concurrent cisplatin and received radiotherapy alone, respectively [19].

However, a severe speech and swallowing impairment is often associated with these aggressive protocols [20]. Fibrosis and oedema with a poorly functioning larynx could be a possible reason for negative outcomes in organpreservation therapy particularly after intensive concurrent chemo-radiation protocols [20]. In the last 15 years transoral approaches for laryngeal cancer either through traditional CO2 laser surgery or through robotic surgery have been increasingly used for glottic and supraglottic T1–T3 laryngeal cancers in experienced hands [21–25]. Local control and survival rates appeared optimal; in particular Peretti et al. [21] reported with trans-oral laser surgery that the 5-year local recurrence rate was 16.8 %, the 5-year disease-specific survival ranged between 71.6 % for T3 and 93.4 % for T1 and the 5-year overall survival was 87.5 % in a group of T1–T3 patients with glottic cancer. In T2–T3 glottic cancer treated through trans-oral laser functional outcomes also appeared optimal: moderate dysphonia was found in 18 % of the patients, while only 4 % presented signs of aspiration [23]. Vilaseca et al. [26] analysed the QOL in 401 disease-free laryngeal cancerpatients 1 year after trans-oral laser surgery and found on the SF-12 that most of the domains were around or above the norms. More recently trans-oral robotic surgery (TORS) has been introduced as an alternative to standard trans-oral laser surgery and is a one of the fastest growing areas of head and neck surgery [27]. Small case series have been recently reported for T1–T3 supraglottic cancers with loco-regional control rates ranging from 80 to 100 %; functional outcomes have not been thoroughly investigated, but preliminary reports suggest short hospital stay and rapid transition to oral intake [28–31]. Application of TORS to glottic–supraglottic cancer is still in its infancy, but newer technical developments will probably allow the spread of this technique [32].

First developed and adopted in Europe, SCLs have gained an increasing acceptance in North America and around the world [33–35]. The theoretical advantage of SCLs vs TL is that since at least one functioning cricoarytenoid joint is maintained (facilitating neoglottal competency), a permanent tracheostoma is not required because the main laryngeal functions (respiration, phonation and swallowing) are preserved. Volitional sphincteric approximation of the mobile arytenoids cartilage and base of tongue (in the case of CHP), or epiglottis (in the case if CHEP) provides mucosal source of vibration, allowing for voice production [36].

Compensatory mechanisms with reorganization of the stepwise sequence of neuromuscular events, lasting several months, are necessary to restore swallowing [37].

Although SCLs represent an important alternative in the treatment of laryngeal cancers, in several Northern European countries as well as in the USA, SCLs are not adopted in oncological protocols. One of the possible reasons behind this choice lies in the fact that post-operative management is complex and functional results vary among centres.

The aim of this review is to analyse the international literature on functional results after SCLs focusing on three main areas: (1) length of hospital stay, time of feeding tube and tracheal-cannula removal; (2) swallowing functional outcome; (3) voice functional outcomes. Knowledge on functional results will help in focussing what is needed in the future to have more standardized procedures and homogeneous outcomes. As trans-oral approaches (traditional or TORS) are becoming increasingly popular, homogeneous outcome measures will be particularly useful when comparing different treatment modalities: TL, SCL, trans-oral laser surgery, TORS and (chemo)radiotherapy.

*Length of hospital stay, tube feeding and tracheostomy*

At the end of SCL, a tracheostomy is performed and a feeding tube is inserted. Our literature review revealed great variability in the mean hospitalization time, feeding tube removal time and tracheotomy tube decannulation time (Table 1) [10, 11, 35, 38–58]. The mean length of hospital stay (where indicated) varied from a minimum of 5 days (as reported by Gonc¸alves et al. [58]) to a maximum of 104 days (as reported by Nakayama et al. [55]). Mean feeding-tube removal time showed similar variability, ranging between 10 and 88 days [37, 40]. Additionally, great heterogeneity was found in mean decannulation times, varying between 8 days (as reported by Laccoureye et al. [43]) and 105 days (as reported by Gonc¸alves et al. [58]). On the contrary, little variability was found in decannulation rates, which range between 85.7 and 100 % [10, 40, 51–56], confirming good respiratory outcomes following SCLs.

Some authors focussed on the analysis of those variables that may affect the mean hospital-stay duration, feeding tube removal time and tracheal-cannula removal time. In particular, the literature shows that arytenoid resection, type of reconstruction and age may play a critical role.

Caicedo-Granados et al. [39] found a longer decannulation time in SCL patients who underwent arytenoidectomy (median time 6 vs 3 weeks for no arytenoidectomy, p = 0.096). Increased length of stay, duration of tube feeding and lower subjective voice and swallowing satisfaction were associated with CHP and increased age in Clayburgh et al.'s [40] study. Naudo et al. [46] analysed the factors affecting duration of hospitalization, decannulation time and time of nasogastric tube in place. The duration of hospitalization was statistically more likely to increase with increased age (p = 0.0006), increased length of time during which the tracheostomy tube was in place (p = 0.001) and increased length of time the nasogastric feeding tube was in situ (p = 0.001). Moreover, the delay in decannulation was statistically more likely to increase with increasing age (p = 0.02), and in the presence of postoperative arytenoid oedema (p = 0.001). The length of time the nasogastric feeding tube was kept in place was also statistically more likely to increase with increasing age (p = 0.004), arytenoid cartilage resection (p = 0.001) and increased length of time the tracheostomy tube was kept in place (p = 0.001). In Park et al.'s study [47], decannulation time was significantly delayed in patients with one arytenoid. Even in SCL (CHEP) patients, the mean tracheal-cannula and nasogastric-tube removal times were significantly different, according to the extended procedure of unilateral arytenoidectomy. In SCL (CHP) patients, the mean tracheal-cannula and nasogastric-tube removal times were found to be delayed in the extended group, but the differences were not statistically significant owing to the small number of patients. Luna-Ortiz et al. [35] reported that average time of tracheal-cannula and nasogastric-tube removal between patients preserving only one or both arytenoids was shorter for the latter, even if the difference found was not statistically significant. Finally, Yuce et al. [57] in their series found statistically significant differences in decannulation time, nasogastric-tube removal time and hospitalization time (p\0.05) with delay in patients with one arytenoid. To the best of our knowledge, no study compared the time of hospital stay and tube feeding among TL, SCLs, trans-oral laser surgery, TORS and patients treated with (chemo)radiotherapy.

In general, poor description was found regarding criteria adopted for the optimal time for hospital stay, feeding tube and tracheal-cannula removal. Such criteria may help to reduce postoperative complications as well as to shorten the time for recovery. Their definition might represent a future goal in the field of open partial laryngectomies.

*Swallowing functional outcomes*

Although SCL leaves one functioning cricoarytenoid unit, defective glottic closure still represents one of the important causes of swallowing impairment. After SCL, neoglottic closure can be achieved thanks to the posterior motion of the tongue base and of the epiglottis (only in CHEP) and the forward and inward rotation movement of one or both remaining arytenoids [37]. Other neoglottic configurations are described in the literature, although they can be observed less frequently [59–61].

Presently, a standard for assessing swallowing function after partial laryngectomy is still not established. The review of the literature has shown a great variability in measures used to investigate swallowing functional outcomes after SCLs, as reported in Table 2. Studies mainly focused on the presence and severity of tracheal aspiration, presence of cough reflex and diet restrictions. Out of 28 publications reporting swallowing outcomes, aspiration was only clinically assessed according to the Leipzig [62] and Pearson [63] scale or to other non-validated scales in ten studies [35, 43–48, 56, 61, 64–72]; moreover the clinical assessment of dysphagia was performed without using any scale in three papers [10, 42, 55]. An instrumental assessment of swallowing was performed in 11 studies [36–38, 44, 51, 60, 68–72], including either a modified barium swallow test (MBS) [73] or a fiberoptic endoscopic evaluation of swallowing (FEES) [74]. Tracheal aspiration, laryngeal penetration, efficacy of cough reflex, pharyngeal pooling and premature spillage are the main signs investigated; swallowing recuperation defects were also studied [37, 44, 59, 60]. A scoring system of 4- or 5-points was mainly used to report instrumental swallowing assessment's results [36, 41, 62, 68, 70]; only a few studies graded dysphagia according to a validated scale, such as the penetration–aspiration scale (PAS) [75] and the Dysphagia Outcome and Severity Scale (DOSS) [76].

Heterogeneous swallowing functional outcomes after SCL are reported in the literature. By the first postoperativemonth, aspiration ranged from 30 to 100 % [35, 43, 44, 52, 60], occurring more frequently with liquids than with solids and resolving spontaneouslywithin 6 months in 15–80.4 %of the cases [43, 46, 56, 65, 66]. An unrestricted diet is safely achieved between the 6th postoperative month and the 1st postoperative year in the 53–100 %of the patients [40, 45, 46, 48, 60, 70, 71, 77]. In the long-term, between 12.9 and 67 %of the patients are reported to have occasional aspiration [36, 50, 67, 69, 71, 72]. However, a certain degree of chronic aspiration was demonstrated to be well tolerated in patients after SCL, with a rate of aspiration pneumonia ranging between 0 and 21.7 % only [43, 46, 48, 54, 56, 65, 67, 69, 72]. A moderate degree of pharyngeal retention of food, the presence of premature spillage and the necessity of multiple swallows per bolus are also often reported [36, 68, 71, 72].

Woisard et al. studied the recuperation of the events of the pharyngeal phase of swallowing [37]. After CHEP, there were frequent recuperation defects consisting of reduced movement of the back of the tongue, faulty backward tilting of the epiglottis, reduced anterior laryngeal movement and reduced laryngeal elevation. After CHP, there was also reduced movement of the back of the tongue, reduced posterior motion of the tongue base, reduced anterior laryngeal movement and reduced laryngeal elevation. Reduced laryngeal elevation and decreased tongue base retraction were also reported by Lewin et al. occurring, respectively, in the 45 and 27 % of the patients [44]. Moreover, slight abnormalities during preparatory and oral phases, impaired pharyngeal constriction and reduced upper esophageal sphincter (UES) opening have been described [38, 60, 71].

During the last few decades, the interest in quality of life (QOL) and disabilities' impact on daily life has progressively increased. In spite of this, the current literature review has shown that only a few studies included an assessment of swallowing-related QOL [35, 41, 60, 70, 71, 77, 78]. In these, the MD Anderson Dysphagia Inventory (MDADI) [79], the swallowing-quality of life (SWALQOL) [80] and the Performance Status Scale for Head and Neck cancer (PSSHN) [81] were used. The mean MDADI total score is reported to range between 78.4 and 92, suggesting that swallowing difficulties have only little impact on daily living activities [40, 51, 70, 78]. Moreover, it is to be noted that between the 80 and the 90 % of the patients undergoing SCL achieve the ability to eat out without restriction [35, 55].

In the majority of the studies, patients underwent swallowing rehabilitation with a speech-and-language therapist (SLT); however, the mean rehabilitation duration is often missing. Luna-Ortiz et al. showed that patients undergoing rehabilitation started oral feeding without aspiration, on average, 8–13 days before patients not undergoing rehabilitation [35]. Lewin et al. Demonstrated that, in the short-term, diet modifications alone did not consistently reduce or prevent aspiration; on the other hand, aspiration reduction or elimination could be achieved through the use of swallowing strategies that the patient learned during the swallowing rehabilitation course [44].

Different authors have investigated the role of different factors, such as age, arytenoid resection, type of reconstruction and radiotherapy on swallowing functional outcomes following SCL. Clayburgh et al. showed a statistically significant association between age [60 and worse scores on the MDADI (r = -0.72) [40]. Benito et al. reported a significant statistical relationship between aspiration and increased age (p = 0.001) [65]. On the other hand, other authors did not find any correlation between age and swallowing abilities, grade of dysphagia and MDADI scores [64, 78, 82]. A significant impact of the type of reconstruction on swallowing functional outcomes was reported by several authors [37, 64, 65]. In particular, Woisard et al. found an aspiration rate and a rate of absence of cough reflex to be double in patients who had undergone CHP compared to those who had a CHEP [37]. CHP was demonstrated to significantly correlate with higher rate of aspiration (p\0.001) in the study of Benito et al. [65] and with worse grade of dysphagia (p = 0.006) in the study carried by Nemr et al. [64]. Other studies showed no influence of CHP reconstruction vs CHEP on swallowing function outcomes or on swallowing-related QOL [40, 44, 78]. Topalolu et al. [51] reported statistically significant differences in food retention and in general swallowing performances between patients with both arytenoids spared and patients with only one arytenoid spared, with worse performance in the latter. They did not find any differences in premature spillage, in the entrance of bolus in the lower airways and in the MDADI. Moreover, arytenoid resection was demonstrated to significantly influence aspiration rate [65] and correlate with higher aspiration rate [47]. However, no correlation between arytenoid resection and swallowing functional outcomes after SCL was reported in several other studies [40, 44, 57, 64, 71, 77, 78, 83].

Finally, Alicandri-Ciufelli et al. [83] found a statistically significant correlation between radiotherapy and a worse dysphagia score, a higher score on the PAS and a worse score on the MDADI, while Topalolu et al. [51] found a statistically significant influence of radiotherapy on food retention, penetration and aspiration but not on premature spillage and on the MDADI. In contrast, no significant impact of radiotherapy on swallowing outcomes was also reported by other authors [44, 66, 77]. Therefore, at the present time, the role of age, arytenoid resection, type of reconstruction and radiotherapy is still controversial. To the best of our knowledge there is little information about the comparison of swallowing function among patients treated with TL, SCLs, trans-oral laser surgery, TORS or (chemo)radiotherapy alone. Only one study compared the swallowing function in patients treated with SCL and radiotherapy, and concluded that even if a permanent tracheotomy was not required, the patients treated with radiotherapy experienced transient swallowing problems related to hypo-pharyngeal mucositis [84].

*Voice functional outcomes*

In spite of the fact that neoglottic swallowing and voicegenerating mechanisms after undergoing SCLs are due to arytenoid movement and therefore more closely resemble the physiology of the normal larynx rather than that of patients who underwent a TL, laryngeal function is still not normal [40]. In particular, voice impairment has been recognized as major complications in patients subjected to SCL, and can significantly affect their physical and emotional condition [41]. The voice quality is one of the most critical aspects of SCL. This surgical approach completely removes the anterior portion of the glottis plane, and creates a neoglottis, composed of at least one arytenoid cartilage and either the epiglottis or the base of the tongue, depending on whether the epiglottis is resected or not. Both vocal folds are sacrificed at the time of tumour resection.

Voice is produced by pulmonary-driven airflow through the reconstructed larynx. Sphincter function of the neoglottis produces close approximation of the arytenoid cartilages and the base of the tongue, or the epiglottis, providing a mucosal source of vibration for phonation [85].

Therefore, failure in the posterior positioning of the tongue base and the anterior suspension of the arytenoids can cause severe neo-glottal insufficiency. Mucosal vibration can also be variable [18]. In particular, Saito et al. [50] identified different combinations of vibrating regions (arytenoid, sinus, arytenoid/sinus, arytenoid/epiglottis and arytenoid/epiglottis/sinus) and demonstrated that patients who had SCL as salvage surgery after (chemo)radiotherapy have a richer variety of vibration patterns, probably because of the mucosal oedema of the neoglottis induced by preoperative (chemo)radiotherapy.

Thus, in SCL patients, the voice is produced using a neoglottis that is inherently patent at rest and in turn demonstrated substantially less volitionally induced valving activity and resistance to airflow during voicing [15, 18, 50, 60, 72, 86]. The loose and unstable neoglottic closure results in a significant loss of air during phonation that requires an increase in expiratory pressure and strength in the closure of the neoglottis to achieve rigidity and improve the vibration.

The functional consequence is a strained, deep and asexualized voice (difficult to modulate and to raise) and a speech that is composed of short sentences, because the patients grow short of breath rapidly [77].

Different authors have used different methods to assess voice in SCL patients and the definition of guidelines to evaluate the functional results of SCLs has been suggested (Table 3). In particular, maximum phonation time (MPT) appears to be the most widely used aerodynamic parameter.

Most authors reported similar data of a highly reduced MPT, with values ranging between 8 and 11 s [10, 17, 36, 56, 68, 70, 77]. MPT implies adequacy of air support for speech and in SCL patients is quite low, probably due to a lesser resistance of the neoglottis with consequent air loss during phonation [56]. Thus, to compensate for the air wastage during phonation the SCL patient needs to increase the neoglottal resistance and the subglottic pressure with consequent vocal fatigue because of the increased physiological effort required to phonate [36]. Interestingly, MPT appears not to be significantly affected by arytenoid removal, suggesting well-tolerated recovery of the glottal closure after removal of the ipsilateral arytenoid and reconstruction of the neoglottis [17].

The GIRBAS scale is one of the most widely used scales for perceptual voice evaluation. The values reported in the international literature confirm that SCL voice is characterized by moderate to severe alterations in roughness and grade, slight to moderate alterations in breathiness, slight or practically absent alterations in asthenicity and slight or moderate alterations in strain [48, 60, 77]. Only a few studies used a more specific perceptual assessment scale, such as the INFVo scale, to evaluate the voice characteristics of patients treated with supracricoid partial laryngectomy [84, 87].

Voice after SCLs has also been analysed acoustically. Authors reported a marked degraded voice signal characterized by wider fundamental frequency (Fo) range and high jitter, shimmer and noise to harmonics ratio (NHR) values [17, 35, 50, 68]. Fo depends on the relation between pressure of the lungs and vibratory source characteristics, which in turn relies on the activity of the laryngeal intrinsic musculature, the length of the vocal folds and the passive tension of the vocal folds mucous membrane. As the vibrating source changes substantially after surgery, this could explain the wider Fo range of the operated patients.Adetermining factor is the thickening of the vibrating neoglottis because the base of the tongue and the arytenoid mucosa and/or epiglottis mucosa are involved. The differing vibratory capacity of the neoglottis is characterized by pitch and peak irregularities.

Because of incomplete closure, the linear vibratory characteristics change to an unstable vibratory pattern with an increase in shimmer and jitter levels. It should also be noted that other authors preferred not to perform any perturbation analysis since a high percentage of subjects treated with SCLs showed non-harmonic voice, and therefore were considered unsuitable for this kind of analysis [70].

Nonetheless, SCL patients possessed good speech intelligibility and only a minimal degree of prosodic insufficiency [17, 35, 36, 48, 87].

Self-assessment data revealed a moderate impact on voice related QOL (V-RQOL) in terms of speech after SCLs, on the emotional, physical and functional levels of the VHI, even if some authors reported high degrees of vocal handicap [14, 40]. It must be noted that V-RQOL brings many factors into play, including the patient's psychosocial traits, cultural and ethnic backgrounds. Therefore, it is not surprising that different authors report different VHI scores on a small number of subjects studied in different countries. Besides, since the voice ismainly used for every day verbal communication, it is possible that vocal QOL is perceived by the patients as not being very compromised, even if the voice per se is rather poor [15, 70]. It must also be noted that recently new tools have been proposed to evaluate the rehabilitation needs and the psychosocial care for patients with laryngeal cancer. In particular, the self-evaluation of communication experiences after laryngectomy (SECEL) is a short, but comprehensive self-report instrument thatmeasures the perceived adjustment to communication experiences and is intended to aid in determining counselling needs in laryngeal cancer patients treated with laryngectomy [88, 89]. To the best of our knowledge, no study tried to compare the functional results in patients treated with SCL and (radio)chemotherapy. A comparison of the functional results of TL and SCL demonstrate a few scarce and diverging results. Wenstein et al. [16] demonstrated that subjects treated with SCL had significant higher domain scores thanTLpatients in general quality of life (QOL)

analysed through SF-36. Torrejano et al. [17] found that TL patients scored significantly better than SCL patients in VR-QOL measures. So et al. [18] compared the speech outcomes of partial and TL and reported a VHI score of 61.7 and 49.8, respectively. Finally Schindler et al. [15] who compared functional vocal results among patients treatedwith SCL,TL and horizontal glottectomy, reported thatTL patients scored significantly higher in the G and R parameters of the GRBAS scale, while no differences were reported in the aerodynamic, acoustic and QOL measures.
In conclusion, the poor voice functional results of SCL remain one of the most critical aspects in this type of surgery. For this reason a modification of the surgical procedure has been recently proposed. Allegra et al. [85] performed a modified supracricoid laryngectomy (MSCL) using the sternohyoid muscles: they are isolated and detached from the hyoid bone and then linked on the midline, placed on the free margin of the cricoid, anchored to the vocal apophysis of the arytenoids and covered by the redundant mucosa overlying the arytenoids. This technique demonstrated that the postoperative course of the patients is similar to the patients treated by SCL, but patients treated by MSCL have a better voice quality with a better fluency, intelligibility and voicing. Patients treated by MSCL also scored lower on the VHI.

*Need for the future*

The analysis on time of hospital stay, feeding tube removal and tracheotomy closure showed a marked variability among authors and centres. Several factors may come into play, including health system organizations in different countries.
While in some centres, ad hoc rehabilitative departments are available after discharge, in others patients are sent home without any further support. Nonetheless, what is most surprising is the fact that the vast majority of authors did not explain the criteria adopted for discharge, feeding-tube removal and tracheal-cannula removal in detail. Therefore, one of the major needs for the future is to have clearer criteria for these important clinical decisions to be applied in a standardized manner by those centres performing SCLs as laryngeal cancer treatment modality. This might reduce important complications, such as aspiration pneumonias and malnutrition, after undergoing SCLs.

The swallowing functional outcome review not only showed wide variability, but also a lack of consensus on how to assess swallowing after SCL. Some authors used instrumental assessments while some others employed only clinical ones often applying not-validated outcome scales.

The major need for the future is therefore to build consensus for a common protocol to be applied for the analysis of swallowing outcomes. The analysis of voice functional outcomes revealed interesting findings; as for the other areas of functional results there was a wide variation. What was most surprising, however, were the tools applied for the assessment, very often adopted from normal laryngeal voicing and not adequate for substitution voice. For instance some authors used traditional acoustic parameters such as jitter and shimmer: these acoustic parameters are used in laryngeal voicing with regular vibratory function, not often found in substitution voices [90, 91]. Also for perceptual assessment, the GIRBAS scale was adopted by many authors without considering the importance of other validated tools such as the INFVo [87, 92, 93]. Even if the VHI is the most commonly used tool worldwide for VRQOL analysis, several authors found that its application in patients post laryngectomy was questionable and other ad hoc validated tools, such as the SECEL, seem better suited [88, 89, 94–96]. The analysis on voice outcome revealed that voice seems to be the most severely impaired function after SCL; the possibility of surgical rehabilitation strategies including, injection laryngoplasty should be investigated in the future. Preliminary data exist on the possibility to fill areas of neoglottic incompetence with polydimethylsiloxane to improve airway protection during swallowing; the possible implications for voice production have not been measured, but there is a theoretical possibility to improve glottis incompetence [97]. Other authors injected autologous fat or bovine collagen into arytenoid mucosa with the aim to increase thickness of the vibrating mucosa; however, no data are available on the improvement on voice production [98].

Throughout the review it appeared that SCLs allow satisfactory functional results but surgical protocols need to be followed by adequate nursing and rehabilitation protocols. At the moment there is, however, no evidence on when rehabilitation should start,which are the criteria to be adopted to start and to end it and what are the voice and swallowing rehabilitation procedures giving the best functional outcomes.

In conclusion, SCLs are proven surgical procedures for the treatment of selected laryngeal cancers; voice and swallowing functional results are often satisfactory, but the variability across centres is still too large. There is a need for the future to have consensus and clinical recommendations on early post-surgical management, criteria adopted for tracheal-cannula and feeding tube removal, voice and swallowing assessment protocol and timing for rehabilitation.

Further information regarding the comparison among different treatment approaches (e.g., trans-oral laser surgery, TORS, TL, SCL and chemoradiotherapy) are also needed to help the clinician to make a better decision involving management of his or her patients

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## Table 1 Duration of hospital day, feeding tube and tracheotomy after SCL

| Author (year) | No. cases | Time hospital stay (days) | NGT removal time (mean, days) | Decannulation | | Remarks |
|---|---|---|---|---|---|---|
| | | | | (Rate) | (Days) | |
| Laccourreye et al. [56] | 20 | / | 18 | 100 % | 10 | 20 CHEP |
| Woisard et al. [37] | 14 | / | 10 | / | 9 | 11 CHEP<br>3 CHP |
| de Vincentiis et al. [10] | 149 | / | 15 (CHEP)<br>28 (CHP) | 98 % (CHEP)<br>85.7 % (CHP) | 25 (CHEP)<br>30 (CHP) | 51 CHEP<br>98 CHP |
| Laccourreye et al. [43] | 69 | / | / | 97.2 % | 8 | 53 CHEP<br>16 CHP |
| Naudo et al. [46] | 190 | 23 | 16 | 99.5 % | 9 | 190 CHEP |
| Bron et al. [84] | 69 | 36 (CHEP)<br>51 (CHP) | 22 (CHEP)<br>18 (CHP) | / | 30 (CHEP)<br>30 (CHP) | 60 CHEP<br>9 CHP |
| Bussi et al. [38] | 44 | 30.5 | 16 | 97.7 % | 91 | 44 CHEP |
| Lima et al. [54] | 27 | | 40 | 92.6 % | 38 | 27 CHEP |
| Luna-Ortiz et al. [35] | 15 | 11 | 23 | / | 12 | 15 CHEP |
| Marioni et al. [45] | 16 | / | 21 | 93.7 % | 56 | 14 CHEP<br>2 CHP |
| Akbas et al. [52] | 45 | 43 (1 ARY)<br>24 (2 ARY) | 40 (1 ARY)<br>21 (2 ARY) | 100 % | 42 (1 ARY)<br>20 (2 ARY) | 45 CHP<br>1 ARY = 17;<br>2 ARY = 28 |
| Farrag et al. [53] | 24 | 6 | 70 (PEG) | 95.8 % | 37 | 18 CHEP<br>6 CHP |
| Pellini et al. [48] | 82 | / | 15 | 91 % | 19.3 | 82 CHP |
| Lewin et al. [44] | 27 | 7.7 | / | / | 37 | 20 CHEP<br>7 CHP |
| Nakayama et al. [55] | 32 | 104 | 21 | 100 % | 15 | 29 CHEP<br>3 CHP |
| Saito et al. [50] | 24 | / | 38 (IVH cannula) | 95.8 % | 52 (stoma closure) | 23 CHEP<br>1 CHP |
| Decotte et al. [42] | 101 | / | / | / | 8 | 87 CHEP<br>14 CHP |
| Gonçalves et al. [58] | 20 | 5 | 71 | 90 % | 105 | 16 CHEP<br>4 CHP |
| Webster et al. [60] | 10 | / | 82 | / | / | 8 CHEP<br>2 CHP |
| Park et al. [47] | 116 | 38.1 (CHEP)<br>50.4 (CHP)<br>43.7 (1 ARY)<br>40.8 (2 ARY) | 22.6 (CHEP)<br>31.6 (CHP)<br>27.3 (1 ARY)<br>24.2 (2 ARY) | / | 16.8 (CHEP)<br>23.2 (CHP)<br>23.3 (1 ARY)<br>16.8 (2 ARY) | 83 CHEP<br>33 CHP<br>1 ARY = 32<br>2 ARY = 84 |
| Rizzotto et al. [49] | 399 | 18 | 15.9 | 98.3 % | 24 | 272 CHEP<br>127 CHP |
| Topaloglu I et al. [51] | 30 | / | 27.3 | 100 % | 23.6 | 30 CHP |
| Caicedo-Granados et al. [39] | 28 | 13 | / | 93 % | 56 | 24 CHEP<br>4 CHP |
| Clayburg et al. [40] | 18 | 7.3 | 88 | 100 % | 27.4 | 13 CHEP<br>5 CHP |
| Maoxiao et al. [59] | 46 | / | / | 93.5 % | 19 | 44 CHEP<br>2 CHP |
| Crosetti et al. [41] | 45 | / | 15 | / | 39 | 36 CHEP<br>9 CHP |

**Table 2 Literature review of swallowing functional outcomes after SCL**

| Author (year) | No. cases | Surgery | RT | Rehabilitation | Follow-up period | Instrumental assessment | Self-assessment | Swallowing scales | Swallowing functional outcomes |
|---|---|---|---|---|---|---|---|---|---|
| Clayburgh et al. [40] | 18 | 13 CHEP<br>5 CHP | NA | Yes | 7 months–5 years | None | MDADI | None | 67 % unrestricted diet<br>Mean MDADI = 78.4 |
| Pinar et al. [66] | 56 | 13 CHEP<br>43 CHP | 25 % post | NA | 14 months–10 years | None | None | Pearson and Leipzig scale | 80.4 % temporary grade 1 or 2 aspiration<br>3.6 % total laryngectomy due to aspiration |
| Topalolu et al. [51] | 30 | CHP | 3.3 % pre, 26.7 % post | NA | 17–97 months | FEES | MDADI | 5-point scale (Zacharek et al. [36]) | Few patients with premature spillage on average satisfactory swallowing ability<br>Mean MDADI = 83.6 |
| Alicandri-Ciufelli et al. [61] | 6 | 5 CHEP<br>1 CHP | NA | Yes | >6 months | None | None | Dysphagia score | 33 % no symptoms of dysphagia;<br>50 % grade 1 aspiration<br>16.7 % grade 2 aspiration |
| Benito et al. [65] | 457 | 272 CHEP<br>161 CHP<br>24 THEP | 3.7 % pre, 12.5 % post | Yes | AVG 8 years | None | None | Pearson and Leipzig scale | 58.9 % normal swallowing by 1st month<br>29.5 % temporary aspiration<br>11.6 % aspiration pneumonia |
| Castro et al. [78] | 26 | 21 CHEP<br>5 CHP | NA | NA | 3–112 months | None | MDADI | None | Mean MDADI = 92 |
| Simonelli et al. [72] | 116 | NA | NA | Yes | 3–13 years | FEES, MBS | None | Pearson and Leipzig scale | 38.8 % aspiration<br>0 % pulmonary complications<br>27.6 % pharyngeal pooling<br>21.5 % premature spillage |
| Webster et al. [60] | 10 | 8 CHEP<br>2 CHP | 40 % pre | Yes | 3 weeks/2 months/1 year | MBS | SWAL-QOL | 4-point scale | 3 weeks: no patients tolerated thin liquids<br>30 % aspiration of purees<br>6 months: 67 % reported eating regular diet<br>1 year: 80 % safely swallowed all consistencies<br>67 % occasional silent aspiration<br>89 % reported eating regular diet |
| Portas et al. [71] | 11 | CHEP | 9 % post | NA | 6–18 months | MBS | SWAL-QOL | PAS, DOSS | 45.5 % aspiration<br>54.5 % normal swallowing |

**Table 2 Continued**

| Author (year) | No. cases | Surgery | RT | Rehabilitation | Follow-up period | Instrumental assessment | Self-assessment | Swallowing scales | Swallowing functional outcomes |
|---|---|---|---|---|---|---|---|---|---|
| Lewin et al. [44] | 27 | 20 CHEP<br>5 CHP<br>2 THEP | 63 % pre | Yes<br>6 times | 1–9.5 weeks/ 2–33 weeks | MBS | None | None | 1st ass: 100 % aspiration with liquids; 55 % aspiration with foods; 27 % silent aspiration<br>2nd ass: 94 % aspiration with liquids; 33 % aspiration with foods; 33.3 % silent aspiration |
| Nakayama et al. [55] | 32 | 29 CHEP<br>3 CHP | NA | Yes, 6–62 days + 18.8 % > 2 months | NA | None | Interview | None | 90 % achieved the ability to eat out<br>6.3 % did not return to work because of swallowing difficulties |
| Nemr et al. [64] | 22 | 15 CHEP<br>7 CHP | NA | Yes | NA | None | None | O'Neils et al.'s protocol (1999) [76] | 59 % moderate dysphagia<br>41 % severe dysphagia |
| Pellini et al. [48] | 82 | CHP | 20.7 % pre | Yes | 3 mo | None | None | Pearson and Leipzig scale | 88 % satisfactory swallowing within 3 months<br>8.5 % aspiration pneumonia |
| Schindler et al. [70] | 20 | NA | 15 % post | Yes | NA | FEES | MDADI | 5-point scale (Zacharek et al. [36]) | On average satisfactory deglutition<br>Mean MDADI = 80 |
| Yücetürk et al. [69] | 10 | CHP | NA | Yes | > 6 mo | MBS | None | Pearson and Leipzig scale | 20 % slight aspiration of liquids<br>0 % aspiration pneumonia<br>0 % dietary limitation for liquids |
| Luna-Ortiz et al. [35] | 15 | CHEP | None | Yes | 1 mo | None | PSSHN | Pearson and Leipzig scale | 20 % no complications and 80 % occasional cough<br>8.3 % ate only soft foods<br>80 % ate in public without any restriction |
| Marioni et al. [45] | 16 | 14 CHEP<br>2 CHP | 6.3 % post | 12.5 % | AVG 22 mo | None | None | Dysphagia score | 93.7 % close-to-normal diet within 12 months |
| Dworkin et al. [68] | 10 | NA | NA | NA | 5–28 months | 70 % FEES; 30 % MBS | None | 5-point scale | Moderate degree of premature spillage and laryngeal penetration; food pooling in all subjects |
| Bron et al. [77] | 17 | CHEP | 11.7 % pre, 17.6 % post | NA | 1–12 years | None | PSSHN | None | 53 % normal diet<br>37 % slight limitations<br>11 % serious change in diet |
| Lima et al. [54] | 27 | CHEP | 7.4 % post | Yes | NA | None | None | None | 92.6 % mild aspiration which resolved spontaneously with SLT<br>4 % severe aspiration and aspiration pneumonia |

**Table 2 Continued**

| Author (year) | No. cases | Surgery | RT | Rehabilitation | Follow-up period | Instrumental assessment | Self-assessment | Swallowing scales | Swallowing functional outcomes |
|---|---|---|---|---|---|---|---|---|---|
| Zacharek et al. [36] | 10 | 6 CHEP<br>4 CHP | NA | NA | 5–28 months | 70 % FEES; 30 % MBS | None | FEES: 5-point scale; MBS: PAS | 30 % aspiration<br>100 % signs of laryngeal penetration with strong cough |
| Bussi et al. [38] | 44 | CHEP | 4.5 % post | Yes | 6–109 months | FEES, MBS | None | None | 93.2 % satisfactory deglutition |
| Laccoureye et al. [43] | 69 | 48 CHEP<br>16 CHP<br>5 THEP | 4.3 % pre | Yes | 3–16 years | None | None | Pearson and Leipzig scale | 52.1 % normal swallowing by the 1st month<br>26.2 % temporary grade 1–2 aspiration for 1–6 months<br>18.8 % grade 3 aspiration<br>21.7 % aspiration pneumonia |
| Naudo et al. [46] | 190 | CHEP | 2.6 % pre, 3.1 % post | Yes | >14 months | None | None | Pearson and Leipzig scale | 68.1 % normal swallowing by the 1st months<br>23.4 % grade 1–2 aspiration for 1–4 months<br>98.4 % normal swallowing by the 1st year<br>8.5 % aspiration pneumonia |
| de Vincentiis et al. [10] | 104 | 48 CHEP<br>56 CHP | NA | NA | NA | None | None | None | 71.2 % no swallowing problems<br>8.7 % occasional inhalation |
| de Vincentiis et al. [67] | 70 | CHP | NA | NA | 12–120 months | None | None | None | 12.9 % occasional aspiration<br>7.1 % aspiration pneumonia |
| Laccoureye et al. [14] | 20 | CHEP | None | NA | >3 years | None | None | Pearson and Leipzig scale | 15 % temporary grade 1 aspiration for 2–8 months<br>5 % aspiration pneumonia |
| Woisard et al. [37] | 14 | 11 CHEP<br>3 CHP | None | NA | 12–96 months | MBS | None | None | CHEP: 36.4 % aspiration of small volume with liquids; 27.3 % diminished/absent cough reflex<br>CHP: 66.7 % aspiration of small volume with liquids; 66.7 % diminished/absent cough reflex |

*RT* radiotherapy, *CHEP* cricohyoidoepiglottopexy, *CHP* cricohyoidopexy, *THEP* tracheohyoidoepiglottopexy, *NA* data not available, *pre* preoperative, *posto* postoperative, *AVG* average, *wk(s)* weeks, *mo* months, *yr(s)* year(s), *FEES* fiberoptic endoscopic evaluation of swallowing, *MBS* modified barium swallow, *MDADI* MD Anderson dysphagia inventory, *SWAL-QOL* swallowing quality of life questionnaire, *PAS* penetration–aspiration scale, *DOSS* Dysphagia Outcome and Severity Scale, *1st ass* 1st assessment, *2nd ass* 2nd assessment

**Table 3 Literature review of voice functional outcome after SCL**

| Author (year) | N. cases | Surgery | RT | Rehabilitation | Follow-up period | Instrumental assessment | Self-assessment | Scales | Voice functional outcomes |
|---|---|---|---|---|---|---|---|---|---|
| Crosetti et al. [41] | 80 | 23 SL<br>36 CHEP<br>9 CHP<br>12 STPL | 16.3 % | Yes | 10 years | None | VHI | GIRBAS | 66.7 % of SCPL patients have moderate grade of dysphonia, 33.3 % have severe dysphonia<br>62.2 % of SCPL patients perceived a low level of vocal handicap, 17.8 % perceived an high degree of vocal handicap |
| Schindler et al. [15] | 96 | 24 TL<br>7 SCPL<br>9 Other partial laryngectomies | NA | NA | NA | Syllable diadochokinesis, MPT, speech rate | VHI | GIRBAS | TL group showed significantly higher scores of G, R<br>Mean VHI in SCPL patients = 30.1 |
| Allegra et al. [85] | 28 | 11 SCPL<br>17 MSCPL | NA | Yes | NA | Laryngostroboscopy | VHI | INFVo | Better quality of voice in patients treated by modified supracricoid partial laryngectomy with a significant difference in intelligibility, fluency, and voicing |
| So et al. [18] | 28 | 15 SCPL<br>13 TL-VP | NA | NA | NA | MPT, maximum loudness, number of syllables per breath, speech intelligibility, Laryngostroboscopy | VHI | None | MPT was longer in the TL-VP<br>No significant difference in the other parameters between the groups<br>Stroboscopic examination demonstrated variable findings with reference to arytenoid mobility, mucosal vibration, and neo-glottic occlusion in the SCPL group |
| Saito et al. [50] | 24 | 23 CHEP<br>1 CHP | NA | NA | 48.8 months | Laryngostroboscopy, F0, MPT, frequency range, intensity, jitter, shimmer, NHR | PSS-HNC<br>V-RQOL | GRBAS | Rough and breathy voice after SCPL<br>mean MPT = 10.6 s<br>F0 = 100 Hz<br>Wider range of intensity in cases without arytenoid removal<br>Jitter = 9.5 %, Shimmer = 17.8 %, NHR = 0.42<br>QOL of patients in terms of speech was tolerable |
| Torrejano et al. [17] | 30 | 10 SCPL<br>20 TL + VP | NA | Yes | 46 months | F0, Jitt % | 5 points questionnaire | GRBAS | Better voice in the TL-VP |
| Portas et al. [71] | 11 | CHEP | 9 % post | NA | 6–18 months | Spectrographic evaluation<br>Auditory perception analyses | VHI | NA | Severe dysphonia = eight patients<br>Moderate dysphonia = three patients<br>High-grade noise on spectrographic evaluation<br>Good quality of life regarding voice |

**Table 3 Continued**

| Author (year) | N. cases | Surgery | RT | Rehabilitation | Follow-up period | Instrumental assessment | Self-assessment | Scales | Voice functional outcomes |
|---|---|---|---|---|---|---|---|---|---|
| Pellini et al. [48] | 82 | CHP | 20.7 % pre | Yes | 3 months | MPT | none | 4-point scale | MPT = 7.9 s<br>Voice quality = 3 % nonhoarse, 40 % slightly hoarse, 31 % moderately hoarse, and 27 % severely hoarse |
| Schindler et al. [70] | 20 | NA | 15 % post | Yes | NA | MPT, syllables diadochokinesis, spectrogram | VHI | 5-point scale, GIRBAS | Moderate to severe impairment of neoglottal vibration<br>MPT = 7.5 s<br>Yanagihara score = 3.7<br>Syllable diadochokinesis = 3.3 syll/s<br>Voice quality of life questionnaires revealed satisfied patients |
| Luna-Ortiz et al. [35] | 15 | CHEP | None | Yes | 1 months | F0, Mean intensity | PSS-HNC | None | Intelligibility average = 90<br>F0 = 243.7 Hz (abnormal in one patient)<br>Intensity was −18 dB below normal |
| Marioni et al. [45] | 16 | 14 CHEP<br>2 CHP | 6.3 % post | 12.5 % | AVG 22 months | None | None | 5-point scale | Vocal quality of all patients' voices was described as significantly rough and breathy<br>Satisfactory voice intelligibility was achieved in 81.2 % |
| Dworkin et al. [68] | 20 | 10 SCPL<br>10 TL | NA | Yes | 5–28 months | F0, Jitter, Shimmer, NHR, MPT, laryngostroboscopy | VHI | 5-point scale | High level of speech intelligibility and fluency<br>Moderate degree of hoarse-strained vocal quality<br>No differences in VHI between TL anc SCPL patients<br>Moderately impaired neoglottal vibratory biomechanics |
| Bron et al. [77] | 17 | CHEP | 11.7 % pre<br>17.6 % post | NA | 1–12 years | F0, vocal intensity, MPT | PSSHN | GRBAS | F0 = 70.1 Hz<br>Decreased intensity range of phonation in SCPL<br>Decreased MPT in SCPL<br>All voices were generally described as rough, breathy, and strained and scored as severe dysphonia |

**Table 3 Continued**

| Author (year) | N. cases | Surgery | RT | Rehabilitation | Follow-up period | Instrumental assessment | Self-assessment | Scales | Voice functional outcomes |
|---|---|---|---|---|---|---|---|---|---|
| Zacharek et al. [36] | 10 | 6 CHEP<br>4 CHP | NA | NA | 5–28 months | F0, Jitter, Shimmer, NHR, laryngostroboscopy | VHI | 5-point scale | High levels of vibratory amplitude variability<br>MPT approximately half the normal value<br>All patients were perceived to have moderate to severe degrees of breathy-hoarse vocal quality<br>VHI mean score = 61 |
| Naudo et al. [46] | 190 | CHEP | 2.6 % pre, 3.1 % post | Yes | >14 months | None | None | None | Phonation by the 12th postoperative month was assessed as good, satisfactory, and insufficient in 86, 11, and 3 % of the patients, respectively |
| de Vincentiis et al. [10] | 104 | 48 CHEP<br>56 CHP | NA | NA | NA | F0, MPT, laryngostroboscopy | None | None | Good social reintegration on a social and working levels; F0 of the voice of operated patients was 154 Hz |
| Laccoureye et al. [56] | 42 | 14 CHEP<br>14 CHP<br>14 NAL | None | NA | NA | MPT, speech rate, phrase grouping, F0, Jitter, Shimmer, NHR | None | None | SCPL speech was statistically less efficient than NAL speech in F0 range, Jitter, Shimmer, NHR, speech rate, MPT and phrase grouping |

*RT* radiotherapy, *CHEP* cricohyoidoepiglottopexy, *CHP* cricohyoidopexy, *STPL* supratracheal laryngectomy, *TL* total laryngectomy, *NA* data not available, *AVG* average, *mo* months, *yr(s)* year(s), *NAL* normal adult laryngeal, *Fo* average fundamental frequency (Hz), *vFo* fundamental frequency variation (%), *vAm* peak-amplitude variation (%), *Jitter* Jitter percent (%), *Shimmer* Shimmer percent (%), *NHR* noise to harmonic ratio, *VTI* voice turbulence index, *SPI* soft phonation index, *DVB* degree of voice breaks (%), *DSH* degree of sub-harmonics (%), *DUV* degree of unvoiced voice (%), *MSCPL* modified supracricoid laryngectomy, *ESGP* estimated subglottic pressure, *MPT* maximum phonation time, *OAF* oral air flow, *SNR* signal-to-noise ratio

## Paper 3

### *Long-term functional results after open partial horizontal laryngectomy type IIa and type IIIa: A comparison study*

*Background.* The purpose of this study was to compare long-term swallowing, voice results, and quality of life (QOL) after open partial horizontal laryngectomy (OPHL) type IIa and type IIIa.

*Methods.* Twenty-three patients after OPHL type IIa and 18 patients after OPHL type IIIa were involved. Swallowing skills and neoglottis' motility and vibrations were videoendoscopically assessed. Aerodynamic measures, spectrogram analysis, aspiration pneumonia, body weight variations, and voice perceptual assessment were performed. Generic voicerelated and swallowing-related QOL were assessed. Data were statistically compared using Mann–Whitney U test or Fisher exact tests, as appropriate.

*Results.* Significant differences were found only for the residue with solids and for the intelligibility (I) parameter of the overall quality impression and intelligibility, additive and unnecessary noise, speech fluency, and presence of voiced segments scale with patients of the OPHL type IIIa group showing worse performances than the OPHL type IIa group.

*Conclusion.* Patients who underwent OPHL type IIa and type IIIa show comparable long-term functional outcomes. OPHL type IIIa represents a valid surgical alternative to OPHL type IIa.

INTRODUCTION

Several treatment options are available in the management of laryngeal cancer, including surgical and nonsurgical approaches. Among these, organ-sparing treatment and surgical function-sparing protocols allow functional preservation and therefore avoid the necessity of a permanent tracheostoma, which causes cosmetic disability and results in a decreased quality of life (QOL).[1–3] At the present time, a consensus on the best treatment option for laryngeal cancer has not been reached. Similar overall survival, diseasefree survival, and locoregional control rates are reported in literature after total laryngectomy, partial laryngectomy, radiotherapy (RT), and chemotherapy.[4–14] Therefore, the study of long-term functional outcomes is essential to guide clinicians in the choice of the therapeutic option. Open partial horizontal laryngectomies (OPHLs) are conservative surgical techniques for the treatment of selected laryngeal carcinomas. In particular, OPHL type II or supracricoid laryngectomy and OPHL type III or supratracheal laryngectomy are indicated in the treatment of T2 to T4 laryngeal tumors with glottic and subglottic extension.

Maintaining at least one functioning cricoarytenoid unit (i.e. half of the posterior cricoid plate), with the corresponding arytenoid and the intact inferior laryngeal nerve of the same side, OPHL type II and type III allow the preservation of the main laryngeal functions (respiration, phonation and swallowing) and not require a permanent tracheostoma. In OPHL type II, the resection interests the entire thyroid cartilage with the inferior limit represented by the upper edge of the cricoid ring, whereas in OPHL type III, the resection is extended toward the cricoid. The suprahyoid part of the epiglottis and both cricoarytenoid units may be spared; on this basis, according to the classification proposed by the European Laryngological Society, OPHL type II and III can be distinguished as follows: (1) in OPHL type IIa and type IIIa, both cricoarytenoid units and the suprahyoid portion of the epiglottis are preserved; (2) in OPHL type IIa and type IIIa plus arytenoid resection (1A), the suprahyoid portion of the epiglottis is preserved and the resection is extended to one cricoarytenoid unit; (3) in OPHL type IIb and type IIIb, both cricoarytenoid units are preserved and the resection is extended to the whole epiglottis; and (4) in OPHL type IIb and type IIIb 1A, the resection is extended to the whole epiglottis and to one cricoarytenoid unit.[15]

With the first description of OPHL type III in 2006, the concept of extension-modulated surgery was introduced in the field of laryngeal cancer treatment.[11,16] Therefore, OPHL type II operations can be intraoperatively converted into OPHL type III by the surgeon, in order to assure the tumor's complete excision. For this reason, it is important to know whether or not an intraoperative modification of the surgical procedure from type II to type III can have an impact on long-term outcomes.

Important laryngeal anatomic modifications are caused both by OPHL type II and type III. The sphincteric action of the neoglottis is achieved through the approximation of the arytenoid cartilage(s) and the base of the tongue, together with the epiglottis in OPHL type IIa and IIIa, providing a mucosal source of vibration for phonation during the airflow passage. An anatomic continuity is preserved between the oropharynx and the lower airways. Therefore, both voice and swallowing functions are affected by these types of surgery and patients could experience dysphonia and some degree of dysphagia, with a possible impact on QOL.

In the literature, several authors investigated long-term functional outcomes after OPHL type II6,[17–26]; moreover, preliminary long-term functional results after OPHL type III were described.[27] However, to the best of our knowledge, only 1 study has compared long-term functional outcomes after OPHL type II and type III.[28] Crosetti et al[28]investigated voice and swallowing function in 23 patients who underwent OPHL type I, 45 patients who underwent OPHL type II, and 12 patients who underwent OPHL type III aged over 70 years in order to analyze the effects of aging on the operated larynx. It is known that the phenomena of presbyphonia and presbyphagia can occur with aging. Therefore, results reported by Crosetti et al[28] cannot be generalized to all patients undergoing OPHL.

The purpose of the present study was to investigate and compare long-term results of swallowing, voice, and QOL after OPHL type IIa and after type IIIa. We focused on type IIa 1A and type IIIa 1A as these are by far the surgical procedures more frequently performed within OPHLs.[11] We hypothesized that a wider extension of surgical resection would be associated with worse functional outcomes and, therefore, that patients undergoing OPHL type IIIa would experience a higher level of dysphonia and dysphagia, as well as a greater perceived disability than patients undergoing OPHL type IIa. Results of the study could guide clinicians in the conduction of preoperative and postoperative counseling on long-term outcomes of OPHL type IIa and type IIIa in order to give patients precise and realistic information if intraoperatively modification of the surgical procedures is hypothesized, according to the modular approach.

## *MATERIALS AND METHODS*

This cross-sectional outcomes study was carried out according to the Declaration of Helsinki and it was previously approved by the institutional review board. All subjects enrolled in the study gave their written informed consent; all data were collected prospectively.

*PATIENTS*

Patients were randomly selected from a database reporting data of patients who underwent OPHL at the Department of Otorhinolaryngology of the Martini Hospital of Turin and of the Civil Hospital of Vittorio Veneto in the last 12 years.

Selection criteria were: OPHL type IIa or type IIIa, arytenoid resection, no RT performed, no evidence of disease at the last follow-up, preservation of respiration and speech, nonenteral feeding (percutaneous endoscopic gastrostomy or nasogastric tube), absence of the tracheostoma, no salvage total laryngectomy performed, and >6 months after surgery. Twenty-three patients who underwent OPHL type IIa and 18 patients who underwent OPHL type IIIa were included in the study. Sociodemographic and clinical factors of the two groups were investigated and are reported in Table 1 because of their impact on functional outcomes and QOL.

Voice and swallowing rehabilitation with a speech and language pathologist (SLP) was performed in 13 of 23 patients (56.5%) who underwent OPHL type IIa and in 9 of 18 patients (50%) who underwent OPHL type IIIa, with a median duration of 12 weeks (range, 4–80 weeks) in the first group and 7 weeks (range, 4–24 weeks) in the second group.

*Swallowing assessment*

Swallowing was assessed through the fiberoptic endoscopic evaluation of swallowing (FEES).[29] The study was conducted using an Olympus Evis Exera II 18 endoscopy system and an Olympus ENF VQ transnasal flexible endoscope (Olympus Corporation, Tokyo, Japan); each FEES was video recorded. Swallowing of liquids, semisolids, and solids was assessed using room temperature blue dyed water, pudding, and crackers. A 5-cc bolus was given to each participant 3 times for liquids and semisolids.

Premature spillage and piecemeal deglutition were scored as present or absent. Spillage was defined as bolus falling over the base of the tongue or lower before whiteout; piecemeal deglutition was defined as division of the bolus into 2 or more swallows successively rather than swallowing the entire bolus in one. Laryngeal penetration and aspiration and the ability to cough or clear aspirated substances were assessed through the 8-point Penetration-Aspiration Scale (PAS); a score of 1 is associated with no materials entering the airway, whereas a score of 8 means aspiration without any effort to reject materials.[30,31] Retention of the bolus was evaluated using the Pooling Score.[32] The Pooling Score, ranging between 4 and 11, is assigned on the basis of the site (range, 1–4), the amount (range, 1–3), and the management of the pooling (range, 2–4); the higher the score, the lower the pooling's site, the greater its amount, the lower the ability to clean it.

The Dysphagia Outcome and Severity Scale (DOSS), a validated and reliable 7-point scale, was used to rate functional severity of dysphagia.[33] The DOSS level, ranging between 7 ("normal in all situations") and 1 ("severe dysphagia, non-peroral nutrition, unable to tolerate any peroral nutrition safely"), is defined on the basis of the objective assessment, the necessity of diet modifications, the independence level, and the type of nutrition required. The onset of aspiration pneumonia after surgery was recorded. The difference between presurgery and postsurgery weight was calculated.

*Voice and speech assessment*

A videolaryngoscopic examination of each patient was made using an Olympus Evis Exera II 18 endoscopy system and an Olympus ENF VQ transnasal flexible endoscope (Olympus Corporation). The patients were asked to produce in order the following tasks: a sustained "i," a low-pitched "i," a high-pitched "i," a low-intensity "i," and a highintensity "i." The following variables were assessed: (a) vibratory characteristics of the neoglottis; (b) degree of arytenoids motion; and (c) sphincteric closure of the larynx.

Each variable was scored on a 5-point rating scale from 1 (poor performance) to 5 (excellent ability), as suggested by Zacharek et al.[21]

The maximum phonation time (MPT) was measured on the production of 3 sustained "a." The longest phonation time was recorded. Diadochokinesis was assessed by asking each subject to utter the syllable "pa" and the trisyllable "pataka" as fast as possible. The Computerized Speech Laboratory (CSL) program, version 5.05, with a 4300 external module (Kay Elemetrics, Lincoln Park, NJ) was used. Syllable and trisyllable diadochokinesis were rated respectively in syllable/second and trisyllable/second.

The patients were asked to read a 56-word and 99-syllable passage34 and they were audio recorded with a microphone Samson Go Mic (Samson Technologies, Hauppauge, NY) and the Apple Soundtrack Pro, version 3.0.1, software using a 50 kHz sample rate (Apple, Cupertino, CA). The time needed to read the passage as well as the syllable/second speed in reading were calculated.

Both the grade, instability, roughness, breathiness, asthenia, and strain (GIRBAS) scale35 and the overall quality impression and intelligibility, additive and unnecessary noise, speech fluency, and the presence of voiced segments rating scale[36,37] were used for the perceptual assessment of voice on the basis of the reading passage's audio recordings.

The GIRBAS scale is a widely used scale that specifically assesses different parameters of voice quality: grade (G), instability (I), roughness (R), breathiness (B), asthenia (A), and strain (S); the score ranges from 0 (normal voice) to 3 (severe dysphonia). The overall quality impression and intelligibility, additive and unnecessary noise, speech fluency, and presence of voiced segments rating scale is a perceptual scale specifically developed for substitution voice; it assesses: overall quality impression and intelligibility (I), additive and unnecessary noise (N), speech fluency (F), and presence of voiced segments (Vo). Each parameter is scored on a visual analog scale from 0 (minimally deviant) to 10 (maximally deviant substitution voicing).

The CSL program, version 5.05, with a 4300 external module of Kay Elemetrics Corporation was used to perform the spectrographic analysis of voice. All the voices were recorded with a microphone that was placed approximately 15 cm from the voice source. A spectrography of the sustained vowels "a, i" at FFT-1024 points ranging between 0 and 8 kHz was performed; the sample frequency was 20,000 Hz. Patients' voices were classified into 4 categories on the basis of the spectrogram analysis, according to the recently proposed modification of Titze's classification.[38]

The following categories were used: (1) type 1 voices, periodic without strong modulations or subharmonics; (2) type 2 voices, with strong modulations, bifurcations, or subharmonics; (3) type 3 voices, smearing of energy across harmonics with visible fundamental frequency and 1 or 2 harmonics; and (4) type 4 voices, aperiodic.

*Perceptual assessment of video and audio recordings*

FEES, videolaryngoscopy, and voice recordings were assessed by 2 independent SLPs blinded to each other and to the surgical procedure the patients underwent.

Each SLP was subjected to a specific training for video and auditory perceptual assessment.

*Quality of life*

The Italian Short Form-36 Items Health Survey (SF-36) questionnaire was completed by each participant to assess QOL, functional health, and well-being.[39,40] The Italian SF-36 is a valid and reliable short-form health survey. It is divided into 8 scales: Physical Functioning (PF), Role-Physical (RP), Bodily Pain (BP), General Health (GH), Vitality (VT), Social Functioning (SF), Role-Emotional (RE), and Mental Health (MH). Each subscale is scored from 0 (worst possible health status) to 100 (best possible health status).

Dysphagia-related disability was investigated through the Italian MD Anderson Dysphagia Inventory (MDADI).[41,42] The Italian MDADI is a reliable and clinically valid dysphagia-specific QOL questionnaire for Italian-speaking patients with head and neck cancer, divided into a global, an emotional, a physical, and a functional subscale. The total score and each subscale's score range from 20 (extremely low functioning) to 100 (high functioning).

Each subject completed the Italian version of the Voice Handicap Index (VHI)[43,44] and the Italian version of the Self-Evaluation of Communication Experiences after Laryngeal Cancer (I-SECEL).[45,46]

The VHI assesses patients' perception of disability related to voice dysfunction. It is made of 3 subscales: emotional, physical, and functional. A total score (possible range 0–120 points) and subscales' scores (range, 0–40) are given; the higher the score, the greater the voice handicap.

The I-SECEL questionnaire specifically assesses communication dysfunction in patients with laryngectomy and their effects on patients' daily living activities. The questionnaire is made of 34 items, divided into 3 subscales: General (5 items), Environmental (14 items), and Attitudinal (15 items). Scores range from 0 to 102 for the total score, from 0 to 15 for the General subscale, from 0 to 42 for the Environmental subscale, and from 0 to 45 for the Attitudinal subscale. The higher the score, the greater the perception of communication dysfunction. A cutoff of 60 for the total score was established to identify patients in need of a specific counseling.

*Statistical analysis*

The statistical analysis was performed with the IBM SPSS Statistics 20.0 package for Windows (SPSS, Chicago, IL). Patient's demographic and results of the two groups were statistically compared using nonparametric Mann–Whitney U test or Fisher's exact test, as appropriate.

The differences were considered statistically significant for a $p<.05$.

*RESULTS*

*Patients*

No significant differences were found between the 2 groups for patient's sociodemographic and treatment variables, except for the T classification, as reported in Table 1. The T classification was statistically higher in the group of the OPHL type IIIa than in the group of the OPHL type IIa.

*Swallowing*

Swallowing functional outcomes and the results of the comparison between OPHL type IIa and type IIIa are shown in Table 2. A significant difference was found only for the residue with solid bolus, with patients of the OPHL type IIIa group showing a significantly higher degree of food retention than patients in the OPHL type IIa group.

Aspiration pneumonia occurred only in 1 patient of the OPHL type IIIa group. On average, patients maintained their preoperative weight. In both groups, premature spillage occurred between 28% and 48% of the patients with all consistencies, whereas fragmentation of the bolus into multiple swallows was observed in < 22% of the patients.

On average, PAS scores were higher with liquids, with a median score of 6 for the patients in the OPHL type II group and 7 in the type III group corresponding to tracheal aspiration, and lower with semisolids, with a median score of 1 in both groups corresponding to normal swallowing. Median pooling score ranged between 5.5 and 7.5 with all consistencies and in both groups, corresponding to mild dysphagia. Finally, 5 of 23 patients (21.7%) in the OPHL type II group and 3 of 18 patients (16.7%) in the OPHL type III group were able to tolerate a full peroral nutrition with normal diet (DOSS score > or = 6), 15 of 23 patients (65.3%), and 12 of 18 patients (66.6%), respectively, could tolerate a full per-oral nutrition but with the necessity of a modified diet and/or independence (DOSS score between 5 and 3), whereas 3 of 23 patients (13%) and 3 of 18 patients (16.7%), respectively, presented severe dysphagia (DOSS score < or = 2).

*Voice and speech*

Patients who underwent OPHL type IIa and those who underwent type IIIa showed comparable long-term voice functional outcomes, as reported in Table 3. Patients with OPHL IIIa scored significantly higher than patients with OPHL type IIa on intelligibility.

On average, patients who underwent OPHL type II showed a good arytenoid motion and sphincteric closure but a poor vibration of the neoglottis; all the 3 parameters were, on average, moderate in patients who underwent OPHL type III. Additional noise, fluency, and unrequested voicing were rarely present in both groups of patients, whereas intelligibility was more impaired. On the GIRBAS scale, 22 of 23 patients (95.7%) who underwent OPHL type II and all type III patients showed moderate or severe degree of dysphonia, 18 of 23 patients (78.3%) and 15 of 18 patients (83.3%), respectively, showed moderate to severe roughness; irregularity, breathiness, asthenia, and strain were almost absent. An MPT <10 seconds was recorded in 18 of 23 patients (78.3%) undergoing OPHL type II and in 17 of 18 patients (94.4%) undergoing OPHL type III. A harmonic structure was clearly visible in 9 of 23 patients (39.1%) in the OPHL type II group and in 8 of 18 patients (44.4%) in the OPHL type III group.

*Quality of life*

QOL outcomes and results of the comparison between OPHL type IIa and type IIIa are shown in Table 4. No statistically significant difference was found for general, voice-related, and swallowing-related QOL. General QOL was well-preserved in both groups. A median score >70 was found for all the SF-36 subscales; the highest scores were obtained on the Role-Physical and Role-Emotional subscales for patients in the OPHL type II group and on the Role-Emotional subscale for patients in the OPHL type III group, whereas the lowest scores were obtained, respectively, on the General Health subscale and on the Bodily Pain subscale. Swallowing related QOL was also well-preserved. A median score >70 was found for the MDADI subscales and total score, with the highest score on the Functional subscale and the lowest score on the Physical subscale in both groups. A mild reduction on voice-related QOL was found. Median VHI total score was 30 for the OPHL type II group and 37.5 for the OPHL type III group, with patients from both groups obtaining a lower score on the Emotional subscale than on the other ones. Finally, a median SECEL total score <36, corresponding to an adequate coping with the new voice, was found for both groups; no patient scored >60.

*DISCUSSION*

Long-term swallowing, voice, and QOL in patients undergoing OPHL type IIa and type IIIa were compared. Only one study previously compared different OPHL type's long-term functional outcomes[28]; however, as it focused on the elderly, its results cannot be generalized to all patients undergoing OPHL. Therefore, the present study reports the first data on this topic. We hypothesized that a greater extension of surgical resection would correspond to worse long-term outcomes. However, no statistically significant differences were found between OPHL type IIa and type IIIa, except for pooling with solid boluses and for the general impression of voice, which were significantly worst in OPHL type IIIa. Therefore, in the long-term, swallowing, voice, and QOL are supposed to be comparable in patients undergoing OPHL type IIa and type IIIa.

Swallowing long-term functional outcomes were comparable in the two groups of patients for all the investigated variables, except for pooling with solid boluses. In general, swallowing was sufficiently restored in both groups, with patients showing better performances with semisolid boluses and worse performances with liquid boluses. Preoperative weight was maintained in most of the patients. Premature spillage occurred between 28% and 48% of the patients with higher rate of spillage with liquids because of their lower viscosity. Aspiration occurred in just a few patients with solid and semisolid boluses, showing a generally good sphincteric action of the neoglottis to separate the lower airways from the oropharynx during swallowing. A poorer performance was recorded with liquids, as aspiration was found in approximately half of the patients. On average, low pooling scores were assigned to patients undergoing both surgical techniques; patients with OPHL type IIIa scored significantly higher than patients with OPHL type IIa with solids.

We hypothesize that the difference in the amount and management of pharyngeal and laryngeal pooling may be due to different degrees of upper esophageal sphincter opening rather than to different laryngeal mechanisms.

However, the significant difference of pooling with solids does not correspond to a higher degree of postswallowing aspiration, as shown by PAS scores. A low rate of aspiration pneumonia was found, suggesting that patients tolerate a certain degree of chronic aspiration well, as already reported in the literature.[26] After OPHL type IIa and type IIIa, a full peroral nutrition was achieved in, respectively, 87% and 83.3% of the patients, although some consistency modifications may be necessary.

Therefore, in the long-term, enteral nutrition can be avoided in the major part of the patients undergoing OPHL.

For concerns about voice and speech long-term functional results, no statistically significant differences were found between OPHL type IIa and type IIIa, except for the general impression of voice investigated through the overall quality impression and intelligibility, additive and unnecessary noise, speech fluency, and presence of voiced segments scale. Voice was more compromised than swallowing in both groups because of the removal of the vocal folds. On average, patients who underwent OPHL type IIa and type IIIa showed moderate to good arytenoid motion and sphincteric closure of the neoglottis, whereas vibration was more impaired. The results of the laryngoscopic assessment are reflected by the perceptual evaluation of voice: the GIRBAS scale described patients' voices as severely dysphonic and hoarse, and occasionally breathy, whereas instability, asthenia, and strain were only rarely reported. The different surgical extension between OPHL type IIa and type IIIa significantly impacts the general impression of voice, as patients undergoing OPHL type IIIa scored significantly higher than patients undergoing OPHL type IIa. Therefore, the present result seems to suggest that not only the vocal folds' removal but also the removal of adjacent structures, such as the cricoid, is critical for voice quality. The deterioration of vocal quality recorded with the perceptual assessment of voices is consistent with the spectrographic analysis, which showed the absence of a clear harmonic structure in more than half of the patients of both groups.

Fluency and voicing are usually not compromised after OPHL and no unintended additive noises accompany voice production. An inadequate MPT (<10 seconds) was found for the majority of the patients[35]; however, it did not impact on spontaneous speech as normal fluency was generally preserved. Diadochokinesis performance after OPHL was found to be good.[34]

General, swallowing-related, and voice-related QOL were comparable in patients who underwent OPHL type IIa or type IIIa with no statistically significant difference between the two groups. SF-36 results reported in the present study are comparable to those of the Italian general population, revealing that QOL is generally satisfactory following OPHL.[39] On average, patients perceived only mild to minimal dysphagia, suggesting that, from the patients' perspective, swallowing ability is sufficiently restored in the long-term.[47] Voice-related QOL questionnaires revealed that perceived disability related to voice disorders after OPHL type IIa and IIIa is only moderate.

Indeed, median VHI scores obtained by patients who underwent OPHL type IIa and IIIa are similar to those generally obtained by patients with vocal fold nodules, polyps, and cysts.[48] All patients showed a good attitude toward their communication dysfunction, as revealed by SECEL scores. Therefore, although postoperative voice resulted to be significantly deteriorated, patients reported to be relatively satisfied speakers, on emotional, physical, and functional levels, suggesting that oral communication is not significantly limited.

Functional long-term results of our patients who underwent OPHL type IIa are similar to those reported in literature. Indeed, other studies had previously documented a certain degree of chronic aspiration in the long-term after OPHL type IIa, in particular with liquids, with a percentage of patients experiencing aspiration between the 17% and the 67%.[21,26,49–52] In our study, pharyngeal and laryngeal pooling food was generally mild. This is in accordance with what was reported by Zacharek et al[21] and by Simonelli et al,[26] whereas Dworkin et al[53] reported a higher degree of food pooling and in a higher percentage of patients. Premature spillage occurred in 30% to 47.8% of the patients, depending on the bolus' consistency.

Simonelli et al[26] reported a slightly lower frequency of premature spillage, occurring only in 21.5% of the patients,[26] whereas results of Dworkin et al[53] confirm our data. Heterogeneous rate of aspiration pneumonia after OPHL type IIa are reported in literature, ranging from 0%, as in our study, to 21.7%.[20,26,54–56] A full per-oral diet was achieved in 87% of the patients undergoing OPHL type IIa; similarly, in literature, the percentage ranges between 67% and 93.7%.[51,57–59] With regard to voice, videolaryngoscopic examination's results, showing a poor to moderate vibration of the neoglottis, whereas good sphincteric closure and arytenoids mobility, confirmed results reported by Zacharek et al[21] and by Schindler et al.[24] Values reported in the international literature confirm that OPHL type IIa voice is characterized by moderate to severe alterations in Roughness and Grade, slight to moderate alterations in Breathiness, slight or practically absent alterations in Asthenia, and slight alterations in Strain.[21,24,25,28,50,57,58,60] An MPT <10 seconds were found for most of our patients who underwent OPHL type IIa; many authors reported a highly reduced MPT after OPHL type IIa, with average values between 5.8 seconds and 10.6 seconds.[21,24,25,57,60]

Our OPHL type IIa group's speech outcomes, investigated through diadochokinesis and reading speed, are similar to those in literature. [24,60] Weinstein et al[2] investigated general QOL in patients who underwent OPHL type II using the SF-36 questionnaire; values reported by Weinstein et al[2] are comparable to results of the present study. The MDADI was previously used to assess swallowing-related QOL in patients who underwent OPHL type II by several authors, who obtained an average total score ranging from 78.4 to 92.[24,59,61] In literature, different authors reported different VHI scores on a small number of subjects studied in different countries. On average, self-assessment data reveal a mild to moderate perception of vocal handicap after OPHL type IIa, as reported in our study[24,28,50]; however, other authors reported a higher degree of vocal handicap and, therefore, higher VHI scores.[21,60] Besides the variability of the results found in different studies, mainly because of the fact that studied populations were generally small, results from our study are in agreement with previously reported data. Therefore, it seems reasonable to affirm that the statistical comparability of patients who underwent OPHL type IIa and the patients who underwent OPHL type IIIa was not due to specific characteristics of the OPHL type IIa studied group.

In literature, many authors studied the impact of different treatment and sociodemographic factors on functional outcomes after OPHL; however, their role is still controversial. [49,50,56,57,59,62–64] As previously reported by our working group, the same surgical techniques were followed by surgeons (authors G.S. and G.R.), respectively, for patients who underwent OPHL type IIa and for patients who underwent OPHL type IIIa; moreover, all patients involved in the study underwent the same diagnostic workup before surgery in order to accurately select candidates to OPHL type IIa and type IIIa and the same rehabilitation protocol in the postoperative course.[11,16] Patients who underwent OPHL type IIa differed from patients who underwent OPHL type IIIa only for the subglottic surgical extension, whereas both cricoarytenoid units and the suprahyoid portion of the epiglottis were preserved in all patients. All patients who underwent preoperative or postoperative RT were excluded. No statistically significant differences were found for distance from surgery, neck dissection, and TNM (except for the T classification).

The significant difference between the T classification of OPHL type IIa and the T classification of type IIIa was reasonable, as on the basis of the extension of the tumor, the surgeon selected the type of reconstruction to perform. The two groups were comparable for age, sex, educational degree, job, and marital status.

Because of the high homogeneity of the patients and of the blind assessment, it seems reasonable to affirm that the 2 groups differed only for the surgical extension and no other factors have influenced present results.

Perceived QOL is strictly related to patient’s expectation, stretching the importance of precise and exact information on functional outcomes during the preoperative and postoperative counseling.[2] This information is also essential to guide patients in the choice of which type of surgery to undergo. Therefore, data from our study are critical in the conduction of the preoperative and postoperative counseling and in the informed consent process.

Limitations of our study were the small number of patients included and lack of precise data on the pathophysiological mechanisms leading to dysphagia and dysphonia in patients who underwent OPHL type IIa and IIIa. In fact, videofluoroscopic (VFS) biomechanical and temporal analysis is needed to cover this area. However, the main purpose of this study was on outcome; for this reason, we preferred to use FEES rather the VFS, as although FEES and VFS are considered both gold standard 65 and complementary procedures,[66] previous studies in which FEES and VFS were used concurrently, FEES was proven to have higher sensibility for both penetration/aspiration[67] and residue.[68] Nonetheless, further studies should be conducted using VFS and include a larger population of patients who undergo OPHL type IIa and type IIIa and extending the comparison of long-term functional results to other OPHL reconstruction techniques.

Moreover, as dysphonia is one of the most critical aspects after OPHL type IIa and type IIIa, even when voice rehabilitation is performed, it would be interesting to investigate whether quality of voice can be improved through surgical or engineering techniques.

In conclusion, similar long-term functional outcomes in terms of swallowing, voice, and QOL are achieved after OPHL type IIa and OPHL type IIIa. Therefore, OPHL type IIIa represents a valid surgical alternative to OPHL type IIa. Present data could guide clinicians in the conduction of preoperative and postoperative counseling and should be taken into account by surgeons in the intraoperative choice of the surgical technique.

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**Table 1** **Sociodemographic and clinical factors in two samples of patients**

| | OPHL IIa +A | OPHL IIIa +A | *p* value |
|---|---|---|---|
| Age[†] | 65 (47–79) | 61 (23–77) | .385 |
| Sex[‡] | | | .243 |
| Male | 20/23 (87) | 18/18 (100) | |
| Female | 3/23 (13) | 0/18 (0) | |
| Educational degree[‡] | | | .476 |
| Primary | 4/23 (17.4) | 5/18 (27.8) | |
| Secondary school | 8/23 (34.8) | 6/18 (33.3) | |
| High school | 8/23 (34.8) | 5/18 (27.8) | |
| Bachelor | 3/23 (13) | 2/18 (11.1) | |
| Job[‡] | | | .706 |
| Full time | 4/23 (17.4) | 4/18 (22.2) | |
| Part time | 0/23 (0) | 1/18 (5.6) | |
| Self-employed | 7/23 (30.5) | 4/18 (22.2) | |
| Unemployed | 1/23 (4.3) | 2/18 (11.1) | |
| Retired | 11/23 (47.8) | 7/18 (38.9) | |
| Marital status[‡] | | | .306 |
| Single | 1/23 (4.3) | 3/18 (16.7) | |
| Married | 20/23 (87.1) | 11/18 (61.1) | |
| Divorced | 1/23 (4.3) | 2/18 (11.1) | |
| Widower | 1/23 (4.3) | 2/18 (11.1) | |
| Distance from surgery, mo[†] | 34 (6–97) | 40.5 (6–84) | .599 |
| Neck dissection[‡] | 20/23 (87) | 17/18 (94.4) | .618 |
| T classification[†] | | | .017* |
| 1 | 2/23 (8.7) | 0/18 (0) | |
| 2 | 12/23 (52.2) | 4/18 (22.2) | |
| 3 | 8/23 (34.8) | 13/18 (72.2) | |
| 4 | 1/23 (4.3) | 1/18 (5.6) | |
| N classification[†] | | | .890 |
| 0 | 20/23 (87) | 16/18 (88.9) | |
| 1 | 1/23 (4.3) | 0/18 (0) | |
| 2 | 0/23 (0) | 0/18 (0) | |
| 3 | 0/23 (0) | 0/18 (0) | |
| X | 2/23 (8.7) | 2/18 (11.1) | |
| M classification[†] | | | 1 |
| 0 | 23/23 (100) | 18/18 (100) | |
| 1 | 0/23 (0) | 0/18 (0) | |

Abbreviations: OPHL, open partial horizontal laryngectomy; +A, arytenoid resection.
* $p < .05$.
[†] Mann–Whitney *U* test.
[‡] Fisher's exact test.
Note: Values are median (range) or numbers (%).

**Table 2** **Comparison of swallowing functional outcomes between open partial horizontal laryngectomy type Iia and type IIIa**

| | OPHL IIa +A | OPHL IIIa +A | *p* value |
|---|---|---|---|
| Pneumonia* | 0/23 (0) | 1/18 (5.6) | .439 |
| Δ Weight, kg† | 2 (−12 to +21) | 0 (−5 to +25) | .862 |
| Spillage liquid* | 11/23 (47.8) | 7/18 (38.9) | .752 |
| Spillage semisolid* | 9/23 (39.1) | 5/18 (28) | .520 |
| Spillage solid* | 7/23 (30) | 8/18 (44.4) | .515 |
| Piecemeal liquid* | 5/23 (22) | 2/18 (11.1) | .438 |
| Piecemeal semisolid* | 3/23 (13) | 2/18 (11.1) | 1 |
| Piecemeal solid* | 4/23 (17.4) | 3/18 (16.7) | 1 |
| PAS liquid† | 6 (1–8) | 7 (1–8) | .860 |
| PAS semisolid† | 1 (1–7) | 1 (1–8) | .802 |
| PAS solid† | 2 (1–8) | 3 (1–8) | .225 |
| Pooling liquid† | 7 (5–9) | 7 (4–9) | .322 |
| Pooling semisolid† | 6 (4–9) | 5.5 (4–9) | .968 |
| Pooling solid† | 6 (4–8) | 7.5 (4–10) | .043* |
| DOSS† | 5 (1–7) | 4 (1–6) | .391 |

Abbreviations: OPHL, open partial horizontal laryngectomy; +A, arytenoid resection; PAS, Penetration-Aspiration Scale; DOSS, Dysphagia Outcome and Severity Score.

* $p < .05$.

† Mann–Whitney *U* test.

Fisher's exact test.

Note: Values are median (range) or numbers (%).

**Table 3** **Comparison of voice functional outcomes between open partial horizontal laryngectomy type Iia and type IIIa using Mann-Whitney U test**

| | OPHL IIa +A | OPHL IIIa +A | *p* value |
|---|---|---|---|
| Vibration | 2 (1–5) | 2.5 (1–5) | .153 |
| Arytenoid motion | 4 (1–5) | 3 (1–5) | .071 |
| Closure | 4 (1–5) | 3 (1–5) | .209 |
| Intelligibility | 3 (0–8.8) | 5.7 (1.1–9.7) | .037* |
| Noise | 0.7 (0–2.5) | 1.2 (0–6.4) | .107 |
| Fluency | 1.3 (0–8) | 1.55 (0–10) | .357 |
| Voiced segments | 0 (0–2.7) | 0 (0–10) | .721 |
| Grade | 3 (1–3) | 3 (2–3) | .725 |
| Instability | 0 (0–1) | 0 (0–0) | .066 |
| Roughness | 2 (0–3) | 2.3 (0–3) | .451 |
| Breathiness | 0 (0–3) | 0 (0–3) | .831 |
| Asthenia | 0 (0–3) | 0 (0–3) | .444 |
| Strain | 0 (0–3) | 0 (0–2) | .494 |
| MPT, s | 7.3 (1.9–18.9) | 6.1 (1.4–11.2) | .248 |
| “pa,” syllable/s | 3.2 (1.4–4.9) | 2.9 (2.1–4.2) | .226 |
| “pataka,” trisyllable/s | 1.2 (0.6–2.2) | 1 (0.5–2) | .310 |
| Reading time, s | 29.4 (21.9–54.5) | 28.2 (22.4–44.2) | .646 |
| Reading rapidity, syllable/s | 3.4 (1.8–4.5) | 3.5 (2.4–4.4) | .589 |
| Titze’s classification | | | |
| 1 | 4 (17.4%) | 4 (22.2%) | .389 |
| 2 | 5 (21.7%) | 4 (22.2%) | |
| 3 | 9 (39.2%) | 9 (50%) | |
| 4 | 5 (21.7%) | 1 (5.6%) | |

Abbreviations: OPHL, open partial horizontal laryngectomy; +A, arytenoid resection; MPT, maximum phonation time.
* $p < .05$.
Note: Values are median (range) or numbers (%).

**Table 4 Comparison of general quality of life, swallowing- and voice-related quality of life between open partial horizontal laryngectomy type Iia and type IIIa using Mann-Whitney U test**

| | OPHL IIa +A | OPHL IIIa +A | *p* value |
|---|---|---|---|
| SF-36 Physical Functioning | 95 (20–100) | 87.5 (15–100) | .080 |
| SF-36 Role-Physical | 100 (0–100) | 75 (0–100) | .332 |
| SF-36 Bodily Pain | 84 (30–100) | 74 (12–100) | .410 |
| SF-36 General Health | 72 (20–100) | 79.5 (45–100) | .905 |
| SF-36 Vitality | 75 (25–100) | 75 (15–90) | .201 |
| SF-36 Social Functioning | 87 (0–100) | 74.5 (25–100) | .820 |
| SF-36 Role-Emotional | 100 (0–100) | 100 (0–100) | .952 |
| SF-36 Mental Health | 80 (20–100) | 80 (24–100) | .406 |
| MDADI Total score | 83 (43–100) | 82 (52–100) | .969 |
| MDADI Physical subscale | 72.5 (40–100) | 77.5 (42.5–100) | .979 |
| MDADI Functional subscale | 96 (44–100) | 94 (44–100) | .914 |
| MDADI Emotional subscale | 83.3 (46.7–100) | 80 (50–100) | .722 |
| MDADI Global subscale | 80 (20–100) | 80 (20–100) | .955 |
| VHI Total score | 30 (0–103) | 37.5 (6–91) | .520 |
| VHI Physical subscale | 15 (0–32) | 13.5 (2–34) | .654 |
| VHI Emotional subscale | 5 (0–36) | 8.5 (0–27) | .234 |
| VHI Functional subscale | 12 (0–35) | 14 (2–30) | .453 |
| SECEL Total score | 29 (20–82) | 35 (13–59) | .275 |
| SECEL General subscale | 12 (4–15) | 11 (7–15) | .456 |
| SECEL Environmental subscale | 13 (5–36) | 17 (3–30) | .344 |
| SECEL Attitudinal subscale | 6 (1–37) | 8.5 (1–21) | .502 |

Abbreviations: OPHL, open partial horizontal laryngectomy; +A, arytenoid resection; SF-36, Italian Short Form-36 Items Health Survey; MDADI, MD Anderson Dysphagia Inventory; VHI, Voice Handicap Index; SECEL, Self-Evaluation of Communication Experiences after Laryngeal Cancer.
Note: Values are median (range) or numbers (%).

# Paper 4

## *How the operated larynx ages*

**Background**: After open partial laryngectomy (HOPL), many patients experience deterioration of laryngeal function over time. The study's aim was to evaluate laryngeal functional outcome at least 10 years after surgery in a cohort of 80 elderly patients.

**Methods:** The incidence of aspiration pneumonia (AP) and objective/subjective laryngeal functional assessments were carried out.

**Results**: Eight patients experienced AP including four with repeated episodes. A significant association was observed between AP and severity of dysphagia ($p < 0.001$). Dysphagia was more pronounced than in a normal population of similar age but less than would be expected. There was a significant association between type of intervention and grade of dysphagia / dysphonia; difference in voice handicap was found, depending on the extent of glottic resection.

**Conclusions**: After HOPL, laryngeal function was impaired but this did not significantly affect quality of life. AP is more frequent in the initial post-operative period, decreasing in subsequent years.

**Introduction**

In the second half of the twentieth century, horizontal open partial laryngectomies (HOPLs), including in this category, supraglottic laryngectomies (SLs), supracricoid laryngectomies (SCPLs) and most recently, supratracheal laryngectomies (STPLs), have become established as a viable surgical option, primary or salvage, for the treatment of laryngeal cancer in its intermediate stage. Many authors[1–3] have reported the oncological and functional results of HOPLs while others have reported data relating to complications and, in particular, on more frequent and problematic complications, represented by chronic aspiration of food and aspiration pneumonia (AP).[4]

Globally, HOPLs have demonstrated the possibility to obtain a high rate of 5-year local/regional control of disease, often in over 70% of cases and they were used widely in the 1980s and 1990s, particularly for SCPLs.[5–7] It is therefore logical to assume that there is now the opportunity to observe a population of elderly patients, cured of laryngeal cancer, and who have experienced aging with an operated larynx.

An accurate literature analysis was carried out and, to our knowledge, there are few papers focusing on the interesting question how the operated larynx ages. Therefore, a retrospective cohort study was carried out on a group of 80 elderly patients (age >70 years) who underwent HOPLs at least 10 years before, focusing on swallowing and phonatory results. Laryngeal function analysis was performed using objective and subjective methods, comparing data on episodes of AP occurring during the follow-up period. Then a comparison was carried out with literature data about the swallowing impairment in elderly subjects who had not undergone any laryngeal surgery, dysfunctions being considered an expression of the physiological aging of the larynx.

The goal was to evaluate functional outcomes at least 10 years after HOPL in a cohort of elderly patients looking for a possible statistically significant correlation between amount of resection and grade of impairment of some swallowing and phonatory parameters detected by self-evaluation and accurate functional tests. The goal was also to examine the relationship between type of surgery and incidence of aspiration pneumonia (AP) during follow-up.

## Materials and Methods

From 1976 to the time of writing, 1486 HOPLs (supraglottic, supracricoid, supratracheal) have been performed at the Departments of Otorhinolaryngology of the Hospital of Vittorio Veneto and the Martini Hospital in Turin (Italy). This group represents a subset of 2986 patients suffering from invasive squamous cell carcinoma of the larynx (SCC) treated during the same period.

The retrospective study was focused on a cohort of 80 patients with the following characteristics: patients without evidence of disease with a minimum follow-up performed in the above mentioned departments of at least 120 months, current age greater than 70 years, and previous interventions of SL, SCPL or STPL. At the time of the last follow up, the current age of the cohort of patients ranged between 70 and 83 years with a mean age of 74.8 years.

Seventy-one patients were male (88.8%) and nine female (11.2%); at the time of surgery, 91% were current or former smokers, with a mean age of 63 years (range 56–73); all patients had a biopsy-proven laryngeal SCC staged from II to IVa according to the 2002 TNM staging classification system.[8]

During the 3 weeks preceding surgical treatment, all patients underwent the same diagnostic work-up that included: flexible videolaryngoscopy, intraoperative rigid endoscopy with 0°/angled telescopes and biopsy during microlaryngoscopy under general anesthesia, laryngeal and neck CT-scan or MRI, bronchoscopy and esophagoscopy to rule out synchronous tumors, chest X-ray or CT-scan to exclude lung tumors or distant metastases, assessment of bronchopulmonary function and of comorbidities for at-risk patients, and nutritional evaluation. The Karnofsky Performance Status Index had to be at least 80 (i.e. patient able to carry out normal activities, even though with difficulty).[9]

In addition to a Karnofsky Index less than 80, exclusion criteria were severe diabetes mellitus, severe bronchopulmonary chronic obstructive disease and severe cardiac disease. Even though historically an age of 70 years has been an important cut-off age for relative surgical indication of some partial laryngectomies, in our experience advanced age is no longer, in itself, an exclusion criterion. After accurate selection of patients on the basis of the absence of important comorbidities and the strong desire of the patient to avoid permanent tracheostomy, age was also considered along with the patient's general condition.

On the basis of pathological findings, 13 patients (16.3%) were subjected to post-operative radiation therapy with a mean dose of 64 Gy delivered to the larynx (three patients, range 62–66 Gy) and 54 Gy to the neck (10 patients, range 50–66 Gy).

***Surgery***

Of the 80 patients, 23 underwent SL, 45 underwent SCPL and 12 underwent STPL. In the subset of SLs, there were 6 extended supraglottic laryngectomies (ESL), 4 to the base of the tongue and 2 to the pyriform fossa. In the subset of SCPLs, the procedures used at the time of reconstruction were cricohyoidoepiglottopexy (SCPL-CHEP) and cricohyoidopexy (SCPL-CHP). Removal of one arytenoid was indicated in the surgical records by adding the notation "+ A" to the abbreviation for the laryngectomy, specifying the side, left or right, of the removed arytenoids. In the subset of STPLs,[10] the procedures used at the time of reconstruction were tracheohyoidoepiglottopexy (STPL-THEP) and tracheohyoidopexy (STPL-THP). Removal of one cricoarytenoid unit was again indicated by adding the notation "+ A" to the abbreviation for the laryngectomy, specifying the side, left or right, of the removed cricoarytenoid unit. Interventions carried out are reported in Table 1.

Neck dissection (ND), classified according to the AAO-HNS,[11] was performed in all of the patients and was unilateral in 36 and bilateral in 44 patients. Neck dissection was elective (level II-III-IV + ev. level VI in the case of subglottic extension) in 67 cN0 patients (83.8%) and curative (level II-V + ev. level VI in the case of subglottic extension) in 13 cN>0 patients (16.3%). Overall, lymph node metastases were detected in 12 patients.

In all patients, resection margins were examined intraoperatively by frozen sections; when positive, the resection was expanded until the margins were negative. The margins of the surgical specimen were always checked again until definitive pathology reports indicated that the margins were closed (<3 mm) in four patients.

***Functional assessment***

All patients underwent the same rehabilitation protocol, with the obvious exception of those with serious early complications. The post-operative protocol consisted of the following: a) Post-operative days 1–4: insertion of un-cuffed tracheal cannula and beginning of phonation; b) Post-operative days 4–6: during daytime, intermittent occlusion of the tracheostoma with a saline-soaked gauze and starting of feeding without the tracheal cannula in position; c) Post-operative day 6 onwards: the nasogastric tube (NGT) was removed as soon as a good level of swallowing of both solids and liquids was achieved.

Grading of post-operative aspiration was performed according to Pearson's scale[12] (0 = none; I = occasional cough but no clinical problems; II= constant cough worsening with meal or swallowing; III= pulmonary complications).

The study took place in 2011, and during the annual follow-up visit, all patients underwent the following evaluations: ENT clinical examination coupled with fiberoptic videolaryngoscopy; accurate assessment of episodes of AP occurring during the follow-up period; evaluation of dysphonia using subjective and objective methods; evaluation of dysphagia using subjective and objective methods.

All episodes of AP and acute pneumonia were considered, documented by chest X-rays and/or by a medical report, in the period from the day of discharge to the date of the last follow-up visit, whether the patient had required hospitalization or had been treated at home.

For the evaluation of dysphonia, all patients were administered the Voice Handicap Index (VHI) questionnaire proposed by Benninger et al. in 1998[13] for the self-assessment of their vocal disability. This is a questionnaire consisting of 30 items referring equally to three different aspects of vocal disorders: physical, functional and emotional. The patient can provide five possible answers, from never to always, assigning a score from 0 to 4. Summing the values assigned to the 30 responses, an overall score is obtained between a minimum value of 0 and a maximum value of 120 that corresponds to the highest level of phonatory disability perceived by the patient. Then a phoniatrician and a speech therapist evaluated the voice in all patients by assigning to each a score based on the GIRBAS scale,[14] after reading a standard text from SIFEL (Italian Society of Phoniatrics and Logopedics).

For the evaluation of dysphagia, all patients were administered the MD Anderson Dysphagia Inventory (MDADI) questionnaire,[15] which consists of 20 questions related to three different aspects of dysphagia: functional, physical and emotional. Again, the patient can provide five possible responses, ranging from never to always, assigning a score from 1 to 5, and obtaining an overall score between a minimum value of 20 and a maximum of 100, which corresponds to the highest level of disability perceived by the patient swallowing. The radiological study of swallowing was performed by videofluoroscopy. The radiographs obtained for each patient were then evaluated together by a radiologist (CB) and a phoniatrician (PC) and each patient was assigned a score based on the DOSS (Dysphagia Outcome and Severity Scale).[16] The DOSS assigns 7 degrees (the highest level of dysphagia corresponds to level 1) and is based on an objective assessment of dysphagia from the videofluoroscopy, and the level of independence during the intake of food and type of food. This score allows us to understand which patients need more attention and care to avoid the risk of AP.

***Statistical analysis***

Statistical analyses were conducted using SAS System 9.2. The association between AP and type of intervention was analyzed using the chi-square test. Fischer's exact test was used since the number of cells with the expected frequency of less than 5 was greater than 50%. The association among the degree of dysphonia, dysphagia, and type of intervention was analyzed using ANOVA tests, whereas the association between AP and degree of dysphagia was analyzed using the Student's *t*-test.

**Results**

At the time of last follow-up, performed by clinical examination of the neck, fiberoptic videolaryngoscopy and chest X-ray, all 80 patients were free of disease.

At the end of the first post-operative month, normal swallowing (Pearson's Scale Grade 0) was achieved in 56/80 patients (70.0%), Grades I and II were observed in 10 (12.5%) and 8 (10.0%) patients, respectively, while AP (Pearson's Grade III) was recorded in 6/80 patients (7.5%). The nasogastric tube remained in place for an average of 15 days after surgery (range 6–67 days), the mean duration of tracheostomy intermittent occlusion was 25 days (range 13–92 days), and the average time of tracheostomy closure was 57 days (range 29–131 days). In our protocol, progressive closure of the tracheostomy is preferred, and occurs spontaneously in the majority of patients following occlusion. For patients, this leads to a sensation of greater safety concerning small episodes of food inhalation, which are relatively frequent, especially in the first weeks after discharge. When the tracheostomy has almost closed, a small plastic skin closure can then be performed. The tracheostomy tube was removed an average of 39 days after surgery (range 13–92 days), always when the patient was able to feed themselves. Two months after surgery, Pearson's Grades I and II were noted in four (5%) and two (2.5%) patients, respectively. Due to intense dysphagia and AP episodes in 8/80 patients (10%), a temporary gastrostomy was needed and in 75% of the cases, this was removed during the first post-operative year. Only in one case was the gastrostomy maintained for a longer period (4 years) due to repeated episodes of AP and severe dysphagia for liquids. Two patients have been subjected to endoscopic procedures of injective laryngoplasty using Vox-Implant which has successfully resolved dysphagia, allowing gastrostomy removal.

From the day of discharge and during the whole period of follow-up, eight patients (10%) experienced at least one episode of AP, including four patients who experienced repeated episodes, for a total of 13 episodes of AP reported in the years after intervention (Table 2). In three cases, hospitalization of the patient was necessary (1 SCPL-CHEP + A, 1 SCPL-CHP + A, 1 STPL-THEP + A), while among the cases treated at home, one patient had undergone extended SL (extended to base of tongue), five patients had been subjected to SCPL (2 SCPL-CHEP, 2 SCPL-CHEP + A, 1 SCPL-CHP + A), and two patients had been subjected to STPL (1 STPL-THEP + A, 1 STPL-THP). Analysis of AP episodes has demonstrated that these occur more frequently in the early years after surgery, but are less frequent a long time after the operation, as illustrated in Figure 1. There is a statistically significant association between AP and type of intervention (Fischer test, P = 0.0131), since a higher rate of AP was observed in the more extended procedures (one arytenoid resection, one cricoarytenoid unit resection, enlargement at the base of the tongue, supratracheal resection).

The results of the videofluoroscopy, assessed using the DOS Scale and divided by type of intervention, are shown in Table 3. The vast majority of patients (58/80; 72.5%) achieved and maintained a very good level of rehabilitation over time, identified by grades 6–7 on the DOS Scale. The SLs can reach grade 6–7 in 87.0% of cases (20/23), SCPLs in 77.8% (35/45), and STPLs in 25% (3/12); the more pronounced levels of dysphagia, grade 3–4 of the DOS Scale, were found in SLs at a rate of 4.3% (1/23), in SCPLs at a rate of 8.9% (4/45) and in STPLs at a rate of 33.3% (4/12).

The study of swallowing function was completed by the self-assessment of dysphagia using the MDADI questionnaire and scores were stratified by type of intervention (Table 4). Overall in 83.8% of patients, the degree of perceived swallowing disability was low with MDADI scores of 20 to 40, and it was possible to observe statistically significant differences between the various categories of intervention (100% of SLs, 82.2% of SCPLs, 58.3% of STPLs). The most significant perceived swallowing disability, with MDADI scores of 61 to 80, was observed in two interventions (4.4%) by SCPL. There was a statistically significant association between type of intervention and degree of dysphagia, evaluated in an objective manner using videofluoroscopy and with the DOS Scale (ANOVA test, P <0.001), both perceived by the patient and self-assessed using MDADI (ANOVA test, P = 0.0125). Also, in this case, the worst levels of dysphagia were associated with the most extensive procedures resulting in anatomic-functional violation of the glottic sphincter, particularly when such violation led to the removal of one arytenoid or the removal of the entire cricoarytenoid unit as in supratracheal laryngectomies.

The results of the voice analysis using the GIRBAS scale as well as the results of self-evaluation using the VHI questionnaire are shown in Table 5 stratified for each type of intervention. Objective assessment with the GIRBAS scale showed that overall, HOPLs enabled patients to achieve and maintain very good voice restoration (GIRBAS score 0–1) in 20% of cases, only those patients who underwent SLs (16/23, 69.5%); 50% of patients [the group consisting of 4/23 SLs (17.4%), 30/45 SCPLs (66.7%) and 6/12 STPLs (50%)] showed a medium value of dysphonia (GIRBAS score 1.01–2); the worst results for dysphonia (GIRBAS score 2.01–3) were found in 30% of patients, the group consisting of 3/23 SLs (13.0%), 15/45 SCPLs (33.3%) and 6/12 STPLs (50%). Similar to what was observed for self-assessment of dysphagia, the study of phonatory function using the VHI questionnaire demonstrated that a large number of patients, representing 60% of the study cohort (69.5% of SLs, 62.2% of SCPLs and 33.3% of STPLs), perceived a low level of vocal handicap (VHI score 0–30), while 11 of 80 patients (13.8%) receiving SCPLs (8/45, 17.8%) or STPLs (3/12, 25%) complained of a high degree of speech handicap. Since there is a remarkable difference in voice handicap between HOPLs depending on the extent of glottic resection, a statistically significant association was found between type of intervention and grade of dysphonia, both perceived by the patients (ANOVA test, P = 0.0125) and evaluated in an objective manner (ANOVA test, P <0.001). Also, in this case, a poorer functional results were found proportional to the amount of larynx resected downwards (best results for SLs then for SCPLs and finally for STPLs).

To understand whether AP was associated with severity of dysphagia, the values of DOS scale and MDADI of the eight patients who had developed AP during the follow-up were considered (Table 6). A clear correlation was observed between pneumonia and severity of dysphagia both evaluated in an objective manner (Student’s *t*-test, P <0.001) and perceived by the patient (Student’s *t*-test, P <0.001).

Patients who complained of repeated episodes of pneumonia were those who had more severe levels of dysphagia. The average DOS Scale value of patients who had at least one episode of pneumonia was 4.38 (range 3–6), whereas in those patients who had never developed an episode of pneumonia, the value was 6.19 (range 4–7). The average MDADI score in patients with at least one episode of pneumonia was 56.38 (range 38–73), whereas in those patients who had never complained of any episode of pneumonia, the score was 33.00 (range 20–67). These data allow us to conclude that these episodes of pneumonia were closely correlated with the degree of dysphagia.

**Discussion**

Over the last three decades, HOPLs have emerged as an important weapon in the surgical treatment of laryngeal cancer at intermediate/advanced stages and, especially in Europe, there are now thousands of patients who have undergone HOPLs and are aging with an operated larynx.[1–3] Dysphagia, dysphonia and aspiration pneumonia have been recognized as the major complications in patients subjected to these interventions and can significantly affect their physical and emotional condition.[4,17]

Starting from the observation that the phenomena referred to as presbyphagia and presbyphonia represent functional alterations that can occur even in normal elderly subjects never subjected to laryngeal surgery, we asked a series of questions.

What can be expected for a patient subjected to HOPL and aging with his operated larynx? Will the degree of dysphagia remain stable over time or will it undergo a physiological deterioration? What is the degree of AP observed in a cohort of elderly patients undergoing HOPLs compared to a cohort of elderly subjects that were never subjected to laryngeal surgery? During follow-up, is it necessary to use corrective behavior to ensure that the patient has a good quality of life?

The quality of voice is one of the most critical aspects of HOPL, especially when the resection is extended to the glottis or downward to the subglottis.[18] In a functional study on 64 patients who underwent SCPL, Makeieff et al.[19] found that the intervention could have a marked social and professional impact. Comparing voice analysis in patients subjected to total laryngectomy and voice prosthesis (TL-VP) vs SCPL, Yoon Kyoung et al.[20] demonstrated that the maximum phonation time was longer in the TL-VP group than in the SCPL group. Finally, Schindler et al.[21] conducted a cross-sectional study on 20 patients who underwent SCPL and in whom perceptual assessment revealed a very harsh voice, acoustic analysis displayed an irregular signal, and aerodynamic measurements showed an inefficient system.

A remarkable difference in voice handicap was found between HOPLs in the study cohort depending on the extent of glottic resection with a statistically significant association between type of intervention and grade of dysphonia, both perceived by the patient and evaluated in an objective manner. A poorer functional result was found proportional to the extent of the larynx resected downwards (best results for SLs, then for SCPLs and finally for STPLs).

There are several studies on swallowing impairment following HOPLs, especially following SCPLs, demonstrating an overall incidence of temporary aspiration varying from 32% to 89%, regardless of patient age at surgery;[22] similarly, the rate of AP in the initial post-operative period ranges from 4.3% to 23%. In a large series of patients, Benito et al.[4] have demonstrated that age (alone) should not be considered as a major contraindication for SCPLs despite the fact that statistical analysis has demonstrated a risk of Grade II–III aspiration (Pearson's scale) only in patients >70 years old in the case of CHP with partial or total arytenoid resection. In another study, Schindler et al. have compared 10 patients aged >65 years at the time of surgery with 10 younger patients, concluding that age (alone) was not a major drawback in these interventions.[21]

The case of the present study cohort is different. The patients undergoing surgery ranged between 56 and 73 years, were analyzed after a minimum follow-up period of 120 months (range 120–232 months) and were subjected to different types of open partial interventions on the larynx (nine different types) that essentially differ in the amount of resection and in the functional violation of glottic and sub-glottic sites. This is therefore a study that directly and indirectly analyzes the function of the neolarynx a considerable period of time after surgery, when, in particular, the function of swallowing may have stabilized considerably and therefore be subjected to possible physiological deterioration of function, referred to as 'presbyphagia'.

In 2011, Van der Maarel-Wierink et al.[23] conducted a systematic literature review of the risk factors for aspiration pneumonia in the elderly and the results showed evidence of a positive relationship between aspiration pneumonia and the risk of dysphagia.
In another literature review, Eisenstadt[24] found that dysphagia and the resulting aspiration may be prevalent in the older population, but symptoms are not always clinically evident. In 1995, using videofluoroscopy, Frederick et al.[25] showed an increase in swallowing alterations with aging. In particular, in subjects older than 60 years, persistence of the bolus in the valleculae and pyriform fossa was observed with increased risk of laryngeal penetration and aspiration, asymmetry and hypertrophy of the crico-pharyngeal muscle and, in some cases, the presence of a Zenker's diverticulum.

These latter features are the same as those found in a subset of our more dysphagic patients who, statistically, were those undergoing more extended resections. In this series, at the end of the first post-operative month, normal swallowing (Pearson's Scale Grade 0) was achieved in 70.0% of patients while 2 months after surgery, some difficulties of swallowing were encountered with Pearson's Grades I and II in 5% and 2.5% of patients. Overall, for 8/80 patients (10%), a temporary gastrostomy was needed and in 75% of these cases, this was removed during the first post-operative year. Only in one case was the gastrostomy maintained for a long period (4 years) due to repeated episodes of AP and severe dysphagia for liquids until the patient had been subjected to two endoscopic procedures of injective laryngoplasty using Vox-Implant that successfully resolved the dysphagia, allowing gastrostomy removal.

After a long-term follow-up period, the swallowing analysis showed that, in patients aging with a larynx subjected to HOPL, the severity of dysphagia in those aged >70 years was of course more pronounced than in a normal population of similar age but certainly less than would be expected as 72.5% of patients, despite the previous intervention of HOPL, achieved and maintained a very good level of rehabilitation, identified by grades 6–7 of the DOS Scale. Since all of these patients were elderly (mean age 74.8 years) at the time of the videofluorographic study of swallowing, it is clear that, in patients who had achieved a good level of swallowing rehabilitation after surgery, dysphagia remains stable over time and, compared to a population of the same age not suffering from particular diseases, is not significantly worse.

These considerations do not apply to patients who have already suffered important swallowing disorders in the immediate post-operative period. The more severe levels of dysphagia, grade 3–4 of the DOS Scale, were found in SLs at a rate of 4.3%, in SCPLs at a rate of 8.8% and in STPLs at a rate of 33.3%. AP episodes occur more frequently in the early years after surgery in the more extended procedures (one arytenoid resection, one cricoarytenoid unit resection, enlargement to the base of the tongue, supratracheal resection) but are less frequent a long time after the operation.

The latter data referring especially to supratracheal laryngectomies require careful and cautious evaluation. In a series of 70 consecutive supratracheal laryngectomies, Rizzotto et al.[2] observed acute complications in 7.1% of patients. The most frequent was AP, in 60% out of all acute complications. Late sequelae occurred in 28.6% of patients. Of these, the majority were due to laryngeal obstruction (70% of late sequelae), most of which were related to chronic edema or mucosal flaps of the neolarynx while in 27.1% of cases, patients suffered from intermittent or persistent aspiration. The authors emphasized that the majority of late sequelae were treated by one or two transoral procedures using a $CO_2$ laser. In patients who developed late sequelae, the larynx was spared in 17/20 (85%), and total laryngectomy was proposed in only one patient for persistent aspiration but he refused preferring to keep the gastrostomy and maintain voice. After these "extreme" function sparing procedures, it is necessary to be prepared for subsequent endoscopic surgery, laser surgery or injective laryngoplasty to correct the anatomical and functional results and to achieve the best possible outcome. Fortunately, in only a few cases, persistent dysphagia and aspiration pneumonia still represent major complications in patients undergoing STPLs and significantly affect their physical and emotional condition.

The reality, therefore, is that, after a supratracheal laryngectomy with a cricoarytenoid unit resection, it is difficult to achieve an optimal degree of recovery of swallowing (grade 7–6 of the DOSS in only 25% of cases), and, in most cases (>75% of cases), the patient still manages to reach and maintain a sufficient level of rehabilitation from dysphagia over time

(DOSS grade >4) which corresponds to an acceptable autonomy of the solid and liquid food oral intake. This aspect can be understood by analyzing the characteristics of supratracheal laryngectomy extending to a cricoarytenoid unit.[10] In this case, from the side of the resected hemy-cricoid plate, there is a clear lack of wall between the hypopharynx and larynx, represented by the posterolateral portion of the cricoid cartilage, which is only replaced by suturing the hypopharyngeal mucosa to the tracheal stump to recreate a good patency of the pyriform sinus (Fig. 2). This defect may represent a route of food entry into the larynx that can be treated by maintaining a proper laryngopharyngeal sensation, recreating a functional neoglottic valve with the contralateral cricoarytenoid unit, constructing a pexy between the trachea and hyoid bone, and enhancing physiological coordination during swallowing.

Since the dysphagia observed in patients who underwent HOPL is undoubtedly the product of anatomical and physiological alterations of the larynx but also due to presbyphagia, what possible explanation can be given for the interesting phenomenon represented by having a degree of dysphagia less than expected (taking into account the amount of larynx resected) and in particular, that the dysphagia does not appear to deteriorate during aging? And also why did data collected from patients using self-assessment questionnaires of dysphagia report rates that were more than satisfactory in 97.5% of cases?

The explanation could be that, in addition to providing the cornerstone of functional recovery, all horizontal partial laryngectomies offer the following surgical highlights: (a) preservation of the superior laryngeal nerves, (b) good patency of the pyriform sinuses, (c) the presence of at least one functioning cricoarytenoid unit and finally, (d) the suspension of the residual larynx to the hyoid bone. This latter condition involves the placement of the cricoid at a level higher than what is physiologically found in the healthy adult, in a position more similar to what is found in the newborn, where a facilitated swallowing act is favored by the higher position of the larynx and large patency of the pyriform sinuses. This is what is obtained by raising the cricoid closer to the base of the tongue, in a more advantageous position for swallowing, and is equivalent to what is observed in the adult during the pharyngeal phase of swallowing. As evidence of this statement, videofluorography frames are shown during the respiratory phase in a newborn (Fig. 3A), in a normal elderly subject

(Fig. 3B), and in an elderly patient who had already undergone SCPL-CHEP (Fig. 3C). As can be seen, the lower edge of the cricoid both in the newborn and in the patient subjected to SCPL-CHEP is located at the level of the vertebral body of C5 and this is a consistent condition in all patients subjected to HOPL; on the other hand, in the elderly patient, the lower edge of the cricoid is located at the level of the vertebral body of C6-C7, in a less advantageous functional position. It can therefore be said that this condition, reproducing the anatomical conditions found in the newborn, tends to counteract the physiological decay of the laryngeal swallowing function, despite the fact that significant portions of the larynx have been sacrificed.

In this way, it is possible to explain the low incidence of AP episodes observed during long-term follow-up and the fact that the clinical evaluation of pulmonary function of patients at last follow-up was still satisfactory (no cases of dyspnea at repose, only four patients with Karnofsky Index less than 80, two patients with Karnofsky Index less than 70). After discharge, 13 episodes of AP were observed, which occurred in only eight out 80 patients. Overall, three episodes of AP occurred in the last 3 years and 10 in the previous 12 years, nine of which occurred in the first 3 years after surgery. In our opinion, this is related to the adoption by physicians and patients of measures to reduce the risk of aspiration (placement of temporary gastrostomy for patients suffering from severe dysphagia, prolonged and repeated chest therapy and swallowing rehabilitation, elimination of food at risk in two patients with more than one episode of pneumonia during follow-up) and the possibility to carry out corrective endoscopic procedures (e.g. injective laryngoplasty in two patients with more than one episode of pneumonia during follow-up).

It is thus established on the basis of indirect findings on the AP episodes that the incidence of these phenomena increases slightly with age but this is not statistically significant, while a statistically significant correlation was confirmed between the extent of resection and the risk of AP, as already observed by Benito et al.[4]

In conclusion, the results of laryngeal functionality in a sample of elderly patients (age >70 years subjected to HOPLs and examined at least 10 years after surgery) are undoubtedly stable and repeatable both for SLs and SCPLs, as already reported by many authors. For STPLs, this is the first study in terms of functional outcome and, although the function of the remaining larynx is poorer, both objective and subjective outcomes have demonstrated the quite satisfactory validity of STPLs in sparing laryngeal function, albeit at the obvious expense of a ‘simplified’ laryngeal framework. This shows the immense ability of this organ to recover the essentials of its function after partial surgical mutilation, provided that tissue has been sacrificed and the organ reconstructed according to ‘functional criteria’.

The results of this study reveal that, despite the disruption of the normal anatomy of the larynx, in patients who underwent HOPLs (and aged with an operated larynx), laryngeal functions, in particular swallowing, are impaired but this did not significantly affect quality of life, especially when compared to the laryngeal functions of elderly subjects who did not receive any procedures on the larynx.

Aspiration pneumonia, the most dangerous complication of HOPL, seems to be more frequent in the initial post-operative period and less so in subsequent years, thanks to the maintenance of temporary gastrostomy, prolonged chest therapy and rehabilitation of swallowing.

Finally, the injective laryngoplasty techniques can now offer effective solutions in the more dysphagic patients.[26]

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**TABLE 1 Surgical procedures in the study cohort**

| Type of procedure | No. (%) |
|---|---|
| **SLs** | **17 (21.2)** |
| **Extended SLs** | **6 (7.5)** |
| to base of tongue | 4 |
| to pyriform sinus | 2 |
| | |
| **SCPLs** | **45 (56.3)** |
| CHEP | 19 |
| CHEP + A | 17 |
| CHP | 4 |
| CHP + A | 5 |
| | |
| **STPLs** | **12 (15)** |
| THEP | 7 |
| THEP + A | 3 |
| THP | 2 |

**TABLE Number (%) of patients with AP and association between AP and type of procedure**

| Surgical procedures | N° patients (%) | No. AP (%) |
|---|---|---|
| SL | 1/23 (4.3) | 2 (15.4) |
| SCPL | 5/45 (11.1) | 6 (46.1) |
| STPL | 2/12 (16.7) | 5 (38.5) |
| Statistical analysis | P = 0.0131 | |

**TABLE 3 Videofluorographic study of swallowing assessed using the DOS scale and listed by type of procedure**

| DOSS | No. | % | Type of procedure | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | SL | Extended SL | CHEP | CHEP + A | CHP | CHP + A | THEP | THEP + A | THP |
| **7** | 34 | 42.5 | 15 | – | 12 | 4 | 1 | 2 | – | – | – |
| **6** | 24 | 30.0 | 1 | 4 | 3 | 11 | 1 | 1 | 1 | 2 | – |
| **5** | 13 | 16.3 | – | 2 | 3 | 1 | 1 | 1 | 5 | – | – |
| **4** | 7 | 8.8 | 1 | – | 1 | 1 | 1 | 1 | 1 | – | 1 |
| **3** | 2 | 2.5 | – | – | – | – | – | – | – | 1 | 1 |
| | Statistical analysis | | | | | | P < 0.001 | | | | |

**TABLE 4 Results of dysphagia self-assessment using the MDADI questionnaire listed by type of procedure**

| MDADI | No. | % | Type of procedure | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | SL | Extended SL | CHEP | CHEP + A | CHP | CHP + A | THEP | THEP + A | THP |
| **20–40** | 67 | 83.8 | 17 | 6 | 15 | 15 | 3 | 4 | 6 | 1 | – |
| **41–60** | 11 | 13.8 | – | – | 3 | 1 | 1 | 1 | 1 | 2 | 2 |
| **61–80** | 2 | 2.5 | – | – | 1 | 1 | – | – | – | – | – |
| **81–100** | | | – | – | – | – | – | – | – | – | – |
| | Statistical analysis | | | | | | P = 0.0125 | | | | |

**TABLE 5** **Results of voice analysis by GIRBAS scale and by self-evaluation using the VHI questionnaire listed by type of procedure**

| | No. | % | Type of procedure | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | **SL** | **Extended SL** | **CHEP** | **CHEP + A** | **CHP** | **CHP + A** | **THEP** | **THEP + A** | **THP** |
| **GIRBAS** | | | | | | | | | | | |
| **0-1** | 16 | 20 | 15 | 1 | – | – | – | – | – | – | – |
| **1.01-2** | 40 | 50 | 1 | 3 | 12 | 11 | 4 | 3 | 4 | 1 | 1 |
| **2.01-3** | 24 | 30 | 1 | 2 | 7 | 6 | | 2 | 3 | 2 | 1 |
| Statistical analysis | | | | | $P < 0.001$ | | | | | | |
| **VHI** | | | | | | | | | | | |
| **0-30** | 48 | 60 | 13 | 3 | 10 | 10 | 3 | 5 | 1 | 2 | 1 |
| **31-60** | 22 | 27.5 | 4 | 3 | 4 | 5 | 1 | – | 4 | 1 | – |
| **61-90** | 9 | 11.3 | – | – | 5 | 2 | – | – | 1 | – | 1 |
| **91-120** | 1 | 1.3 | – | – | – | – | – | – | 1 | – | – |
| Statistical analysis | | | | | $P = 0.0125$ | | | | | | |

**TABLE 6** **Correlation between number of AP episodes and grade of dysphagia**

| Patient | Procedure | No. of AP episodes | DOSS grade | MDADI grade |
|---|---|---|---|---|
| 1 | THP | 3 | 3 | 58 |
| 2 | THEP + A | 2 | 3 | 55 |
| 3 | Extended SL | 2 | 5 | 38 |
| 4 | CHEP | 2 | 5 | 67 |
| 5 | CHEP | 1 | 4 | 58 |
| 6 | CHP | 1 | 4 | 43 |
| 7 | CHEP | 1 | 6 | 59 |
| 8 | CHEP | 1 | 5 | 73 |
| Statistical analysis | | | $P <0.001$ | $P <0.001$ |

**Fig. 1.** **Frequency of AP episodes during the follow-up period.**

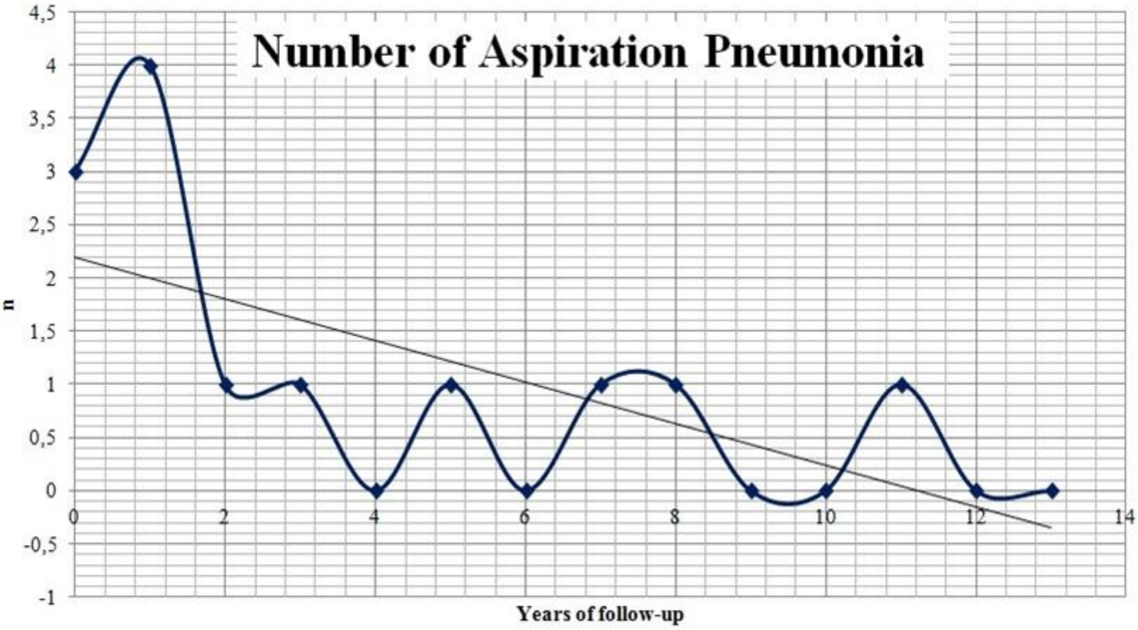



**Fig. 2. Supratracheal laryngectomy, highlighting the reconstructive step with suturing of the hypopharyngeal mucosa to the tracheal stump in order to recreate a good patency of the pyriform sinus.**

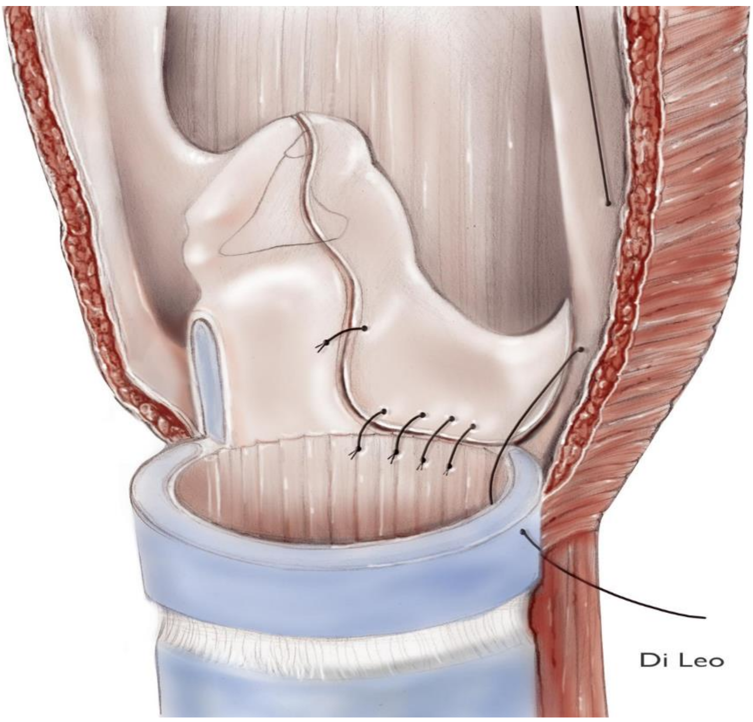
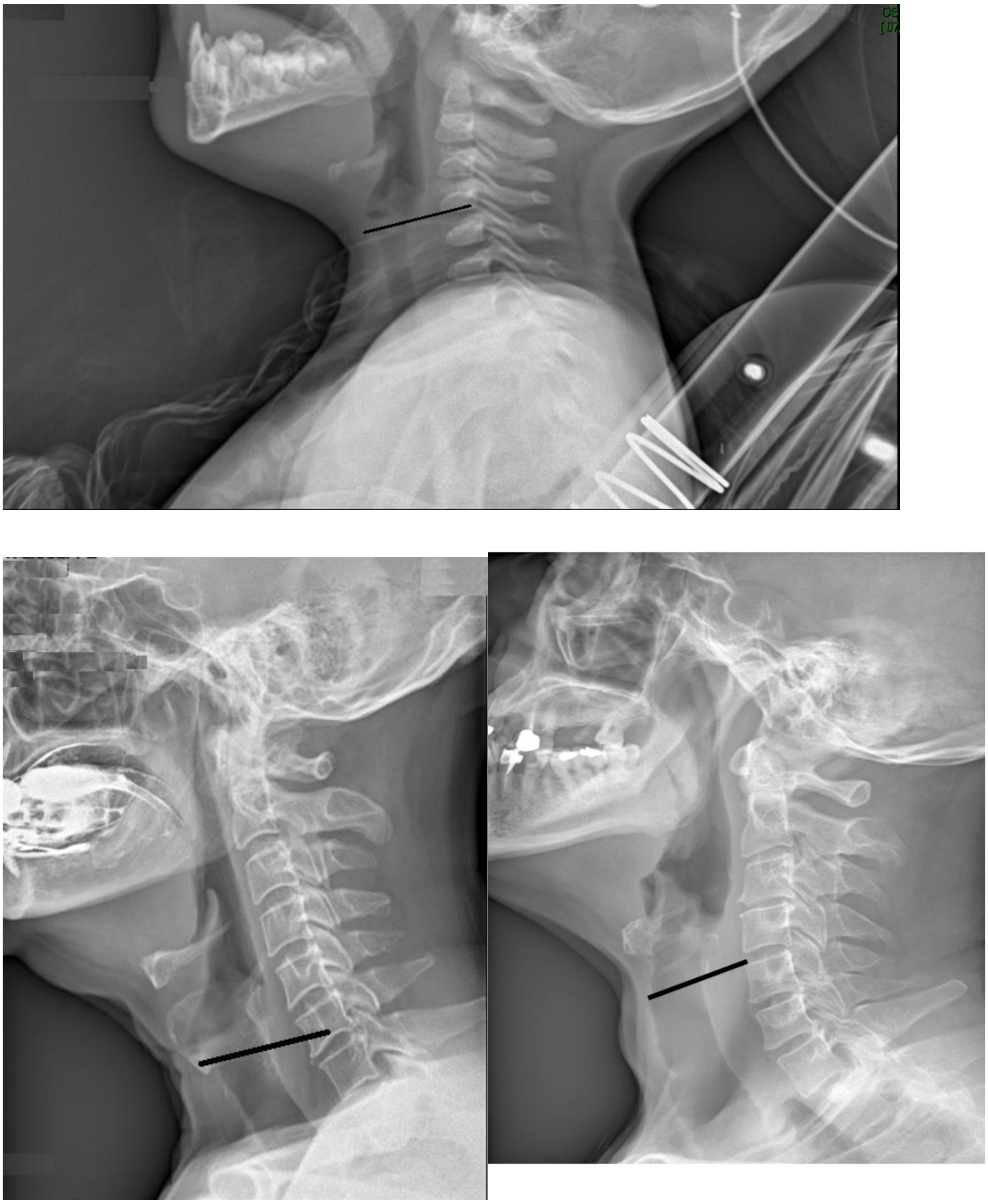


**Fig. 3. Videofluoroscopy during the respiratory phase in a newborn (A), in a normal elderly subject (B), and in an elderly patient who had already undergone SCPL-CHEP + A (C). The line is placed at the level of the lower edge of the cricoid plate.**



# Paper 5

## *Telephonic voice intelligibility after laryngeal cancer treatment: is therapeutic approach significant?*

**Abstract**

***Objective.*** The aim was to investigate telephonic voice intelligibility in patients treated for laryngeal cancer using different approaches.

***Study Design.*** A cross-sectional outcome study.

***Methods.*** In total, 90 patients treated for laryngeal cancer using different approaches and 12 healthy volunteers were recruited. Each patient and each healthy control read a list of words and sentences during a telephone call. Six auditors listened to each telephonic recording and transcribed the words and sentences they understood. Mean intelligibility rates for each treatment were assessed and compared.

***Results.*** Regarding words, the poorest intelligibility was noted for type II open partial horizontal laryngectomies, followed by total laryngectomies. The best intelligibility was found for transoral laser microsurgery, followed by radiotherapy alone. For sentences, the poorest intelligibility was noted for type II open partial horizontal laryngectomies, followed by chemo-radiotherapy. The best intelligibility was found for radiotherapy alone and transoral laser microsurgery.

***Conclusion.*** More aggressive surgery as well as chemo-radiotherapy correlated with significantly poorer outcomes. Transoral laser microsurgery or radiotherapy alone ensured the best telephonic voice intelligibility. Intermediate-advanced T stages at diagnosis also showed significantly poorer intelligibility outcomes, suggesting that T stage represents an independent negative prognostic factor for voice intelligibility after treatment.

**Key words:** laryngectomy, transoral laser microsurgery, radiotherapy, chemoradiotherapy, laryngeal cancer, telephone communication

## Introduction

Surgical and non-surgical treatment for laryngeal cancer can lead to voice impairment, with a severe impact on oral communication. This aspect can play a critical role affecting communication-related quality of life (QOL). People aging with verbal communication disabilities face demanding challenges in areas such as maintaining social roles, identity and accessing daily services [1]. The telephone is certainly one of the most impactful interaction tools within verbal communication. The number of mobile-cellular subscriptions worldwide is approaching the number of people on Earth and mobile cellular subscriptions today reach almost 7 billion, corresponding to a penetration rate of 96% [2]. As a rule, people with voice impairment after surgical treatment for laryngeal cancer complain of serious problems in communication by phone. In fact, laryngeal cancer treatment may impact on the control of both pitch and intensity of voice, with a significant deterioration of voice quality, prosody and – as a consequence – intelligibility.

Several treatment options are available today for the management of laryngeal cancer, including surgical and non-surgical approaches. Among these, non-surgical organ-sparing treatments and surgical function-sparing approaches allow preservation of the main laryngeal functions and avoid permanent tracheostoma, which causes cosmetic disability and results in a decreased QOL [3-5]. A consensus on the best treatment option for laryngeal cancer has not yet been reached and probably never will be. Similar overall survival, disease-free survival and loco-regional control rates are reported in the literature after total laryngectomy, partial laryngectomy, radiotherapy and chemotherapy [6-16]. Therefore, studies on long-term functional outcomes may be useful to guide both patients and clinicians in the choice of therapeutic option most consistent with the corresponding expectations and needs.

The aim of the present study was to investigate and compare telephonic voice intelligibility following different types of treatment for laryngeal cancer. The therapeutic options considered were: transoral laser microsurgery cordectomy (TLM) [17]; open partial horizontal laryngectomies (OPHLs) [18]; total laryngectomy (TL); radiotherapy alone (RT); and chemo-radiotherapy (CT/RT).

The hypothesis was that more aggressive surgical and non-surgical therapies, which are strictly correlated to T stage at diagnosis, would be associated with poorer telephonic voice intelligibility outcomes. The results of the study could give clinicians and patients new useful information about the impact of laryngeal cancer on telephonic communication, an important part of our everyday lives.

## Materials and Methods

This cross-sectional outcome study was carried out according to the Declaration of Helsinki and it was previously approved by the Institutional Review Board. All subjects enrolled in the study gave their written informed consent; all data were collected prospectively.

### *Population*

Ninety patients (14 females and 76 males) were selected randomly from a database of patients who underwent different types of treatment for laryngeal cancer between 1993 and 2013. Twenty had been treated with non-surgical organ-sparing approaches: 10 patients underwent RT, 10 patients underwent CT/RT; 70 patients had been treated with different types of surgery: 12 TL with tracheoesophageal puncture (TEP), 31 OPHL and 27 TLM. According to the European Laryngological Society classification, the OPHL group was composed of 10 type I OPHLs, 11 type II OPHLs and 10 type III OPHLs, while the TLM group was composed of 15 type I–II laser cordectomies and 12 type III–V cordectomies (Table 1). Among the group of patients undergoing surgery, none had been subjected to adjuvant therapy post-operatively. Selection criteria were: no evidence of disease at the last follow-up and at least 12 months after treatment. Age was 67.53 ± 8.49 years (mean ± SD) and the mean time after treatment was 58.87 ± 37.64 months. Twelve healthy volunteers (3 females and 9 males) were enrolled as controls. Mean age for the control group was 65.91 ± 6.54 years (mean ± SD).

### *Intelligibility on the phone: detection procedure*

Each subject was asked to read a list of 20 words and 5 brief sentences during a telephone call. Words and sentences were randomly selected from a pool of 400 bi/trisyllabic words and 200 short affirmative sentences (from 4 to 6 words) officially used in Italian vocal audiometry so that each subject received a different list. Telephone calls were made using Apple iPhone 4S smartphones (Apple, Cupertino, CA, USA). Each telephone call was recorded with Audacity software (version 2.0.5 for Windows) and matched to the respective list. In order to consider all possible types of interlocutor, six trained normal hearing auditors of different ages blindly listened to the telephonic recordings and wrote down the words and sentences they understood. Three of them were medical doctors (two of them were ENT residents, and one was an ENT specialist) and were familiar with the types of phonatory outcome related to the different surgical and non-surgical therapies, while the other three were not medical doctors and were unaware of the latter aspect. Each listener could listen once to each word and sentence before writing it down. The lists of words and sentences written by the listeners were then compared to the original ones by another researcher to obtain the number of correctly reported words and sentences. Only words and phrases perfectly matching the original lists read by the patients were considered to be correct.

### *Statistical analysis*

Statistical analysis was performed with STATA 13 software for Windows (StataCorp LP). The two-way mixed Intra-Class Correlation (ICC) index and the 95% confidence interval (CI) were calculated to evaluate inter-rater reliability. The ICC index describes how strongly units in the same group resemble each other (ICC = 1 indicates a perfect correspondence). ICC indexes were calculated for the 6 listeners together and separately for the three medical doctors (expert listeners) and for the three non-expert listeners. Poisson multilevel regression was employed to calculate the mean intelligibility rates for words and sentences, considering the results of the six listeners. The "patient variable" was considered to be a random factor, while the "treatment variable" or the "T stage variable" were separately considered to be fixed variables. Mean intelligibility rates and 95% CI were first calculated for each treatment group and for the control group; then they were calculated for cT stage of disease at diagnosis (T1 Vs T2 Vs T3 Vs T4 and T1+T2 Vs T3+T4) and for the control group. The results were then compared. The differences were considered to be statistically significant for $p < 0.05$.

## Results

No statistically significant differences concerning age, gender and time after treatment were found between the various groups. Regarding inter-rater reliability, an ICC index of 0.82 was found for words and 0.61 for sentences. Expert listeners had an ICC index of 0.83 for words and 0.64 for sentences. Non-expert listeners had an ICC index of 0.91 for words and 0.63 for sentences. ICC values and 95% CI are shown in Table 2.

***Intelligibility of words***

Mean telephonic intelligibility rates (MTIRs) (with 95% CI) for words for each treatment group and for the control group are shown graphically in Figure 1. Not one of the groups of patients or controls reached 100% telephonic intelligibility for words. Controls, TLM, RT and type I OPHL showed the highest MTIRs, while CT/RT, TL, and type II and type III OPHLs revealed poorer intelligibility results. The MTIR obtained for controls was significantly higher than the MTIRs obtained for type I–II TLM (p=0.042), type III–V TLM (p=0.003), TL (p<0.001), type I OPHL (p<0.001), type II OPHL (p<0.001), type III OPHL (p=0.001), RT (p=0.015), and CT/RT (p=0.006). The MTIR obtained for type II OPHLs was significantly lower than those obtained for type I–II TLM (p<0.001), type III–V TLM (p=0.002), RT (p=0.002), type I OPHLs (p=0.002) and CT/RT (p=0.008). The MTIR for TL was significantly lower than those for type I–II TLM (p<0.001), type III–V TLM (p=0.003), RT (p=0.004) and type I OPHLs (p=0.003). The MTIR for type III OPHLs was significantly lower than those obtained for type I–II TLM (p=0.004), type III–V TLM (p=0.022), RT (p=0.025), and type I OPHLs (p=0.028). The MTIR obtained for type I OPHLs was significantly lower than for type I–II TLM (p=0.029). Figure 2 shows the intelligibility variations according to type of treatment in comparison to the control group (which revealed the best outcome). MTIRs (with 95% CI) for words for each T stage group (T1, T2, T3 and T4) and for the control group are shown graphically in Figure 3. The MTIR obtained for controls was significantly higher than those obtained for the T1 group (p<0.001), T2 group (p=0.001), T3 group (p<0.001) and T4 group (p<0.001). The MTIR obtained for the T1 group was significantly higher than those obtained for the T2 group (p=0.023), T3 group (p=0.004) and T4 group (p<0.001). Among the MTIRs for the T2, T3 and T4 groups, there were no statistically significant differences. Figure 4 shows the intelligibility variations according to T stage of disease at diagnosis in comparison to the control group (which revealed the best outcome).

***Intelligibility of sentences***

MTIRs (with 95% CI) for sentences for each treatment group and for the control group are shown graphically in Figure 5. Concerning sentences, 100% telephonic intelligibility was only reached by the control group. Controls, TLM, RT and type I OPHL showed the highest MTIRs, while CT/RT, TL, and type II and type III OPHLs revealed poorer MTIRs. The MTIR obtained for controls was significantly higher than the MTIRs obtained for type I–II TLM (p=0.003), type III–V TLM (p=0.017), TL (p<0.001), type I OPHL (p=0.019), type II OPHL (p=0.003), type III OPHL (p=0.011), RT (p=0.027), and CT/RT (p=0.023). The MTIR obtained for type II OPHL was significantly lower than the MTIRs obtained for RT (p=0.004), type I–II TLM (p=0.005), type III–V TLM (p=0.006), type I OPHL (p=0.008) and type III OPHL (p=0.031). The MTIR obtained for the CT/RT group was significantly lower than those for RT (p=0.032) and type I–II TLM (p=0.040). The MTIR for TL was significantly lower than those for RT (p<0.001), type I–II TLM (p<0.001), type III–V TLM (p=0.040), and type I OPHL (p=0.007). The MTIR obtained for type III OPHL was significantly lower than those for type I–II TLM (p=0.034). Figure 6 shows the intelligibility variations according to type of treatment in comparison to the control group (which revealed the best outcome). MTIRs (with 95% CI) for sentences for each T stage group (T1, T2, T3 and T4) and for the control group are shown graphically in Figure 7. The MTIR obtained for controls was significantly higher than those obtained for the T1 group (p=0.001), T2 group (p=0.009), T3 group (p=0.007) and T4 group (p<0.001). The MTIR obtained for the T1 group was significantly higher than those obtained for the T2 group (p=0.028), T3 group (p=0.017) and T4 group (p<0.001). Among the MTIRs for the T2, T3 and T4 groups, there were no statistically significant differences. Figure 8 shows the intelligibility variations according to T stage at diagnosis in comparison to the control group (which revealed the best outcome).

## Discussion

A recent survey by SuperMoney [19] on a sample of 40,000 Italian phone users showed that time spent on the phone (between calls, emails, messages and web surfing) is constantly growing. Concerning telephone calls, between 2011 and 2012 a 13.19% increase in dialed calls and a 3.81% increase in received calls was registered as well as an increase in average call duration of 3.41% (a mean of 4.5 minutes). In the analyzed sample, a mean time of 37 minutes was dedicated to phone calls every day, suggesting that the telephone is having a high and growing impact on everyday communication-related QOL.

In the present study, telephonic voice intelligibility outcomes in a group of 90 patients who had undergone different treatments for laryngeal cancer were compared. To the best of our knowledge, no systematic data on this subject is present in the literature, although many authors have studied long-term functional outcomes – including voice quality – after different surgical and non-surgical therapeutic approaches [20-43].

Long-term functional outcomes after OPHLs – in particular, type II OPHLs – have been investigated widely. Voice quality is certainly the "Achilles Heel" of type II OPHL. In this surgery, both vocal folds are sacrificed and the voice is produced by vibration of the arytenoid mucosa against the epiglottis/tongue base. The site of the mucosal wave is normally observed between the anterior aspect of the body of one or both arytenoids and the tongue base or epiglottis [4]. Thus, the vocal signal after type II OPHL shows substantially less volitionally induced valving activity and resistance to airflow during voicing [21-24], resulting in a strained, deep and asexuated voice (difficult to modulate and to raise) and speech that is composed of short sentences, because the patients rapidly become short of breath [18, 25-27]. Functional results of type III OPHLs have recently been analyzed [28], showing similar outcomes to type II OPHLs [29], with severe voice impairment but well preserved oral communication, and with almost all patients showing a good attitude towards their communication dysfunction.

TLs also result in a deterioration of the voice (less than one might expect) and lower voice-related quality of life (VRQOL) than in the general population [3-5]. Today, phonation after TL can be obtained by TEP and prosthesis or esophageal speech [30-33]. In the current study, only patients speaking by TEP were recruited as this is the gold standard allowing the recovery of a good conversational voice. Many authors have studied the long-term functional outcomes of TL and compared them to those obtained with partial laryngectomies (in particular, type II OPHLs) [4, 23, 26, 27, 34]. Concerning VRQOL, most authors have reported a moderate reduction in VRQOL after type II OPHL; however, the reports are somewhat contradictory [4, 23, 26, 27, 34]. Laser cordectomies guarantee better voice outcomes than radical or reconstructive larynx surgery. Many authors have studied voice quality after TLM, reporting good functional results, with minimal impact on a patient's QOL. Peretti and colleagues [35, 36] studied voice outcomes after TLM for Tis-T1 carcinomas, reporting significant voice improvement after type I and II cordectomies, with voice attaining nearly normal parameters. In contrast, after type III, IV and V cordectomies, the vocal outcome was not significantly different from the preoperative pattern. Favorable functional outcomes were also found for T2 and selected T3 glottic tumors treated with TLM.

Some authors compared voice quality after TLM or RT. Czecior et al. [37] found no significant voice quality differences in patients treated for early glottic cancer with regard to self-assessment, perceptual assessment based on the GIRBAS scale, phonation closure and maximal phonation time. Aaltonen et al. [38] reported similar overall voice quality between TLM and RT groups, even if voice was more breathy and the glottal gap was wider in patients treated with laser surgery than in those who received radiation therapy. Cohen et al. [39] studied VRQOL in T1 glottic cancer comparing irradiation and laser endoscopic excision and reported comparable levels of voice handicap in both groups.

Concerning organ preservation approaches with CT/RT, Lau et al. [40] studied voice quality after CT/RT in patients with locally advanced cancer; differences with controls were observed with shimmer, jitter, harmonics-to-noise ratio, and maximum phonation time (MPT). Al-Mamgani et al. [41] found that the addition of chemotherapy to radiotherapy in T3 laryngeal cancer does not determine a statistically significant increase in Voice Handicap Index (VHI). Campos et al. [42] compared voice outcomes in patients who underwent RT or CT/RT, showing that chemo-radiation organ preservation protocols may preserve the organ but may cause reduced function with communication sequelae. Carrara et al. [43] studied concurrent CT/RT for laryngeal cancer, finding mild to moderate voice abnormalities, yet allowing intelligible communication.

Focusing on the results of the present study, the ICC index showed a good inter-rater reliability for words, while ICC was not satisfactory for sentences. This result could be related to the different professional backgrounds of the listeners: three of them were expert listeners trained to communicate with patients during follow-up after surgical and non-surgical therapies, while the other three were not experts and were unaware of what kind of voice quality to expect from the patients. Moreover, sentences were composed of 4 to 6 words and only perfectly reported sentences were considered correct during the matching procedure. Separate ICC indexes were then calculated for experts and non-experts for both words and sentences. ICC indexes for words were higher than ICC indexes for sentences both for experts and non-experts. The higher inter-rater variability found for phrases could suggest that a certain expertise in verbal communication with patients who had undergone various therapies for laryngeal cancer plays a crucial role in telephonic voice comprehension. Concerning telephonic intelligibility, as could be expected, type II and type III OPHLs, and TLs tended to give poorer MTIRs when compared to TLM, RT and type I OPHLs. Surprisingly, with regard to sentences, MTIRs for CT/RT were slightly lower than for TL and type III OPHL, and significantly lower than MTIRs for TLM and RT. On the other hand, telephonic intelligibility (both for words and for sentences) showed a significant correlation with the T stage of disease at diagnosis: the higher the T stage at diagnosis, the lower the telephonic intelligibility after treatment. These data could reflect the increased aggressiveness of the treatments on the larynx, proportional to T stage at diagnosis, resulting in poorer voice quality. This handicap might be enhanced during telephone speech due to the absence of a non-verbal communicative component. Moreover, many patients complained of some performance anxiety on the phone because, when the receiver is not prepared or is not expecting the call, he/she often hangs up the phone thinking it may be a prank call or a maniac call. This kind of event is more prevalent in female subjects.

TLM showed excellent outcomes in telephonic intelligibility (both type I–II and type III–V cordectomy groups), similar to those obtained with RT. In both groups, only patients with stage I–II were included. TLM reached the highest MTIR for words, whereas RT showed the best MTIR for sentences. Both TLM and RT represent minimally aggressive treatment options for laryngeal cancer. In fact, they focus on the glottis, which is almost always spared, thus respecting the whole architecture of the organ. They give good voice outcomes and, as a consequence, good intelligibility outcomes as well. Good MTIRs were also found for type I OPHL: this does not require removal of the vocal folds giving a satisfactory quality of voice. It is important to remember that we did not take into account patients undergoing adjuvant treatments. It must be remembered that, because of the advanced pT and/or pN stage, patients often undergo adjuvant (chemo)radiotherapy, with significantly worse phonatory outcomes.

Reconstructive open surgery such as type II or type III OPHLs and radical options such as TL showed poorer intelligibility outcomes but poor MTIRs have also been found for non-surgical organ sparing protocols with CT/RT, especially with sentences. While it is not surprising that a surgical procedure which causes loss of the glottis may worsen the voice, especially on the phone, a similar observation after a non-surgical treatment is less intuitive, even if the initial T-stage is advanced and, consequently, voice already has a poor quality before treatment. This result could reflect a certain laryngeal function exhaustibility, even if the organ is preserved, confirming the hypothesis that aggressive (surgical and non-surgical) therapeutic approaches correlate with more severe late communication sequelae.

**Conclusion**

The data obtained showed a clear deterioration of telephone intelligibility after more aggressive treatments for laryngeal cancer related to the site and stage of the tumor. Among these therapeutic approaches, the results for TL with TEP were statistically comparable to those for type II–III OPHLs, while type II OPHL showed the poorest results. Non-surgical organ sparing treatments with CT/RT showed similar telephonic intelligibility outcomes although slightly better, proving that the intermediate-advanced T stage represents an independent negative prognostic factor for voice intelligibility after treatment. These results should be taken into account, especially when the need to communicate by phone is absolutely necessary for the patient's QOL.

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**Table 1. Study population demographics**

| Type of treatment | N and % | Mean age (years) | Sex | Stage | Time from treatment (months) |
|---|---|---|---|---|---|
| Type I–II TLM | 15 (16.67%) | 68.1 | M = 12<br>F = 3 | I = 13<br>II = 2 | 57.25 |
| Type III–V TLM | 12 (13.33%) | 71 | M = 11<br>F = 1 | I = 8<br>II = 4 | 57.66 |
| TL | 12 (13.33%) | 68 | M = 9<br>F = 3 | III = 3<br>IVa = 9 | 56.83 |
| Type I OPHL | 10 (11.11%) | 64.8 | M = 10 | II = 4<br>III = 6 | 60.6 |
| Type II OPHL | 11 (12.22%) | 67.45 | M = 10<br>F = 1 | II = 3<br>III = 8 | 58.45 |
| Type III OPHL | 10 (11.11%) | 65.5 | M = 9<br>F = 1 | III = 8<br>IVa= 2 | 57.8 |
| RT | 10 (11.11%) | 67.1 | M = 8<br>F = 2 | I = 7<br>II = 3 | 63.6 |
| CT/RT | 10 (11.11%) | 69.1 | M = 7<br>F = 3 | III = 8<br>IVa = 2 | 60.2 |
| | 90 | | | | |

CT/RT, chemo-radiotherapy; OPHL, open partial horizontal laryngectomy; RT, radiotherapy; TL, total laryngectomy; TLM, transoral laser microsurgery.

**Table 2. Intra-Class Correlation (ICC) index**

| | ICC<br>Mean and 95% CI | ICC experts<br>Mean and 95% CI | ICC non-experts<br>Mean and 95% CI |
|---|---|---|---|
| Words | 0.82<br>(0.74 0.87) | 0.83<br>(0.71 0.89) | 0.91<br>(0.88 0.94) |
| Sentences | 0.61<br>(0.52 0.69) | 0.64<br>(0.54 0.73) | 0.63<br>(0.51 0.72) |

CI, confidence interval.

**Figure 1.** **Intelligibility rates for words according to type of treatment and for the control group. CT/RT, chemo-radiotherapy; OPHL, open partial horizontal laryngectomy; RT, radiotherapy; TL, total laryngectomy; TLM, transoral laser microsurgery.**

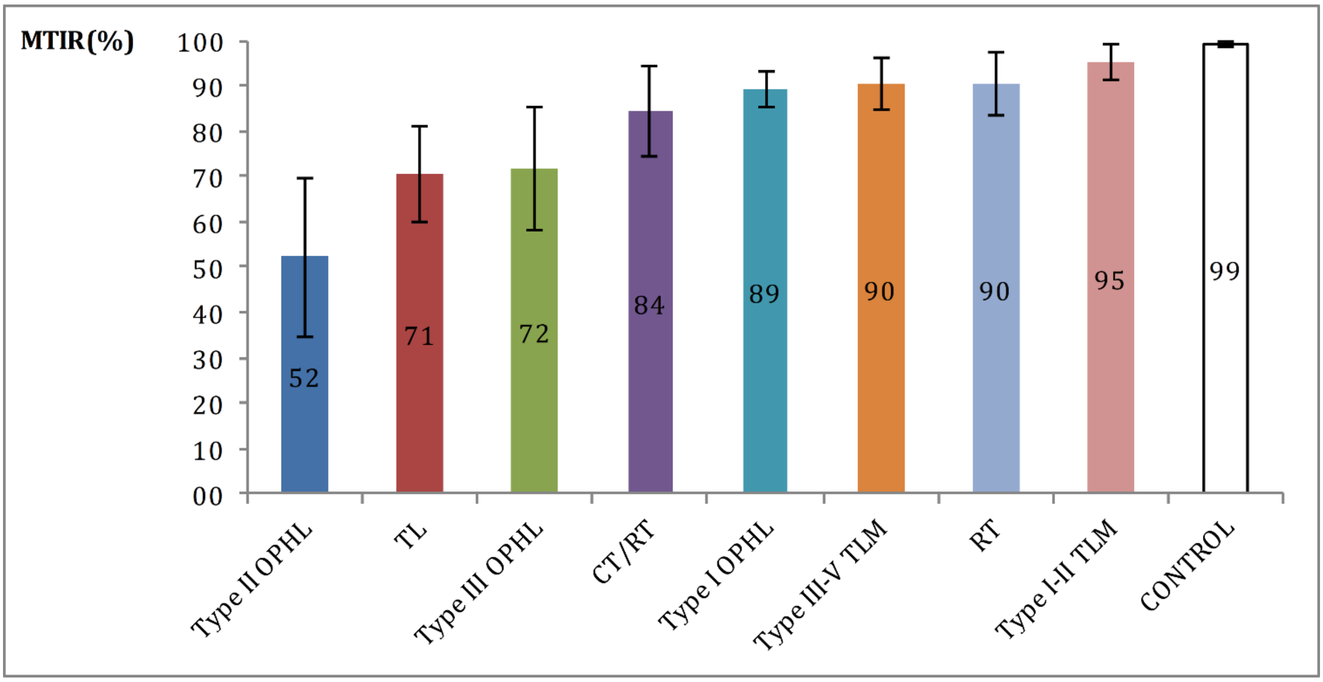


**Figure 2.** **Intelligibility variations for words according to type of treatment in relation to the control group (red line). CT/RT, chemo-radiotherapy; OPHL, open partial horizontal laryngectomy; RT, radiotherapy; TL, total laryngectomy; TLM, transoral laser microsurgery.**

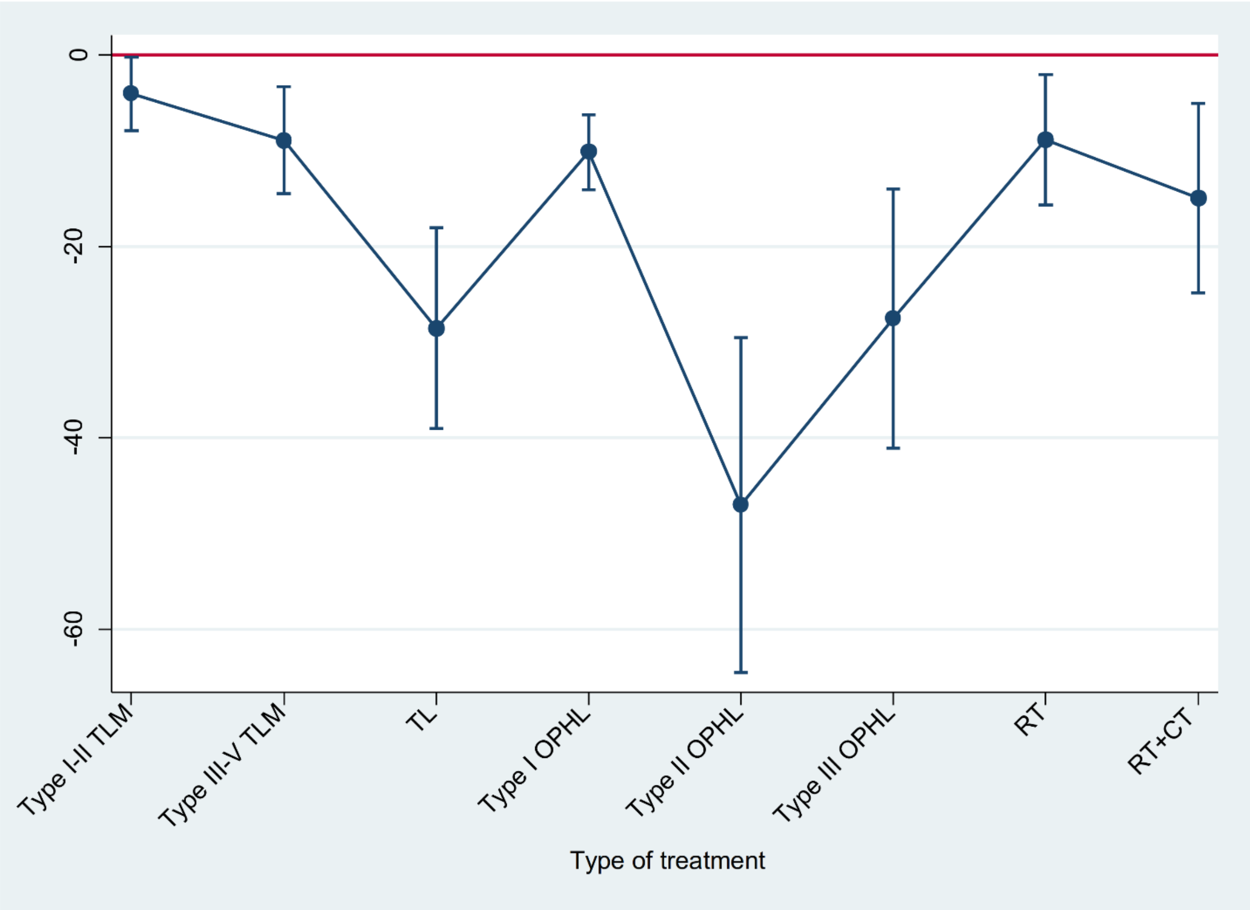


**Figure 3.** **Intelligibility rates for words according to T stage of disease at diagnosis and for the control group.**

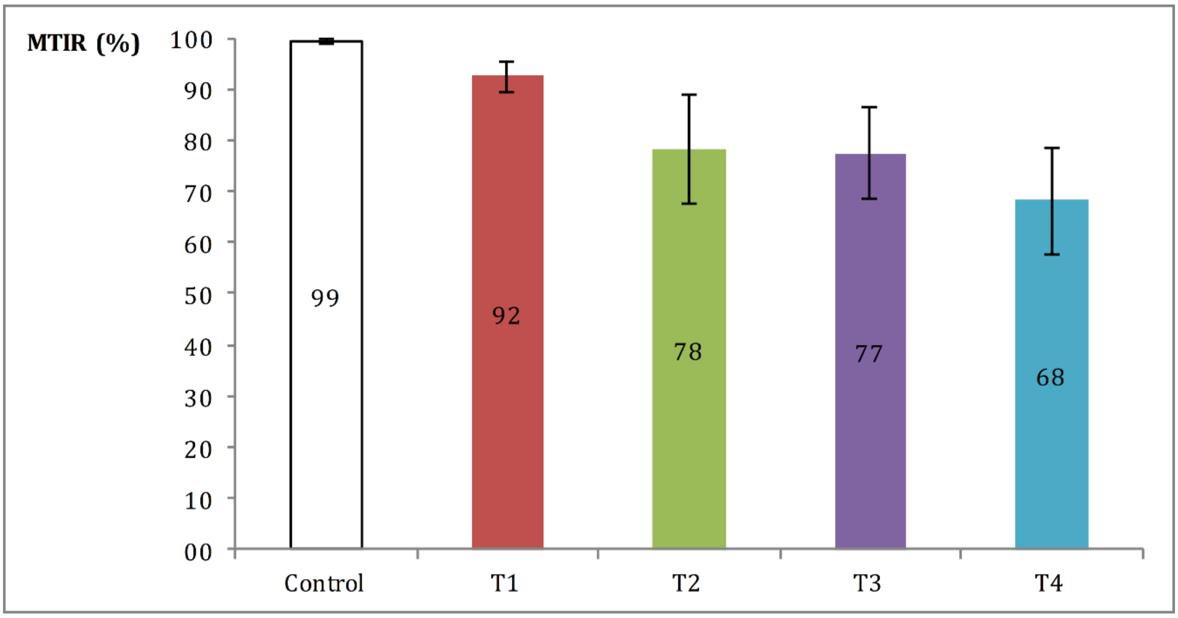



**Figure 4.** **Intelligibility variations for words according to T stage of disease at diagnosis in relation to the control group (red line).**

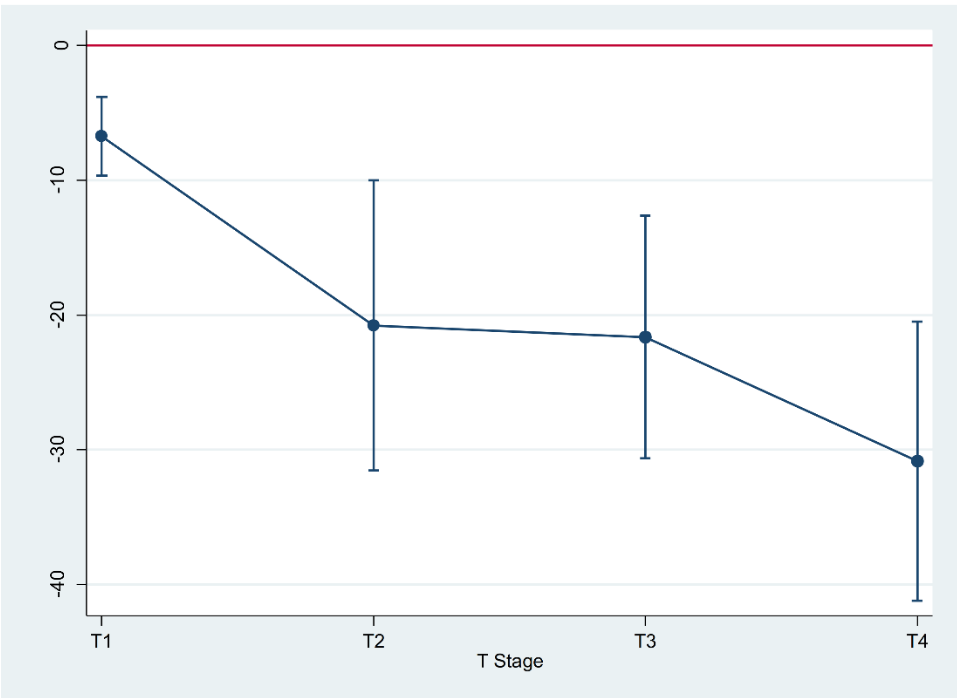


**Figure 5.** **Intelligibility rates for sentences according to type of treatment and for the control group. CT/RT, chemo-radiotherapy; OPHL, open partial horizontal laryngectomy; RT, radiotherapy; TL, total laryngectomy; TLM, transoral laser microsurgery**.

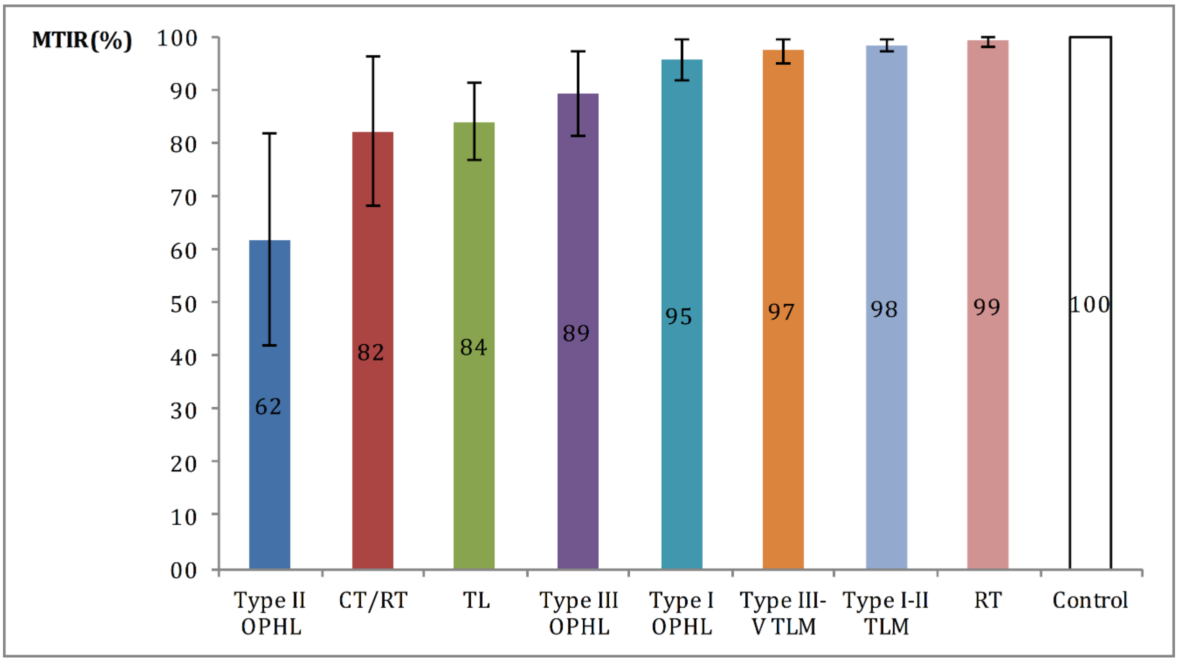


**Figure 6**. **Intelligibility variation for sentences according to type of treatment in relation to the control group (red line). CT/RT, chemo-radiotherapy; OPHL, open partial horizontal laryngectomy; RT, radiotherapy; TL, total laryngectomy; TLM, transoral laser microsurgery.**

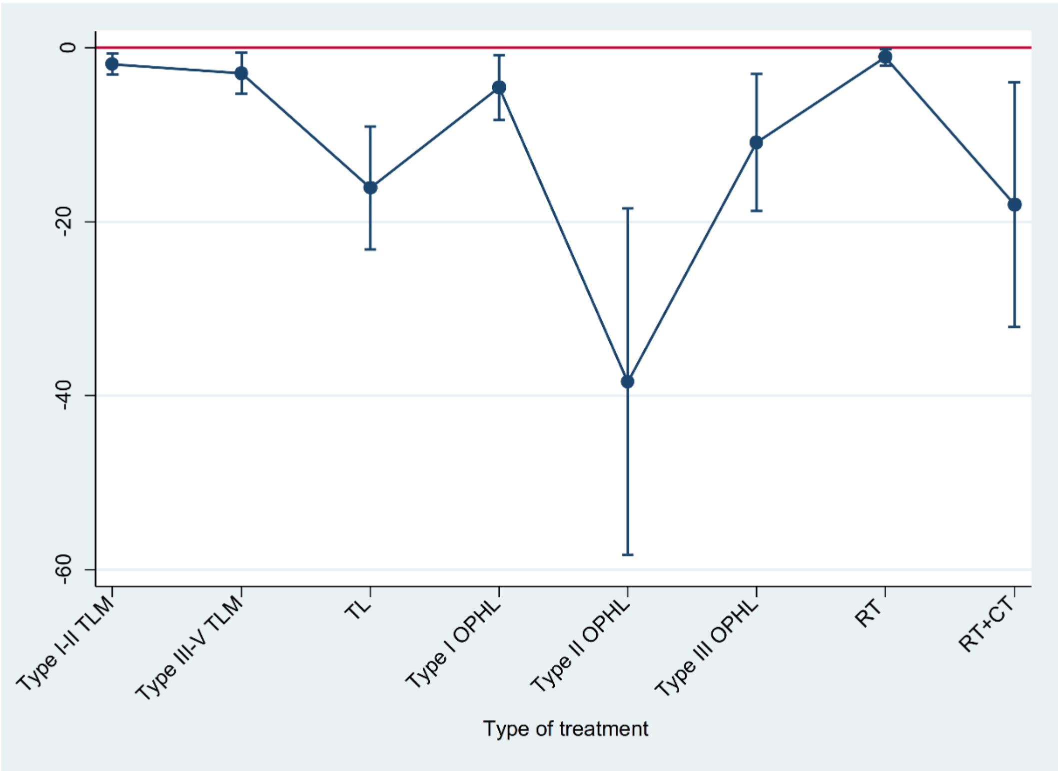


**Figure 7.** **Intelligibility rates for sentences according to T stage of disease at diagnosis and for the control group.**

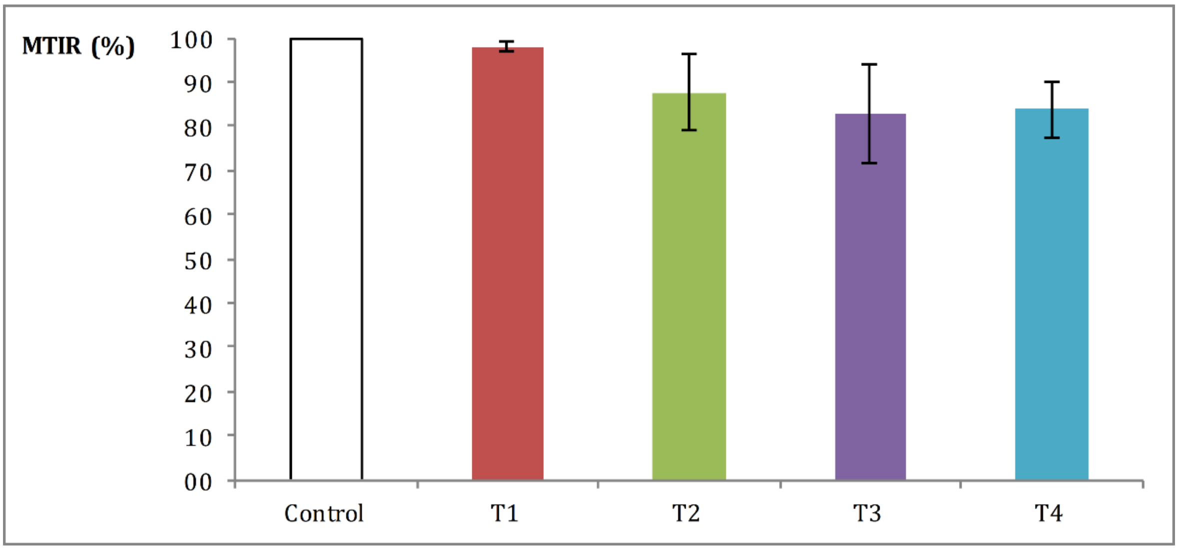
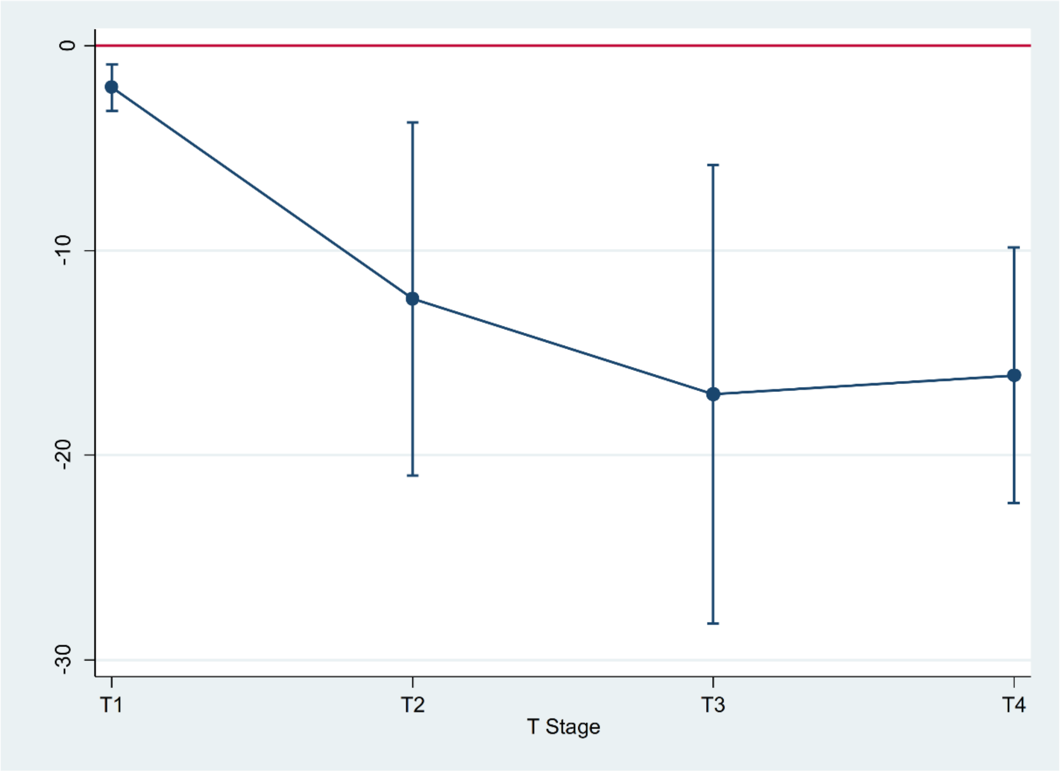



**Figure 8.** **Intelligibility variations for sentences according to T stage of disease at diagnosis in relation to the control group (red line).**



## Paper 6

### *Unravelling the risk factors that underlie laryngeal surgery in elderly*


**Summary**

Older patients are not considered good candidates to undergo more challenging therapeutic treatments, e.g. highly invasive surgery and complex chemotherapy. However, their exclusion from standard therapeutic options is not justifiable. Herein, we reviewed 212 patients aged ≥ 70, affected with laryngeal squamous cell carcinoma, and treated with transoral laser microsurgery or open neck (partial / total) laryngectomy with radical intent. The main aim was to compare patient outcomes to identify predictive factors that can be used by surgeons to choose the most appropriate treatment option. In our cohort, patients affected with more advanced tumour and hence treated by invasive open neck surgeries (above all TL) are more prone to develop complications and undergo fatal outcome than those with early disease treated by laser microsurgery, independently of age at surgery. In conclusion, elderly patients affected by laryngeal cancer can be treated similarly to younger patients, keeping in mind that more invasive surgeries are associated with a higher risk of developing complications. The advantages of mini-invasive surgery make it a possible first choice treatment in very old and frail patients suffering from laryngeal cancer, especially considering the recent success in treatment of some advanced stage tumours. Furthermore, comorbidities, by themselves, should not be used as exclusion criteria for subjecting an elderly patient to a different treatment that is from standard therapy.


**Introduction**

The progresses in science, technology and lifestyle are allowing people to live longer and better than those who lived even 50 years ago: as a global average, life expectancy at birth has increased from 46.9 to 70.0 years in the period 1950-2015, and is expected to be 75.9 years in 2050 and 81.8 in 2100 [1]. The "other side of the coin", however, resides in the concomitant increase in diagnosis of diseases that have the age as main aetiological factor (e.g. cardiovascular diseases, dementia, diabetes etc.). Among these, cancer can be considered as an archetype, inasmuch as incidence rates increase with age [2]. As a direct consequence, in the near future, the number of elderly with cancer will increase substantially [3]. In particular, amongst the different cancer histotypes, epidemiological studies foresee an increase up to 64% in diagnosis of head and neck squamous cell carcinoma (HNSCC) within the next 20 years [4 5].

The guidelines for the treatment of HNSCC, and more specifically laryngeal SCC, require chemoradiotherapy and/or invasive surgery on the basis of tumour stage and the need to preserve organ functionality [6]. In this context, less invasive/function-sparing surgical techniques have arisen in the last decade, although they are often limited to early stage tumours or require careful selection of patients [7-9]. In this scenario, the elderly are not considered good candidates to undergo more challenging therapeutic treatments, especially highly invasive surgery and complex chemoradiotherapy [10-12]. In addition, the management of head and neck cancer in the elderly has been historically heterogeneous, often marred by many prejudices, mainly based on both patient age and general health perceptions. In fact, aging is related to the decline of many physiological and cognitive functions, which may emphasise (and sometimes falsely require) the need to treat the elderly in a different and more limited mode than younger patients, even if no significant comorbidities are present [13]. Nowadays, this common perception is changing: the exclusion of elderly patients from standard therapeutic options is becoming less justifiable, taking advantage potentially of all therapeutic alternatives available after a proper screening. It is therefore essential to better establish the risk to which the patient is subjected for each proposed therapeutic option, be it surgical or non surgical [14].

In this 12-year multicentric retrospective study, we reviewed 212 patients aged at least 70, affected by laryngeal SCC, and treated with radical intent by 3 different types of surgical treatment: transoral laser microsurgery (TLM), open partial horizontal laryngectomy (OPHL) and total laryngectomy (TL). The population was further subgrouped into those 70-79 years old and over-80 based on age at surgery. The main aims of this study are to evaluate the incidence of complications after laryngeal surgery and identify predictive factors for the occurrence of complications in order to provide surgeons with information to choose the most appropriate treatment option. Due to the excellent oncological results achieved in “young” adult patients with TLM, even for more advanced stage tumours [15], the third purpose was to compare outcomes of TLM in elderly and frail patients, with those undergoing more invasive OPHL or TL surgeries.

## Materials and methods

*Patients*

All patients underwent laryngeal surgery at the Hospital of Modena or at the Martini – San Luigi Gonzaga Hospitals of Turin. As previously described 16, selection was based on routinely performed clinical assessment 3 weeks before surgery to evaluate the superficial and depth extent of the tumour.

Inclusion criteria were: age at surgery ≥ 70 years, histological diagnosis of laryngeal SCC and surgical treatment with a curative purpose as single modality or as part of a multimodality approach. Comorbidities, such as diabetes mellitus, hypertension, chronic obstructive pulmonary disease, cardiac disease (i.e. chronic heart failure, arrhythmia, and coronary artery disease), and hepatic, metabolic and cerebrovascular diseases, were not considered as exclusion criteria. OPHL are interventions considered at high risk for complications related to dysfunctional sequelae.

Therefore, more stringent selection criteria were adopted to exclude patients with certain risk factors related to:

• the patient, e.g. inability to climb two flights of stairs, mental status characterised by episodes of disorientation and confusion, clinical and radiological signs of pre-existing presbyphagia and severe osteophytosis at the cervical spine;

• family situation, e.g. absence of caregivers and declared impossibility of adhering to a complete rehabilitation programme;

• tumour, e.g. advanced stage disease needing more extensive resection (classified as OPHL type I + BOT, type IIb + ARY , type III + CAU).

Characteristics of the patient cohort are summarised in Table I.

*Surgery and postoperative care*

After informed consent was obtained, 212 patients underwent laryngeal surgery between January 1, 2001, and  December 31, 2012. The choice of the surgery was based on tumour stage and comorbidities, but not considering chronological age as a discriminatory factor.

Surgical procedures were transoral laser microsurgery / cordectomy in 113 patients (53.3%), open partial horizontal laryngectomy in 30 patients (14.2%), and total laryngectomy with or without pharyngectomy in 69 patients (32.5%).

One hundred-twenty patients (56.6%) underwent tracheostomy. On the basis of pathological findings (pN+ and/or extracapsular spread, extralaryngeal extent, positive margins), 33 patients (15.6%) were subjected to adjuvant radiotherapy: the primary site and all draining lymph nodes were 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/2Gy; range 62-68 Gy). Furthermore, 7 patients (3.3%) received 40 mg/m2 cisplatin weekly during the course of RT because of a higher risk of local recurrence.

*Statistical analysis*

The incidence of complications and type of surgery among different groups were evaluated by chi-square tests. The length of time from the date of diagnosis to the date of death (OS) or to the date of death for laryngeal SCC (disease-specific survival) was estimated using Kaplan-Meier curves. At the end of the study, the dates of last consultation for patients still alive were used for type-I censoring.

Log-rank and Gehan-Breslow-Wilcoxon tests (for early events) were used to compare Kaplan-Meier estimates between groups (type of surgery and postoperative complications). The CHAID (chi-square automatic interaction detection) method 17 was used to detect the optimal subdivision in order to maximise the differences in response within the different variables. Logistic regression was used to evaluate independent risk factors for development of perioperative and postoperative complications (within 30 days). These included age at surgery $\geq$ 80 years, gender, presence of comorbidities, type of surgery and duration of surgery.

Kaplan-Meier curves, log-rank and Gehan-Breslow-Wilcoxon tests were performed using Graphpad Prism version 6.0c (GraphPad Software, San Diego, CA, USA), whereas CHAID analysis and multivariate logistic regression were performed with IBMR SPSSR Statistics version 22 (IBM Corp., Armonk, NY, USA), with $p < 0.05$ as the statistically significant cut-off value.

## Results

*Patient comorbidities*

While 59 of 212 (27.8%) elderly patients who underwent laryngeal surgery did not present concomitant diseases, 86 (40.6%) patients were affected by two or more comorbidities, whereas 67 patients (31.6%) had one comorbidity. The most frequent comorbidities were hypertension (53%), cardiac disease (17%), diabetes mellitus (17%) and chronic obstructive pulmonary disease (COPD) (12%). The severity of each comorbidity was scored and recorded according to the American Society of Anesthesiologists (ASA) physical status classification system 18 (Table II).

*Surgery and postoperative morbidity*

The mean surgical time was $2.17 \pm 1.48$ h, ranging from 0.5 h to 6.5 h in patients aged 70-79 and from 0.5 h to 4.5 h in patients $\geq 80$ years ($p < 0.01$). Amongst treated patients, 25 patients were postoperatively transferred to the intensive care unit (ICU) where they resided for an average time between 4.4 days (70-79 years old patients) and 1.6 days (patients aged $\geq 80$; $p = 0.475$). The mean length of hospitalisation was 19.0 days in 70-79 patients and 12.3 in those $\geq 80$ ($p < 0.05$).

Perioperative or postoperative complications affected 43 of 212 patients (20.3%) of whom 36 of 171 (21.0%) in the age range 70-79 and 7 of 41 (17.1%) in $\geq 80$ years ($p = 0.799$).

Furthermore, stratifying patients for the type of surgery no differences between groups were observed, although open neck techniques showed a significant higher incidence of complications with respect to TLM ($p < 0.001$, Fig. 1).

In 70-79-year-old patients, 19 suffered systemic complications (mainly cardiovascular and pulmonary), 13 patients had local complications (mainly bleedings, fistulas and wound infections) and 4 developed both systemic and local complications. Two patients suffered 2 systemic complications, whereas 1 patient had 2 local complications.

Two patients (5.6%) died postoperatively. In the $\geq 80$ year group, 7 patients developed systemic complications (mainly psychiatric): two patients had more than 1 systemic complication, whereas 1 patient also suffered a local complication (haemorrhage). One patient (14.3%) died postoperatively (Table III). Finally, 48 of 212 patients (22.6%)

underwent a second surgical procedure, whereas 11 of 212 patients (5.2%) underwent a third salvage surgery.

Data from the cohort of patients undergoing OPHL are reported in Table IV.

*Correlation of age, type of surgery and complications with survival*

Patients were followed for a mean period of 3.05 years (range 15 days – 8.61 years). At the last follow-up, 139 of 212 patients (65.55%) were alive without disease, 25 died with disease (11.8%), 39 died for other reason than head and neck cancer (18.4%), whereas 4 were alive with disease (1.9%). The remaining 5 patients were lost to followup (2.35%).

At 5-years, overall survival (OS 58.0%) correlated with patient age at surgery. In fact, OS was 64.0% in 70-79 years old patients and 33.9% in those aged ≥ 80 ($p < 0.05$), with 50% mortality at 4.04 years (Fig. 2A).

On the contrary, 5-year disease-specific survival (DSS, 79.7%) was not significantly affected by patient age: in fact, DSS was 83.3% and 62.8% in those 70-79 and ≥ 80, respectively (Fig. 2B; $p = 0.062$).

Furthermore, by stratifying the data, the type of surgery or the occurrence of complications greatly affected OS (Fig. 3). In fact, patients treated by total laryngectomy were more prone to fatal a outcome ($p < 0.001$ and $p < 0.05$ with TLM and open partial horizontal laryngectomy, respectively), both as early event and at 5-year OS (37.2%, with 50% mortality at 4.04 years). No significant differences in 5-year OS were seen between patients undergoing TLM (67.7%) and open partial horizontal laryngectomy (77.9%). Similarly, 5-year OS of patients who experienced perioperative and postoperative complications was 37.5% (50% mortality at 3.50 years), which was significantly lower (as early events, also) than 62.3% (50% mortality at 6.82 years) seen in the other patients.

Age at surgery had a different impact on 5-year OS on the basis of both type of surgery and occurrence of complications (Fig. 4). In fact, patients aged 70-79 and undergoing TLM had a better 5-year OS (74.2%) than those aged ≥ 80 undergoing the same technique (48.3%, 50% mortality at 4.46 years, $p < 0.05$). Likewise, younger patients who did not experience a complication had a 5-year OS of 66.7%, which was significantly high than the older group (42.9%, 50% mortality at 4.46 years, $p < 0.05$). However, more invasive surgery as well as the presence of perioperative and postoperative complications greatly correlated with survival of ≥ 80 patients (0.0% at 5 years), whose 50% mortality was detected at 1.21 years and 0.37 years considering total laryngectomy and occurrence of complications, respectively. Patients aged 70-79 had better prognosis as an early event ($p < 0.01$) as well as 5-year OS ($p < 0.01$) for both total laryngectomy (44.8%, 50% mortality at 4.34 years) and occurrence of complications (49.7%, 50% mortality at 3.50 years).

No comparisons are available for open partial horizontal laryngectomy because all treated patients were aged 70-79 at the time of surgery.

*Risk analysis on the development of complications*

Age ≥ 80, sex, comorbidities and ASA physical status classification did not show statistically relevant differences considering the onset of perioperative and postoperative complications, in contrast to the duration and type of surgery. In fact, if surgery length was more than 2 hours, patients had a risk of developing complications of 37.2% compared to 10.4% for patients with surgical time ≤ 2 hours ($p < 0.001$).

Likewise, patients undergoing open neck laryngectomy had a higher risk of developing complications (46.4% and 26.7% in patients treated with TL or OPHL, respectively) compared to those treated with an endoscopic technique (TLM – cordectomy, 2.7%, $p < 0.001$).

On the basis of multivariate logistical regression, we calculated the following prediction model:

$$P = \frac{1}{1 + e^{-[0.262 - 0.401(a) - 0.259(b) - 0.021(c) - 0.024(d) - 0.806(e) - 3.423(f) - 0.139(g)]}}$$

where: (a) = patient aged 70-79; (b) = woman; (c) = presence of at least 2 comorbidities; (d) = presence of 1 comorbidity; (e) = treatment by open partial laryngectomy; (f) = treatment by TLM; (g) time of surgery ≤ 2 h.

For total laryngectomy, the formula gave a complication rate of 46.0%-56.5% in ≥ 80 patients and 36.3%-46.5% in those aged 70-79. Similarly, the model foresaw a complication

rate of 30.5%-36.7% in patients ≥ 80 treated by OPHL, while it was 22.7%-28.0% in those aged 70-79.
TLM-cordectomy had very little impact on the development of complications, regardless of age. In fact, the complication risk was 2.7%-4.1% and 1.8%-2.8% for patients aged ≥80 and 70-79, respectively.

**Discussion**

Because of the ageing population, clinicians are treating older patients more often than in the past. This, and the introduction of less invasive surgical techniques, has modified the strategies that surgeons apply to treat patients suffering from laryngeal cancer [19]. The elderly are often treated by patient-tailored and less invasive/timeconsuming procedures, making the surgeon consider both survival expectation and quality of life after surgery.
Radical surgery on older patients with advanced cancer is, however, not frequent. The impact of oncological surgery, in particular open surgery, on the delicate equilibrium of the elderly has been the subject of various studies [20-22]. Total laryngectomy separates the airways from the digestive tract, and does not expose the patient to the risk of damage for the ability to swallow, at the expense of a sudden loss of speech (usually irreversible). On the other hand, partial laryngectomy can provide the same oncological radicality while preserving the function of the larynx, even if at a lower quality, and avoiding definitive tracheostomy. The main disadvantages consist in a more restrictive selection of patients, which must be based on parameters related to the tumour, functional and cognitive abilities, absence of serious comorbidities and compliance of the patient and care-giver to an arduous rehabilitative programme, making OPHL an exception and not the rule in the management of laryngeal tumours in old (and mainly in very old) patients. However, the functional results of this surgery are long-lasting [23].
In the elderly, TLM warrants a separate discussion. It is usually employed in treatment of early stage tumour, mainly but not exclusively for glottic neoplasms [24 25].
However, the technique has been recently reported to be an effective surgical option even in the eradication of locally advanced stage laryngeal tumours due to the low rate of cervical node metastases 26. TLM, in fact, demonstrates a high level of local control, low morbidity,

almost total absence of permanent tracheostomy, good compliance of patient to the operation and short hospitalisation times (less than two post-operative days).

Historically, age has been considered as either a negative prognostic factor in advanced laryngeal carcinoma [27] or irrelevant in the early stage for developing local relapses [28] and hence for disease-free survival [29]. Furthermore, age does not have a significant impact on the long-term laryngeal function outcome after open partial laryngectomy, if the patient is selected carefully [30]. In this context, a better understanding of the impact of age and comorbidities on post-operative outcomes in term of survival and complications may help surgeons in suggesting the best therapeutic option to patients [18 22-25].

In the present study, we examined a cohort of old (aged 70-79) and very old (aged ≥ 80) patients (Table I) who underwent three different types of radical surgery.

With the exclusion of OPHL that was performed only on 70-79-year-old patients due to the heavy and complex rehabilitation programme needed, the distribution of surgical techniques between groups did not reveal any statistical differences ($p = 0.139$, c2 test). Nonetheless, the lack of OPHL use in ≥ 80 patients did not statistically alter the reliability of comparisons (data not shown). For this reason, OPHL surgery was considered herein. These are aggressive surgical procedures, initially resulting in severe swallowing dysfunction, most notably aspiration, but normally permitting eventual return to oral nutrition for most patients[31].

Some independent factors influencing post-OPHL aspiration have been well studied: advanced age, extent of supraglottic resection, absence of piriform sinus repositioning and total resection of one arytenoid [32].

Several authors agree that age, in itself, does not constitute an absolute contraindication, but rather a condition of increased risk. Hence, the need to be more restrictive in elderly patient selection and, if recommended, considering in advance a strategy for a simplified management of dysphagia, such as percutaneous gastrostomy [20 23 30 32].

In our experience, it is important to pay attention to: a) the mental status of elderly patients which must be quite normal in order to carry out the complex post-OPHL rehabilitation; b) the presence of motivated caregivers; c) pictures of severe osteophytosis at the cervical spine; and d) clinical and radiological signs of pre-existing presbyphagia.

As resections extended to supraglottic and subglottic sites are often associated with dysphagic sequelae, we prefer to adopt such surgery only in cases requiring resection of the glottis, saving the epiglottic tip, and enlarging to one arytenoid, if necessary [10 33-35]. Adopting this strategy,

the complication rate was acceptable (8/30-26.6%), with only one case of fatal cardiac complication, considering a cohort characterised by a mean age of 73.2 +/- 2.2 years. Despite our analyses, patients ≥ 80, who can be considered to be more frail than those 70-79 due to poorer 5-year overall survival (33.9% *vs* 64.0%, $p < 0.05$), the lack of difference in 5-year disease-specific survival (62.8% *vs* 83.3%, $p = 0.173$) demonstrated that the different mortality rate is not due to causes related to the cancer. In order to ascertain whether it depended merely on the reduced life expectancy of ≥ 80 patients, we analysed the impact of several covariate factors. In particular, the occurrence of perioperative and postoperative complications greatly impaired the overall survival of both 70-79 and ≥ 80 patients.

Nevertheless, their occurrence was in relation to the type of surgery employed. The more invasive open neck surgeries provided a statistically higher percentage of patients with complications (up to 46.4%) than TLM (2.6%). However, stratifying the data for age at surgery, the percentage of patients who experienced complications was not statistically different between the two groups ($p = 0.694$, TLM; $p = 0.793$, TL). As a consequence, patients treated by total laryngectomy had the worst overall survival, whereas those undergoing TLM or OPHL had a similar 5-year outcomes. These results are in apparent contrast with the findings of Clayman et al. who compared the actuarial survival curve of the general population for people over 80: the global survival of elderly patients was not negatively influenced by a major operation [36]. Indeed, TLM was mainly adopted to treat patients affected by early carcinomas, and according to guidelines, open neck surgeries were predominantly performed on those with advanced stage tumours (Fig. 5). Accordingly, patients undergoing major operations were generally affected by more advanced pathology than those treated by less invasive techniques. As a vicious cycle, patients treated by open neck surgeries (above all TL) for a more advanced tumour are understandably more prone to develop complications and undergo fatal outcome, independently from the age at surgery. These findings are consistent with the work of Peters et al. [37], who carried out a large retrospective study on patients in the age range ≤ 40 - ≥ 80 affected by head and neck cancer.

They concluded that age itself does not seem to be a contraindication for major head and neck surgery, although the elderly are generally affected by more comorbidities than younger patients. In this regard, it is necessary to underline how, particularly in the elderly, the selection process for curative treatment tends to exclude all patients whose comorbidities are more serious than the average for their given age. This is not a simple process, and is mostly left to the judgment of the clinician rather than an analysis of morbidity indexes. In fact, it is not justifiable to adopt a "protective" therapy for the elderly that differs from the gold standard, apart from cases in which patients present serious comorbidities. The only exception could be when heavy adjuvant therapy is necessary, since elderly patients' compliance to lengthy treatment may be lower. In fact, as already reported, "only surgery-related variables, such as tumour stage and time of intervention, are significantly associated with surgical complications" [37].

Calculating the risk for each patient to undergo perioperative and postoperative complications by multivariate logistic regression, in our cohort the presence of comorbidities was not correlated with the onset of complications. In fact, the only significant covariate factor was the employment of more invasive types of surgery. The divergence with respect to the previous study could due to the operation time evaluated, which did not include the anaesthesiologic time herein.

**Conclusions**

In conclusion, we infer that elderly patients affected by laryngeal cancer can be treated just as younger patients, keeping in mind that more invasive surgeries are associated with a higher risk of complications. Therefore, while for endoscopic surgery there is no reason to limit or "ponder" whether to perform surgery or not for patients of any age, open surgery on patients ≥ 80 must be thoroughly evaluated due to the higher rate of complications. The advantages of mini-invasive surgery place it as a possible first choice treatment in very old and frail patients suffering from laryngeal cancer, especially considering the recent success in the treatment of some advanced stage tumours 26. Furthermore, comorbidities, in themselves, cannot justify subjecting the elderly to a treatment other than standard. Rather, the severity of these conditions defines whether the patient should be exposed to major surgical options.

Sharing and improving our knowledge in elderly patients is helpful for all physicians due to the ageing population, with the aim to improve the quality of life and overall survival in the elderly.

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**Table 1** **Characteristic of the 212 elderly patients undergoing laryngeal surgery according to age, sex, tumor localization and pathological status**

| Age, y | | | | | | No. of patients (%) |
|---|---|---|---|---|---|---|
| Mean | | | | | | 75.8 ± 4.5 |
| Range | | | | | | 70-91 |
| 70-79 | | | | | | 171/212 (80.7%) |
| ≥ 80 | | | | | | 41/212 (19.3%) |
| **Sex** | | | | | | |
| Male | | | | | | 199/212 (93.9%) |
| Female | | | | | | 13/212 (6.1%) |
| **Localisation** | | | | | | |
| Glottis | | | | | | 173/212 (81.6%) |
| Supraglottis | | | | | | 39/212 (18.4%) |
| **Pathological Status** | | | | | | |
| | **N0** | **N1** | **N2a** | **N2b** | **N2c** | |
| pTis | 12 | | | | | 12/212 (5.7%) |
| pT1 | 95 | | | | | 95/212 (44.8%) |
| pT2 | 28 | | | | | 28/212 (13.2%) |
| pT3 | 28 | 3 | | | | 31/212 (14.6%) |
| pT4 | 21 | 14 | 6 | 4 | 1 | 46/212 (21.7%) |

**Table 2 Distribution of patients according to the American Society of Anesthesiologists (ASA) physical status classification system**

| ASA | No. of patients (%) |
|---|---|
| 1 | 14/212 (6.6%) |
| 2 | 79/212 (37.3%) |
| 3 | 99/212 (46.7%) |
| 4 | 20/212 (9.4%) |

**Table 3 Complications in patients**

| | | | Number of events (%) | |
|---|---|---|---|---|
| | | | 70-79 | ≥ 80 |
| **Complications** | **Local** | Fistula | 8/36 (22.2%) | 0/7 (0.0%) |
| | | Infections | 4/36 (11.1%) | 0/7 (0.0%) |
| | | Haemorrhage | 5/36 (13.9%) | 1/7 (14.3%) |
| | | Haematoma | 0/36 (0.0%) | 0/7 (0.0%) |
| | | Necrosis | 0/36 (0.0%) | 0/7 (0.0%) |
| | | Dehiscence | 0/36 (0.0%) | 0/7 (0.0%) |
| | **Systemic** | Pneumonia | 8/36 (22.2%) | 1/7 (14.3%) |
| | | Cardiovascular* | 13/36 (36.1%) | 2/7 (28.6%) |
| | | Psychiatric# | 2/36 (5.6%) | 7/7 (100%) |
| | | Death | 2/36 (5.6%) | 1/7 (14.3%) |
| | | Nephropathy | 2/36 (5.6%) | 0/7 (0.0%) |
| | | Cerebrovascular event | 0/36 (0.0%) | 0/7 (0.0%) |
| | | Hyperglycaemia | 1/36 (2.8%) | 0/7 (0.0%) |
| | | Sepsis | 0/36 (0.0%) | 0/7 (0.0%) |

** Cardiovascular complications included acute myocardial infarction, arrhythmia, and cardiac arrest # $p < 0.001$ (Fisher's exact test)*

**Table 4 Characteristics of patients undergoing open partial horizontal laryngectomy**

| Surgery, ELS Classification | | No. of patients (%) |
|---|---|---|
| Type IIa | | 11/30 (36.7%) |
| Type IIa + ARY | | 19/30 (63.3%) |
| **Age, y** | | |
| Mean | | 73.2±2.2 |
| Range | | 70-78 |
| **Comorbidities** | | **No. of events (%)** |
| | Arrhythmia | 1/19 (5.3%) |
| | Arteriopathy | 1/19 (5.3%) |
| | Cardiopathy | 3/19 (15.8%) |
| | Hypertension | 15/19 (78.9%) |
| | Ictus | 1/19 (5.3%) |
| | Dyslipidaemia | 3/19 (15.8%) |
| | Hypothyroidism | 1/19 (5.3%) |
| | Diabetes | 2/19 (10.5%) |
| | Epilepsy | 1/19 (5.3%) |
| | HCV infection | 1/19 (5.3%) |
| | Chronic obstructive pulmonary disease | 5/19 (26.3%) |
| **Complications** | | |
| Local | Infections | 2/8 (25.0%) |
| | Haemorrhage | 3/8 (37.5%) |
| Systemic | Pneumonia | 1/8 (12.5%) |
| | Cardiovascular | 5/8 (62.5%) |
| | Death | 1/8 (12.5%) |

**Figure 1** **Incidence of complications on patients treated by transoral laser microsurgery (TLM), open partial horizontal laryngectomy (OPHL) or total laryngectomy (TL)**

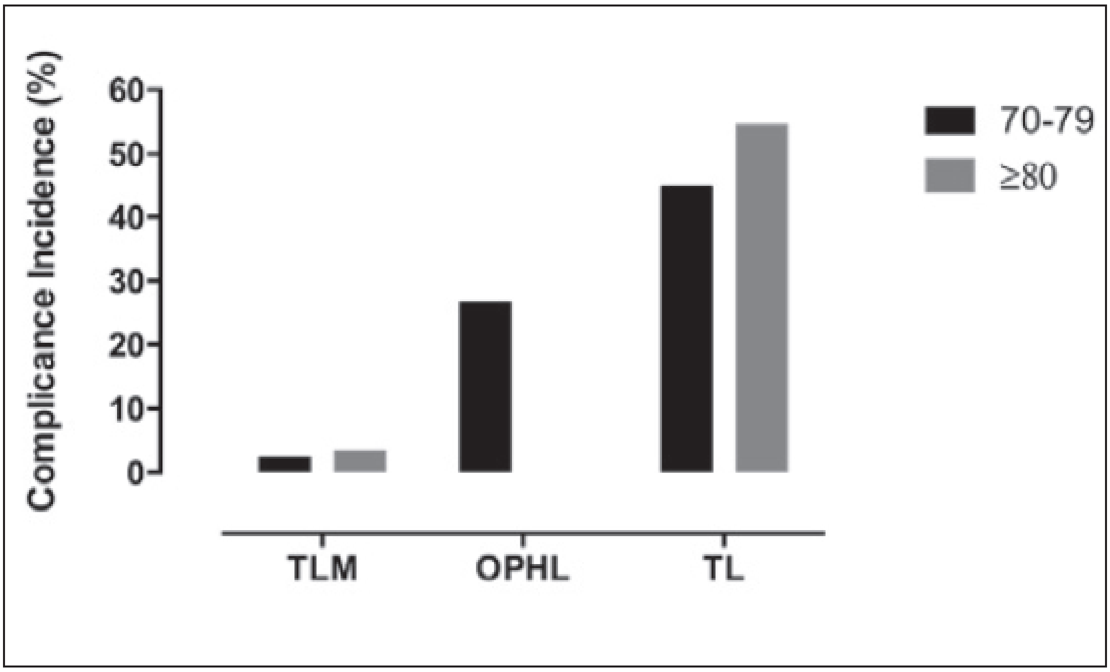


**Figure 2 Overall survival (A) and disease specific survival (B) over a 5-year period in 212 patients with laryngeal cancer. Dotted lines indicate the patient cohort according to the age at surgery *p < 0.05**

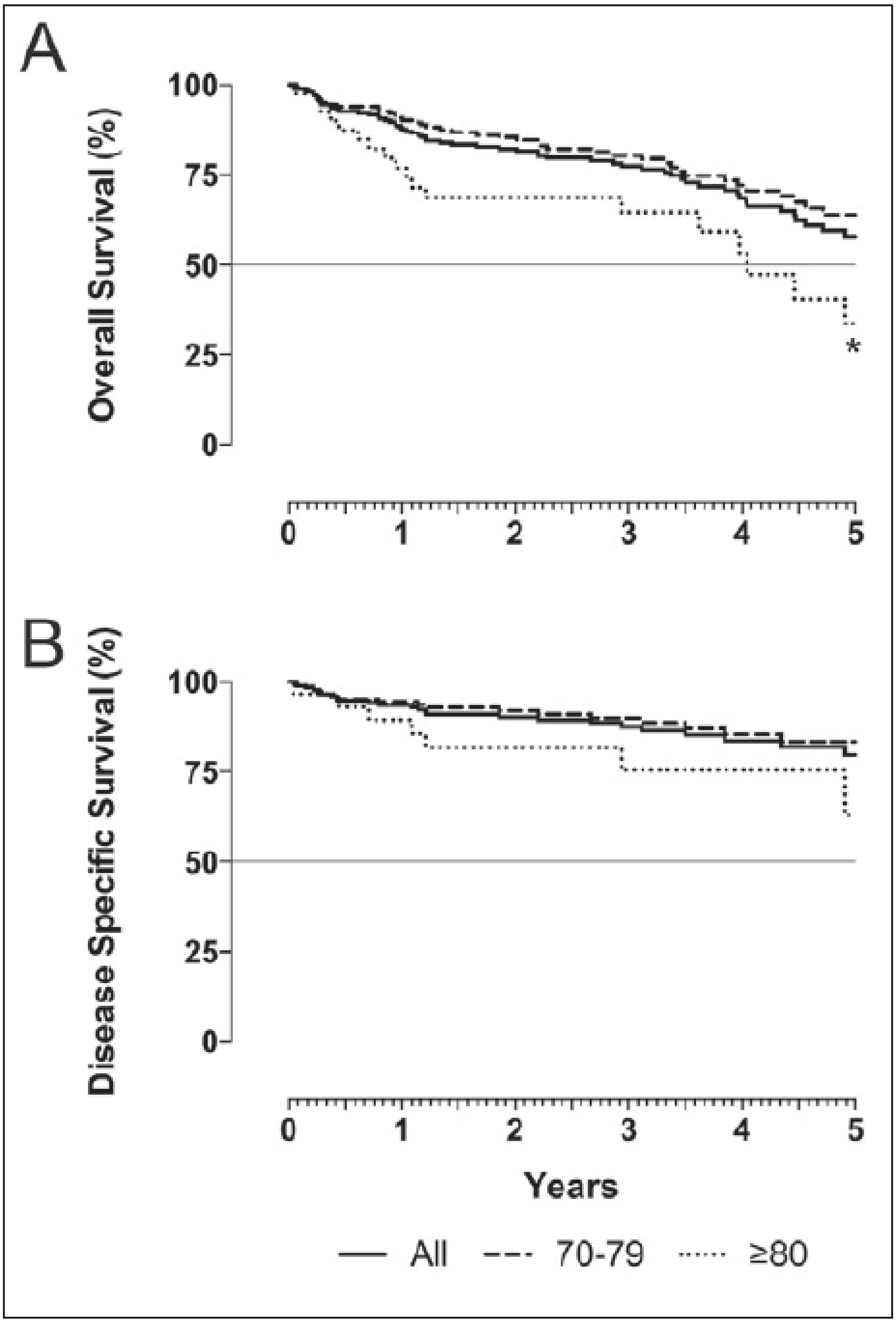


**Figure 3 Overall survival over a 5-year period in patients who underwent different surgical procedures (A) or who experienced peri- and /or post-opertaive complications (B) *** p < 0.001 (Log-Rank test); ### p < 0.001 (Gehan-Breslow –Wilcoxon test for ealry events)**

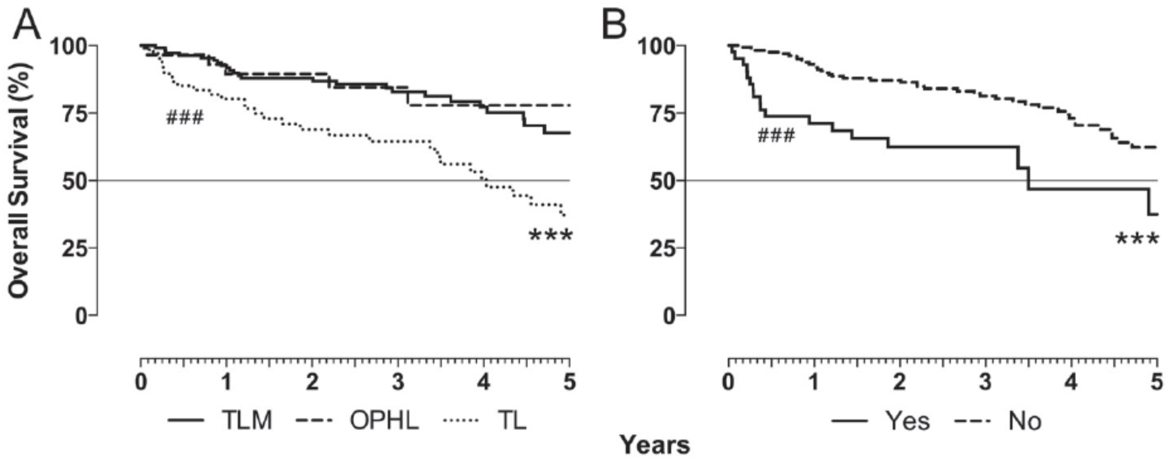


**Figure 4 Overall survival over a 5-year period in patients stratified according to the age at the surgery who underwent transoral laser microsurgery (A) or total laryngectomy (B) and who did not experience (C) or otherwise show complications (D) * p < 0.05 , ** p > 0.01 (Log-Rank test), ## p < 0.01 (Gehan-Breslow –Wilcoxon test for ealry events)**

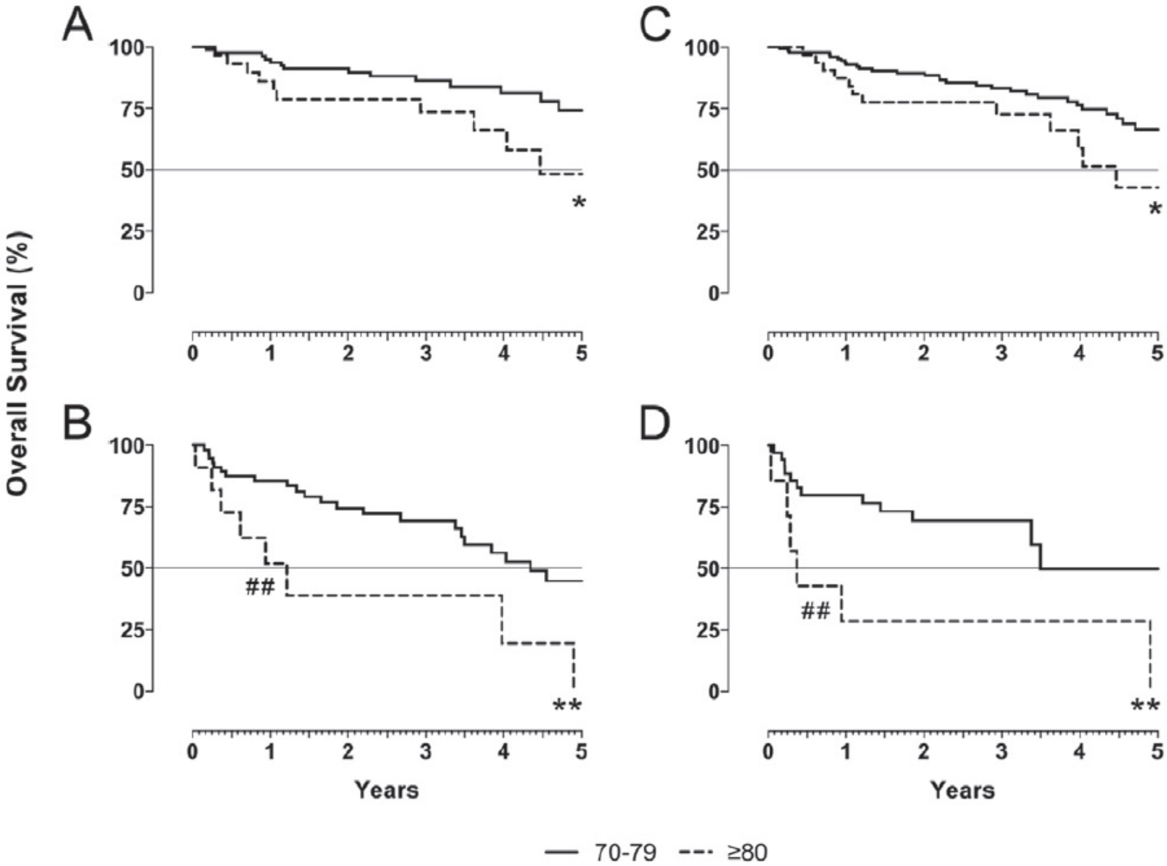
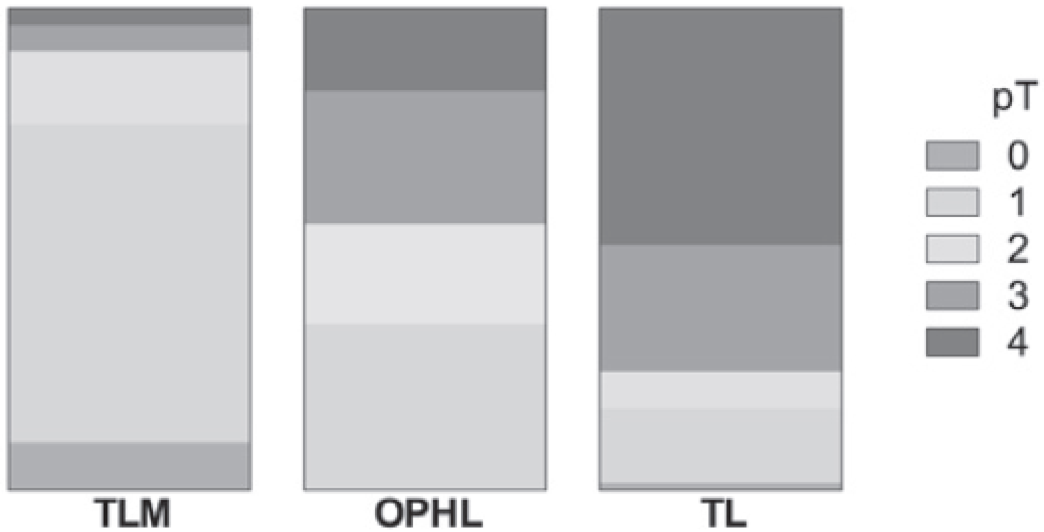


**Figure 5 Surgical procedures in relation to pT classification**



# THIRD CHAPTER

## Paper 1

### *Open partial horizontal laryngectomies: is it time to adopt a modular form of consent for the intervention?*

*Summary*

Nowadays, open partial horizontal laryngectomies (OPHLs) are well-established procedures for treatment of laryngeal cancer. Their uniqueness is the possibility to modulate the intervention intraoperatively, according to eventual tumour extension. An OPHL procedure is not easy to understand: there are several types of procedures and the possibility to modulate the intervention can produce confusion and lack of adherence to the treatment from the patient. Even if the surgery is tailored to a patient's specific lesion, a unified consent form that discloses any possible extensions, including a total laryngectomy, is still needed. We reviewed the English literature on informed consent, and propose comprehensive Information and Consent Forms for OPHLs. The Information Form is intended to answer any possible questions about the procedure, while remaining easy to read and understand for the patient. It includes sections on laryngeal anatomy and physiology, surgical aims and indications, alternatives to surgery, complications, and physiology of the operated larynx. The Consent Form is written in a "modular" way: the surgeon defines the precise extension of the lesion, chooses the best OPHL procedure and highlights all possible expected extensions specific for the patient. Our intention, providing these forms both in Italian and in English, is to optimise communication between the patient and surgeon, improving surgical procedure arrangements and preventing any possible misunderstandings and medico-legal litigation.

### Introduction

Supraglottic, supracricoid, and supratracheal laryngectomies are well accepted surgical procedures for the treatment of laryngeal cancer that provide excellent oncological and functional results [1-4]. Since many different surgical techniques have been described over the years, a new classification of these procedures has been recently proposed by the working committee on nomenclature of the European Laryngological Society [5], based on the craniocaudal extent of laryngeal structures resected. According to the proposed classification system, three types of open partial horizontal laryngectomies (OPHL) have been defined: Type I (supraglottic), Type II (supracricoid) and Type III (supratracheal). Each type may be extended to adjacent laryngeal and/or pharyngeal sites: OPHL Type I can be extended to one arytenoid, the base of tongue, or to a piriform sinus; OPHL Type II can be extended to one arytenoid; OPHL Type III can be extended to one cricoarytenoid unit. Moreover, OPHL Types II and III are further distinguished by the suffix “a” or “b” depending on the sparing or removal of the suprahyoid epiglottis. This classification reflects the complexity of this surgery and its wide range of variability. Thanks to this classification, all the possible variations, in terms of extent of resection, are now clearly defined.

One of the advantages of OPHLs is the possibility to tailor the procedure to the specific extent of disease. Surgeons can shift from one OPHL Type to another, even intraoperatively, if oncological safety cannot be clearly achieved with the scheduled procedure. On the basis of pathological findings in frozen sections, the procedure can be extended to adjacent sites, according to the classification, or it can shift to another OPHL Type. However, shifting to a different OPHL Type can result in a higher complication rate or longer rehabilitation time. In extreme cases, the procedure can be converted to a total laryngectomy, causing a radical change in the patient’s lifestyle after surgery. Patients must be aware of the possibility and accept this eventuality.

When approaching an OPHL, the surgeon should refer to a surgical plan rather than to a single procedure. The amazing advantage of tailoring the procedure to the extent of disease reveals two essential difficulties: 1) it may be hard for the patient to understand the meaning and the complexity of an OPHL, together with its benefits, risks, potential complications and alternatives; 2) OPHLs lack a unified consent form that includes every possible extension of every possible procedure, including total laryngectomy.

These difficulties can be hard to manage, both for the surgeon and patient. Furthermore, providing appropriate preoperative information to a patient undergoing surgery is dictated by the law and may prevent litigations.

We propose the use of a unified Consent Form (CF), in which the surgeon can specify the predicted OPHL Type and can detail all possible extensions. This CF can be customised to each patient in a “modular” way, exactly as the procedure.
In association with the CF, we propose an Information Form (IF), containing explanations on laryngeal anatomy and physiology, rational of OPHLs, description of each procedure with all possible extensions, alternatives to surgery, eventual complications and physiology of the operated larynx.
In our opinion, these forms could become a very useful tool for both patients and surgeons in planning surgery and in limiting unpleasant misunderstandings and medico-legal litigations.

## Materials and methods

We reviewed the English literature looking for the essential elements of an appropriate informed consent (IC) form. IC is a legal term, defined as “voluntary authorisation, by a patient or research subject, with full comprehension of the risk involved, for diagnostic or investigative procedures, and for medical and surgical treatment” (year introduced: 1973 (1971), http://www.ncbi.nlm.nih. gov/mesh/68007258?ordinalpos=1&itool=EntrezSystem2.PEntrez.Mesh_ResultsPanel.Mesh_RVD ocSum). IC is supported by three cornerstones: preconditions, information and consent [6].
The *preconditions* for IC are competence and voluntariness. A patient is a person with the right of self-determination [7]. They must have the competence to make decisions, and they must express voluntariness, without external influence. The surgeon must be sure of the presence of these preconditions before proposing any surgical procedure.
*Information* is the second cornerstone. The 1995 WHO Declaration on the Promotion of Patients’ Rights states that the patient has the right to be fully informed about their health status. This includes information about: their condition, proposed medical procedures, potential risks and benefits of each procedure, alternatives to the proposed procedures (including the effects of non-treatment), and about the diagnosis, prognosis and progress of treatment [8]. The surgeon should discuss with the patient a well defined care plan, and must be sure that they understand the information.

*Consent* is the registration of the patient's decision and the authorisation to proceed. Depending on each country's legislation, consent can be obtained orally or in writing. A consent form should be readable and written at a 12-year-old's reading level [9]. According to the Constitution of the Italian Republic, art. 32, "no one can be forced to a specific medical treatment, except if this is stated by law". In Italy, consent to a surgical procedure is obtained verbally; a written form is not mandatory, but is advisable to prove that IC was obtained.
Our intention is to produce a booklet that could respond to all the questions patients have about the surgical procedure. We utilized both our personal experience and literature on indications, surgical techniques, possible extensions, possible alternatives, physiology of the operated larynx and possible complications [1-4 10-15]. In addition, with the assistance of a forensic scientist, we managed to write a readable and complete CF, in which the surgeon has the possibility to specify the suggested procedure and to clearly define every eventual extension according to the OPHL classification [5].

**Results**

The IF and the CF are available in both English and Italian at **_____** .

*Information Form (IF)*

The booklet is intended for persons without any medical knowledge. We try to explain medical terms in simple words, and include figures when needed. The first section deals with laryngeal anatomy and physiology, with a figure to make it easier to understand. Then, the surgical procedures are presented according to the OPHL classification[5], describing the levels of resection with an image; the aim of surgery is discussed, focusing particularly on oncological safety. The next section is about indications for each type of OPHL. Next, we describe the crucial concept of dynamism present in this type of surgery, presented here as "modular" surgery, followed by a description of all possible variations, including the possibility of shifting to a total laryngectomy. A passage about all possible alternatives to the intervention follows, in which radiation and chemo-radiation therapy are described; this passage includes the possibility of not doing anything. We then describe how the procedure is performed, what the patient should expect after surgery, and how the neo-larynx will work. Finally, all possible complications are disclosed.

*Consent Form (CF)*

Our intention is to write a CF with the possibility to “modulate” the surgical procedure, depending on intraoperative findings. Multiple choice lists have been included, so that it can be tailored to every possible case.

It begins with an introductory section that must be filledin with the personal details of the patient and surgeon. The surgeon is called to define the precise dimension of the lesion with the help of a multiple choice list, in which all laryngeal and extra-laryngeal subsites that can be involved are included. Later, the surgeon must choose from a second multiple-choice list, the specific scheduled procedure. A third multiple choice list includes all possible extensions of the procedure according to the OPHL classification [5]: the most likely extensions that could result from intraoperative findings are highlighted. In the final passage, the declaration of the consent to the procedure must be signed by both the patient and the surgeon.

Note that the use of some technical terms is fundamental in the CF: medical terms are essential for the precise definition of the scheduled surgical procedure and possible expected extensions. The need for medical terms reflects the complexity of the procedure. By using simplified terms, we could lose the accuracy required in a CF.

**Discussion**

The concept of informed consent has developed over time, since medieval times to the present [16-18]. Past juridical sentences on litigations between patients and doctors, together with the memory of what happened during the Second World War in the Nazi concentration camps, have lead the way to the current legislation on informed consent.

At present, the three cornerstones of Informed Consent are: preconditions, information and consent [6].

*Preconditions*

They express the right of self-determination of the patient, who must decide freely for himself, without any kind of influence. Generally, competence is recognised by the surgeon if communication appears to be “normal”. However, in a review on patient competence, Appelbaum [19] surprisingly found that the number of “incompetent” patients was higher than expected, and that doctors are unable to differentiate between competent and incompetent patients. OPHLs require a strong alliance between surgeon and patient: during the postoperative period patient collaboration, and firm compliance are essential for rehabilitation. For this reason, psychiatric disorders represent absolute contraindications to OPHLs [11].

*Information*

Communication is fundamental: most legal cases are not due to failures in treatment, but due to failure in communication [20]. Often informed consent is obtained by residents, who may not exactly know what to tell a patient [21].

A written leaflet, as our IF, would undoubtedly be helpful to inform patients. It is demonstrated that oral information is retained very poorly, and patients tend to forget crucial parts [22]. Better informed patients will have more realistic expectations, higher satisfaction and demonstrate more treatment cooperation [23].

Information must be as complete as possible. Albera et al. [24 25] demonstrated that informing the patient not only about the disease, but also about the logical course that leads the doctor to a certain diagnosis and a description of the proposed treatment possibilities, including treatment modalities excluded, is appreciated by more than 90% of patients.

Some patients prefer not being informed about the procedure and completely rely on the surgeon's decisions [26].

Even in these cases, a written form provided in advance may be helpful to the patient whether they would need some information. Furthermore, the IF can be a useful tool to instruct nonmedical staff or non-specialised doctors about this procedure

*Consent*

A patient that agrees to an OPHL is not accepting a single procedure, but a system of similar procedures strictly related with one another, linked by the common concept of removing a horizontal portion of the larynx, while maintaining the function of at least one crico-arytenoid unit.

They must accept the possibility that the procedure may become more extended, implying that the rate of complications may become higher and the time of rehabilitation may become longer. For example, if frozen sections reveal positive margins on the subglottic mucosa during an OPHL Type II, the procedure will be converted to an OPHL Type III, which still provides the same excellent oncological and functional outcomes, but will have a longer hospital stay and rehabilitation time, and a higher rate of immediate and late complications [2 10 27]. In this CF, the surgeon has the possibility to highlight the most plausible extensions for each patient, if unexpected infiltration of surrounding tissues is discovered during surgery.

OPHLs have some limitations: if the tumour spreads to some particular regions (i.e. the posterior paraglottic space or both the arytenoid cartilages), the procedure can no longer be performed, and must be intraoperatively converted into a total laryngectomy to achieve oncological safety. This will happen only in extreme cases, but the patient must know about this eventuality, because it will produce a significant change in their lifestyle. Even though this possibility can never be completely excluded, only a very limited subset of patients has a concrete risk for this extreme measure; for this reason, this eventuality can be highlighted in our CF. In all cases in which the extent of the tumour determines the indication for a more extreme Type III partial laryngectomy (and this occurs for most tumors with sub-glottic extension or extension towards the posterior commissure), this imposes a serious ethical consideration. In fact, in many specialised centres, these cases are considered to be "amenable with total laryngectomy" and therefore, up-front directed to non-surgical treatment in order to spare the larynx. When discussing a conservative surgical option with the patient, it must be explained clearly that if the resection margins are positive in frozen sections, the option immediately following that is total laryngectomy, thus "jumping" the option of concomitant chemoradiotherapy, which has a degree of recommendation IA.

Our "modular" CF does not limit itself to registration of the patient's decision and authorisation to proceed: it represents an agreement on a surgical plan that can be tailored to each patient's specific disease. This agreement will be an insurance for both: the patient, to have the best surgical procedure according to oncological safety, and the surgeon, to perform an OPHL without any concern of extending the procedure if needed.

It is crucial to remember that the IF does not replace the surgeon's oral explanations to the patient. The surgeon performing the procedure should first orally discuss matters with the patient, and then provide the IF and the CF. The conversation should be tailored to the patient's sociocultural conditions, with appropriate and clear vocabulary, and the patient should be urged to ask for any further information.

At the end of the discussion, the IF is provided to the patient, and the CF is completed by the surgeon and subsequently signed by both. This should happen some days before surgery, in order to give the patient enough time to meditate. The patient is asked again for any questions the day before the procedure.

**Conclusions**

The primary goal of OPHLs is always oncological safety. For this reason, the surgeon must be allowed to extend the procedure as far as needed, according to the possible extensions reported [5]. In this article, we propose the use of a written IF that tries to be as complete and as clear as possible, and a CF that can reproduce the "modular" concept of OPHLs. The patient-surgeon relationship is based on trust: with these forms our intention is to improve the level of patient-surgeon cooperation and to avoid any possible litigation by improving comprehension of the procedure and reaching complete agreement on surgical planning.

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**DECLARATION OF PATIENT'S CONSENT TO PARTIAL HORIZONTAL LARYNGECTOMY**

**Provided by...................................................**
**As…………......................................................**

Mr/Mrs ..........................................................................................
Place of birth.....................................................................................
Date of birth .......................................................................................
Address …..........................................................................................
City ……............................................................................................
Dear Mr/Mrs,
You are affected by
.................................................................................................................................
.................................................................................................................................
According to the extent and location of your tumour, you are candidate for partial horizontal laryngectomy.
To inform you as clearly and as completely as possible about the surgical procedure, together with this form, **an Information Form has been provided to you**, which contains information about partial horizontal laryngectomies. You are kindly invited to carefully read both these documents. You don't have to be concerned by the information contained therein; this information is mandatory to allow you to freely and consciously decide whether to undergo or not the procedure. You can ask your Surgeon for any more information at any moment.
It is crucial that you tell to your Surgeon, to doctors who will collect your medical history and to the Anesthesiologist, the drugs that you are taking (in particular analgesics, anti-inflammatories, painkillers, anti-hypertensives, anticoagulants, etc.).
It is important as well to tell whether you ever experienced any allergies, especially to drugs, and if you have ever undergone a general anesthesia. Finally, you should provide all your clinical documentation (laboratory, clinical and radiological examinations, etc.)

**Extent of the disease**
Dear Mr/Mrs, your tumour involves:
☐ Epiglottis
☐ Base of tongue or glossoepiglottic folds
☐ Mucosa of the piriform sinus
☐ Aryepiglottic fold ☐ right ☐ left
☐ Laryngeal vestibule
☐ Pre-epiglottic space
☐ False vocal fold ☐ right ☐ left
☐ Laryngeal ventricule ☐ right ☐ left
☐ Vocal fold ☐ right ☐ left
☐ Anterior commissure
☐ Arytenoid cartilage ☐ right ☐ left
☐ Thyroid cartilage
☐ Paraglottic space ☐ right ☐ left

☐ Cricoid cartilage
☐ Crico-arytenoid unit ☐ right ☐ left
☐ Subglottic mucosa
☐ Crico-thyroid membrane
☐ Prelaryngeal soft tissues

**Surgical Procedure**
There are different types of partial horizontal laryngectomies, as already discussed in the Information Form. According to the extent of your lesion, the scheduled surgical procedure is:
☐ Horizontal Supraglottic Laryngectomy (OPHL type I)
  ☐ extended to one arytenoid cartilage (OPHL type I + ARY)
  ☐ extended to the base of the tongue (OPHL type I + BOT)
  ☐ extended to the piriform sinus (OPHL type I + PIR)

☐ Supracricoid laryngectomy with crico-hyoido-epiglottopexy (OPHL type IIa)
  ☐ extended to one arytenoid cartilage (OPHL type IIa + ARY)

☐ Supracricoid laryngectomy with crico-hyoidopexy (OPHL type IIb)
  ☐ extended to one arytenoid cartilage (OPHL type IIb + ARY)

☐ Supratracheal laryngectomy with tracheo-hyoido-epiglottopexy (OPHL type IIIa)
  ☐ extended to one crico-arytenoid unit (OPHL type IIIa + CAU)

☐ Supratracheal laryngectomy with tracheo-hyoidopexy (OPHL type IIIb)
  ☐ extended to one crico-arytenoid unit (OPHL type IIIb + CAU)

**Possible Intraoperative Modulation**
Partial horizontal laryngectomy is a “modular” surgical procedure. According to the intraoperative pathological consultation, it may be necessary to convert the surgery. In your particular case, although other options can never be completely excluded, most plausible extensions may be:

☐ Extension of a horizontal supraglottic laryngectomy (OPHL type I) to one adjacent subsite (arytenoid, base of the tongue, mucosa of the piriform sinus – OPHL type I + ARY, type I + BOT, type I + PIR respectively);

☐ Extension of a supracricoid laryngectomy (OPHL type II) to one arytenoid (OPHL type IIa + ARY or type IIb + ARY);

☐ Extension of a supratracheal laryngectomy to one crico-arytenoid unit OPHL type IIIa + CAU or type IIIb + CAU).

☐ Conversion of the scheduled procedure into a:

  ☐ Supracricoid laryngectomy with crico-hyoidopexy (OPHL type IIb), with eventual extension to one arytenoid (OPHL type IIb +ARY);

 Supratracheal laryngectomy with tracheo-hyoido-epiglottopexy (OPHL type IIIa), with eventual extension to one crico-arytenoid unit (OPHL type IIIa + CAU);
 Supratracheal laryngectomy with tracheo-hyoidopexy (OPHL type IIIb), with eventual extension to one crico-arytenoid unit (OPHL type IIIb + CAU);
 Total laryngectomy.

Surgeon's annotation on possible extensions
......................................................................................................................................
......................................................................................................................................

Furthermore, you confirm that:
 You didn't ask for any more information;
 You asked further information about:
......................................................................................................................................
......................................................................................................................................
......................................................................................................................................

**DECLARATION OF CONSENT**

During oral explanations of the procedure and after reading the Information Form, I received information about:

• Anatomy and physiology of the larynx;
• Horizontal partial laryngectomies: indications and aim of surgery and how it is performed;
• The possibiliy that the scheduled surgery may be intraoperatively extended or converted according to the OPHL system, to achieve oncological safety;
• How the larynx will work after surgery, and the need for a postoperative reabilitation periord with the Speech Therapist;
• Achievable benefits of the procedure, and the possibility of obtaining them according to the results reported in the literature and to my personal condition; the possibility that revision surgeries may be necessary for any defects, even aesthetic, not always secondary to technical errors;
• Risks of the procedure, according to the incidence reported in the literature and to my personal condition; the possibility that any surgical procedure may lead to unforeseeable risks;
• Possible alternatives to surgery, in particular a radiation or chemo-radiation treatment, with relative risks and benefits;
• Possible complications after surgery, and how to try to avoid these complications;
• **The possibility that, if necessary according to the intraoperative findings, to achieve the complete removal of the disease, the procedure may be intraoperativelly converted to a total laryngectomy, without the need for an additional consent. In this case a definitive tracheostomy will be performed.**

During oral explanations of the procedure and after reading the Information Form, I obtained any information I asked for.

After reading the Information Form and after oral explanation, **I received a copy of this Consent Form**, and I was asked to carefully think about the information provided by my Surgeon, to ask for any further information, to reveal my doubts even about medical terms, and finally to declare my consent to the procedure.

I declare that I was informed about the risks of partial horizontal laryngectomies, that the Surgeon answered all my questions, that I completely understood all the information provided in the Information form and during oral explanations, and that I had enough time to think about it. Then, today **I express/I don’t express** my conscious and informed consent to the scheduled surgical procedure that will be performed by the surgical team under general anesthesia, and I authorize the specific surgical technique. I am aware that, according to oncological safety, the procedure may be intraoperatively extended or converted, even into a total laryngectomy. I am aware that, in the need to save my life from imminent and not predictable danger or to avoid serious harm to my person, any medial or surgical procedure will be attempted to prevent or limit this danger, in order to safely complete the surgery.
**I authorise/I don’t authorise** the surgical team to treat any disease revealed during surgery and previously unknown, according to Surgeon’s knowledge and judgment, even with modification to the scheduled surgical procedure.
**I authorise/I don’t authorise** the use of tissues and/or organs removed during surgery to obtain a pathological diagnosis, and also for eventual procedures aiming at the improvement of scientific knowledge.
Finally, **I authorise/I don’t authorise** the use of images and videos taken during surgery, which may be used in scientific publications, with complete respect of my privacy.

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