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(Article begins on next page)

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Management of T4a laryngeal cancer

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Abstract

Background: Despite the recommendations contained in the guidelines, a general rise in non-surgical treatments and declining use of total laryngectomy has occurred during the last decades, as well as some evidence of declining survival for advanced laryngeal cancer in many countries.

Goal: To compare the results of surgical and non-surgical approach for T4a laryngeal cancer in term of curative effects, complications, and functional results by means of a systematic review of the more recent literature.

Recent findings: Most recent data clearly demonstrate the superiority of total laryngectomy and post-operative radiotherapy, which produce a substantial long-term control and survival rates for patients with T4 larynx cancer. The most negative prognostic factor is represented by N status. Open partial laryngectomy, to the light of good and encouraging oncological/functional results, could represents an alternative to total laryngectomy for selected patients affected by laryngeal cancer in specific T4a subcategories, i.e. limited anterior extension. Considering the worse oncologic results, principally in patients with poor general conditions and T4a cancer, non-surgical larynx preservation should only be addressed to carefully selected patients who refused total laryngectomy, characterized by more limited T4a disease, minimal involvement through the cartilage and without pre-treatment derangement of laryngeal functions.

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].

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 (VII edition) [5] divided T4 into 2 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 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 TLM or 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 Affairs (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 T4 tumors after a rigorous selection of patients.

Recent survey comparing surgical and non-surgical approaches for patients with T4a Larynx cancer

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 (T3 -T4a) 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 T4a 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 T4a 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 T4a 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 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 with T4a 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].

Recent evaluations have highlighted disappointing long-term results in terms of OS regarding different non-surgical organ-sparing protocols. Considering this end-point, in fact, deaths unrelated with LC were interestingly higher after CCRT (30.8%) if compared with those following IC (20.8%) or RT (16.9%) [17]. It was strongly suspected a toxic role in CCRT leading to increasing fatal occurrences. Anyhow further investigations would be necessary to definitively determine the causative differences [17].

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, 18-20]. This finding, according to some Authors, associates laryngeal preservation in T4 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 sequelae: 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 [21]. However, the sole preservation of the larynx 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 [22].

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 [23].

Based on these considerations and focusing the attention only on T4a 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 [24-28], 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 [29]. 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

[30, 31]. In fact, anterior encroachment 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 [32]. 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 T4a [33].

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 T4a 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 [34]. 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.

Salvage surgery in locally advanced laryngeal cancer

With the increasing use of chemoradiation as primary treatments also for advanced LC, the loco-regional complications related to failure of these treatments have increased in term of persistent or recurrent disease, laryngeal dysfunction or radionecrosis and severe neck fibrosis [35].

Despite endoscopy and the availability of modern imaging studies, diagnosis of recurrent or persistent tumor may be difficult. The main hurdles reside in: different growth pattern of radio-recurrent LC with respect to that of primary carcinoma, multiple tumor foci localized below an intact mucosa that are masked by edema and fibrosis, confused patient reported symptoms, and impaired laryngeal mobility [36].

In this scenario, salvage surgery represented the only therapeutic weapon available (Table 5). Regarding the advanced LC, salvage TL remains the gold standard, whereas the employment of organ-sparing protocols such as the OPHL could be considered anecdotal. In case of salvage after CCRT failure, there is no reason to debate about the indication of TL.

Salvage TL is certainly more prone to complications as compared to the up-front one. Evidences from the literature reported that complications after salvage TL are higher in patients undergoing CCRT than in patients treated by RT alone. In fact, chemotherapy deteriorates general health, nutritional and performance status of the patient. Furthermore, exacerbating the obliterative endoarteritis and fibrosis induced by radiation in local tissues, it participates to the creation of micro-vascular damage with tissue hypoxia and impaired wound healing [37].

The most common major complication of TL, and in particular in case of salvage one, is pharyngocutaneous fistula (PCF).

To avoid the PCF complications, several studies analyzed the role of “onlay” vascularized flap reconstruction with the rationale to incorporate no-irradiated well vascularized tissue to aid hypoxic tissues and consequently wound healing, reinforce the pharyngeal repair site or augment the circumference of the neopharynx. The incidence of PCF is higher after primary closure than after closure with the interposition of a well vascularized flap (Table 6).

The salivary bypass tube is another useful device with positive results in reducing the risk of PCF. In fact, it can be used to stent the reconstruction, calibrate the new digestive tract, and decrease salivary exposure of the anastomotic suture line. Consequently, the pharyngoesophageal reconstruction rapidly heals and the rate of fistula and stricture decreases [38, 39].

However, the morbidity associated with a PCF is undoubtedly greater, thus supporting the aphorism that “prevention is better than any subsequent management and treatment of PCF” [31].

Difficulties in assessing long term quality of life and laryngeal function

Following the extensive application of non-surgical preservation protocols in the treatment of locally advanced LC, the need to identify functional endpoints able to reflect more closely the aspects of the real quality of life after treatment arose. In fact, despite side effects correlated with TL are evident (decrease in all communication related parameters), those induced by chemo-radiotherapy on life quality and functional outcomes (e.g. swallowing) may not always be correlated with an anatomically preserved larynx [40]. Findings concerning functional outcomes from retrospective series are limited by the lack of consistent / uniform data collection, instrumental swallowing evaluation, and patient-reported outcomes with validated metrics [13].

In 2009, the Larynx Preservation Consensus Panel [10] identified four composite functional/mortality endpoints in designing larynx preservation trials: 1) LED: laryngoesophageal dysfunction free survival (any death, local disease recurrence, salvage total laryngectomy, tracheotomy and/or feeding tube placement/persistence after 2 years as an event, censoring all others); 2) LxFS: laryngectomy-free survival (the date of salvage or completion total laryngectomy or the date of death, censoring all others); 3) FFL:

actuarial freedom from laryngectomy (the date of salvage or completion total laryngectomy, censoring all others); and 4) FFLED: actuarial freedom from laryngoesophageal dysfunction (local disease recurrence, salvage total laryngectomy, tracheotomy and/or feeding tube placement/persistence after 2 years as an event, censoring all others including deaths).

The limited number of patients available for long-term effect analysis, due to the low OS after CCRT, and the lack of correlation between patients' perceptions and objective studies resulted in a reduced statistical power, and highlighted the importance of documenting swallow function before, during, and after chemo-radiation treatment [31]. Therefore, it is currently not possible to draw an accurate picture of the real benefits of the laryngeal preservation in terms of quality of life. In the RTOG study, severe late toxicity was reported in 43% of patients at the long-term analysis [17]. Anyhow, further investigations with properly designed studies specifically addressing laryngeal function are needed.

Analyzing the telephone intelligibility of LC patients undergoing different therapeutic approaches, Crosetti et al. [41] recently found that more aggressive surgery as well as chemo-radiotherapy correlated with significantly poorer outcomes. Otherwise, TLM or RT 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.

Conclusions

After several years in which TL seemed to fade, it returned to great actuality.

Long-term survival is achievable for patients with T4a LC and the most negative prognostic factor is represented by N status. Currently new strong evidences are confirming the role of TL as up-front treatment for advanced LC or salvage treatment in case of organ sparing protocols' failure.

CCRT option presents worse results in terms of oncological and functional rates, principally in T4a cancers and in patients with poor general conditions. Therefore, non-surgical laryngeal preservation should be addressed to carefully selected patients who refused TL, characterized by more limited T4 disease, minimal involvement through the cartilage without derangements of laryngeal function prior the treatment.

OPHL, to the light of good and encouraging oncological results, could represents an alternative to TL only for selected patients affected by LC in specific T4 subcategories (in particular for those with anterior extension).

Nowadays, however, TL-PORT remains the gold standard of treatment in locally advanced LC, with stable and acceptable results in terms of oncological, functional and life quality outcomes.

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 S -> RT	64%	68%/2 ys
EORTC 24891 [42]	202 pz,	Hypo pharynx, II-IV	PF -> RT vs S -> RT	22%/5 ys	- PF -> RT 38% / 5 ys - S -> RT 33%/5 ys
GETTEC [43]	68 pz	Larynx, II-IV	PF -> RT vs S -> RT	42%	- PF -> RT 69% / 2 ys - S -> RT 84%/2 ys
RTOG 91,11 [17]	547 pz	Larynx, III-IV	PF -> RT vs CRT vs RT	- PF -> RT 71%/5 ys - CRT 84%/5 ys - RT 66%/5ys	- PF -> RT 59%/5 ys - CRT 55%/5 ys - RT 54%/5ys
GORTEC 2000-01 [44]	213 pz	Larynx, Hypo pharynx, III-IV	PF -> RT vs TPF -> RT	- PF -> RT 57% /3 ys - TPF -> RT 70%/3 ys	- PF -> RT 60% /3 ys - TPF -> RT 60%/3 ys
EORTC 24954-22950 [45]	450 pz	Larynx, Hypo pharynx, III-IV	PF -> RT vs aPF -> RT (6w)	- PF -> RT 48%/5ys - aPF -> RT (6w) 52%/5ys	- PF -> RT 53%/5ys - aPF -> RT (6w) 60%/5ys
POSNER [46]	166 pz	Larynx, Hypo pharynx, III-IV	PF -> CRT vs TPF -> CRT	- PF -> CRT 32% LFS / 3ys - TPF -> CRT 52% LFS/3 ys	- PF -> CRT 40% / 3 ys - TPF -> CRT 57% /3 ys
TREMPIN [47]	153 pz	Larynx, Hypo pharynx, III-IV	TPF -> CRT vs TPF -> Cet+RT	- TPF -> CRT 93% 3 months - TPF -> Cet+RT 93% 3 months	- TPF -> CRT 85% 1,5 ys - TPF -> Cet+RT 86% 1,5 ys
PRADES [48]	71 pz	Pyriiform sinus, III-IV	PF -> S or RT vs P-RT	- PF -> S 68%/2 ys - RT vs P-RT 92% / 2 ys	- PF -> S DFS36%/2 ys - 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 T3-T4a 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 yrs - TL 78% - OPHL 68% - CRT 54%	DSS 87%/2ys		T3+T4a: CRT 45% 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 24 studies	T4a	TL, RT, CRT	81%/2 ys 60%/5 ys Review: / 2aa: - LT 90-100% - RT 12-21% - CRT 30-65%				Primary TL provides a high survival rate for T4a. High rate of laryngeal dysfunction after CRT.
Dziegielewski, 2012 [50]	Longitudinal cohort study	258	T3,T4	TL-PORT/CT, RT, CRT	2ys -5ys T3: - TL- PORT /CT 2 ys 89% 5 ys 70% - RT 2 ys 48% 5 ys 18% - CRT 2 ys 66% 5 ys 52% OS / 2 e /5 aa T4a: - TL-PORT/CT 2 ys 60% 5 ys 49% - RT 2 ys 12% 5 ys 5% - CRT 2 ys 32% 5 ys 16%	DFS / 2ys T3: - TL-PORT/CT 94% LRC - 0% LP - RT 66% LRC - 28% LP - CRT LRC 53% LCR -48% LP DFS/ 2ys T4a: - TL-PORT/CT 67% LRC - 0% LP - RT 30% LRC - 3% LP - CRT 54% LRC - 29% LP			TL-R/CT provides superior survival for T3 and T4a LC versus RT or CRT.
Grover, 2014 [51]	Retrospective cohort study	969	T4a	TL-PORT and LP-CRT	Median OS: - TL-PORT 61 months - 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, 2014 [19]	Retrospective cohort study	182	T3 and T4	TL-PORT (91% T4), RT, CRT	OS / 5 ys T3: - TL-PORT 49% - RT 47% - CRT 45% OS / 5 ys T4a: - TL-PORT 48% - RT 34% - CRT 42%		T3+T4a: - TL-PORT 87% - RT 65% - CRT 76%		No differences in survival. T3 : > CRT T4: > TL-PORT
Timmermans, 2015 [52]	Population based study	2072 T3 and 1722 T4	T3-T4	TL-PORT/CT, RT and CRT	OS / 5 ys T3: - TL-PORT/CT 49% - RT 47% - CRT 45% OS / 5 ys T4a: - TL-PORT/CT 48% - RT 34% - CRT 42%			LFI T3: - RT 81% - CRT 77% LFI T4a: - RT 81% - 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: - TL or PL 41% - CRT 40% /5 ys T4a: - TL or PL 54% - CRT 53%			LP total CRT 79% 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 - TL-PORT 47-48 months - LP 38 months	DSS/5 ys - TL-PORT 60% - LP 48,5%	ys : - TL-PORT 84% - 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: - TL-PORT 66% - IC-RT 60,8% - CRT 61% - RT alone 71,6%	DFS: - TL-PORT 56,6% - IC-RT 41% - CRT 44,9% - RT alone 57,8% 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% OS/ 5 ys 52,4% OS/ 10 ys 33,3%	DFS/ 2 ys 55% DFS/ 5 ys 42,6% DFS/ 10 ys 31,8%	LCR/ 2 ys 77% LCR/ 5 ys 74% LCR/10ys65,9		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 - TL-PORT 78,8% - LP-CRT 52,9% OS/5 ys stat sign only T4a		LC/2 ys - TL-PORT 76% - LP-CRT 54,6% LC/5 ys Not stat sign		TL-PORT significant advantage in OS and LCR T4a laryngeal cancer
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 - surgery 41% - 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 pT3 87,8% pT4a 71,2%	DFS 84,2% pT3 87,9% pT4a 68,1%	LRC 86,3% pT3 89,7% pT4a 71,7%	LFP 91,2% pT4a 78,0% 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 [19]	PF -> RT S -> RT	TD 3; mucositis 38% TD 5 ; mucositis 24%	
EORTC 24891 [42]	PF -> RT vs S -> RT	7 toxic effects, 1 TD 1 vascular disease, 1 depressive illness	
GETTEC [43]	PF -> RT vs S -> RT PF -> RT vs	Digestive 3%, hematological 1% Digestive 0%, hematological 0% Hematological 52% mucositis 34%, laryngeal 13%	Skin toxicity 5-0%, mucosal 5-0%, larynx toxicity 1-6%, dysphagia 15-3%, subcutaneous 11-1%
RTOG 91,11 [17]	CRT vs	Hematological 47% mucositis 43%, laryngeal 18%	Skin toxicity 1-0%, mucosal 3-0%, larynx toxicity 17-6%, dysphagia 22-3%, subcutaneous 9-1%
	RT	Hematological 3% mucositis 34%, laryngeal 16%	Skin toxicity 2-1%, mucosal 3-1%, larynx toxicity 21-3%, dysphagia 22-2%, subcutaneous 9-2%
GORTEC 2000-01 [44]	PF -> RT vs	2TD, neutropenia 17,6%, infections 5,8%, stomatitis 7,8%, thrombocytopenia 7,8%, creatinine elevation 2%	G4 larynx toxicity 13,6%, mucosal 0%, xerostomia 2,2%, subcutaneous 6,6%
	TPF -> RT	5TD, neutropenia 31,5%, infections 10,9%, stomatitis 4,6%, thrombocytopenia 1,8%, creatinine elevation 0%	G4 larynx toxicity 6,2%, mucosal 1%, xerostomia 6,1%, subcutaneous 4%
EORTC 24954-22950 [45]	PF -> RT vs aPF -> RT (6w)	Mucositis 32%, skin reaction 6%, dysphagia 33% Mucositis 21%, skin reaction 0%, dysphagia 20%	Mucosal 25%, neuropathy 14%, subcutaneous 31% Mucosal 28%, neuropathy 11%, subcutaneous 28%
	TPF -> CRT vs	Mucositis 43-3%	Mucosal 3,5%, xerostomia 10,3%, subcutaneous fibrosis 7%, neuropathy 3,4%, laryngoesophageal 8,6%
TREMPIN [47]	TPF -> Cet+RT	Mucositis 52-2%	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 T1 2 T2 41 T3 14 T4 4	OPHL type II	OS / 3 ys 83% OS / 5 ys 79%						3,0%
Laccourreye, 1998 [61]	60	T3-T4a	Neo-adjuvant CT - OPHL type II	87,9% / 3 ys 72,7% / 5 ys		98,3%	91,7%		8,3% local failure	
De Vincentis, 1998 [62]	149		OPHL type II (CHP 98 pz CHEP 51 pz)	2 groups: OS 1° 88,1% OS 2° 95,0%			98%			6,0%
Bron, 2000 [63]	69	T1-T4a pT1 10 pT2 30 pT3 9 pT4 5 local relapse 15	OPHL type II 13% adjuvant RT	OS / 5ys 66,5% - glottic : 69,1% - supraglottic : 45,6%	DSS /5 ys 80,1% - glottic : 83,2% - supraglottic : 51,4%	LC/5 ys 84,0% LCR no RT Pz 94,5%		87,0%	49,1%	6,1%
Gallo, 2005 [64]	253	T1-T4a T1 27 T2 147 T3 64 T4 15	OPHL type II 180 CHP 73 CHEP	85,8% / 3 ys 79,1% / 5 ys 57,6% / 10 ys 57,6% / 16 ys		LRC 91,3%	92,1%			8,7%
Lima, 2005 [65]	43	T3-T4a glottic	OPHL type II (CHEP)		DSS / 5 ys 78,0% DFS / 5 ys 83,0%	LRC / 5 ys 85,0%			25,5%	
Laudadio, 2006 [66]	206	T1b-T4a T1b 66 T2 89 T3 46 T4 5	OPHL Type II 9,2% CHP 90,8% CHEP	pT3 88,7% pT4 78,9%	DFS / 3 ys 85,4% DFS / 5 ys 85,0% pT3 77,6% pT4a 53,8%					15,0%
Rizzotto, 2015 [67]	115	T2-T4a pT2 14 pT3 50 pT4a 51	OPHL Type III	78,9%/5ys pT4a 80,4%	DFS 68,5% /5 ys pT4a 60,8%	69,6% / 5 ys pT4a 62,7%		LFP 78,3% pT4a 59,3%	6,1% acute 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

Table 5 Complications, survival outcomes and prognostic risk factors in patients with salvage surgery after organ-sparing protocols for SCC of larynx

Author - year publication	N° of patients	Previous treatment	Salvage surgery	Complications	Fistula	LR	OS	DSS	Risk factors
Paleri, 2011 [68]	350	CRT	SPL			87%/2ys	83%/3ys	91%/2ys	
Putten, 2011 [69]	120	CRT	STL			70%/5ys	50%/5ys	58%/5ys	Risk factors: level of albumin and hemoglobin, N+
Klozar, 2012 [70]	208	CRT	STL		34%				
Erdag, 2013 [71]	36		STL		50%				
Sewnaik, 2012 [72]	24	CRT	STL	92%					
Patel, 2013 [73]	359	CRT	STL		27%				
De Vincentiis, 2013 [74]	68	(C)RT - TLM	SPL (23 pz) STL (45 pz)						OS and DFS < STL than SPL (prognostic factor involvement of resection margins)
Santoro, 2013 [75]	75	RT	SPL (16%) STL (84%)		32,7%				OS and DFS < STL than SPL (prognostic factor rT)
Li, 2013 [76]	100	CRT	STL			70%/5 ys		55-70%/5ys	
Basheeth, 2013 [37]	45	CRT	STL	44%					
Sayles, 2014 [77]	33 studies	CRT RT alone	STL		34% 22,8%				
Sayles, 2014 [77]	33 studies	CRT	PTL STL		14,3% 27,6%				
Timmermans 2014 [78]	98	CRT	STL		26%				
Powell, 2014 [79]	45	CRT	STL		22%				
Süslü, 2015 [80]	151	CRT	STL		13%				
Busoni, 2015 [81]	86		PTL STL post-RT STL post-CRT		19% 28,6% 30,3%				
Putten, 2015 [82]	22	CRT	STL	73%	23%	58%/5ys	27%/5ys	36%/5 ys	
Wulff, 2016 [83]	142	CRT	STL	60%	41,6%		37,7%/5ys	54,9%/5ys	N+ and positive margins

STL = salvage total laryngectomy, SPL salvage partial laryngectomy

Table 6 Comparison of PCF in patients with salvage laryngectomy with and without flap reinforcement

Author - year publication	N° of patients	Treatment	Fistula with flap	Fistula without flap	Results and conclusions
Patel, 2009 [84]	359	PMF FVT	15% 25%	34%	With PMF reinforcement, PCF rate after salvage laryngectomy dropped to 0% in this study
Busoni, 2013 [81]	20	Conservative FVT			Fistula after PTL → conservative treatment Fistula after STL → flaps
Santoro, 2013 [75]	29	Conservative FVT	80,5% 8,3% PFM 21% local flaps	34%	Flaps reduce the risk of fistula
Powell, 2014 [79]	45	FVT/PMF	0%	26%	lower rate of PCF with tissue transfer compared with primary closure of the neopharynx.
Sayles, 2014 [77]	33 studies	Onlay flap	10%	28%	Prophylactic flaps used in an "onlay" technique reduce fistula incidence in STL
Paleri, 2014 [35]	591				Flaps reduce the risk of fistula
Anschutz, 2016 [85]	48	PMMF	0%	42,1%	PMMIF is useful to prevent PCF in STL following CRT.

PMF = pectoralis myofascial flap, FVT = free vascularized tissue

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