

# Total Laryngectomy for Treatment of T4 Laryngeal Cancer: Trends and Survival Outcomes

Jaspreet Singh Badwal<sup>1,2</sup>

<sup>1</sup>Apollo Cancer Institute, Jubilee Hills, Hyderabad, India

<sup>2</sup>Cachar Cancer Hospital & Research Centre, Assam, India

Article history: Received: 15.09.2017 Accepted: 14.08.2018 Published: 06.08.2018

## ABSTRACT:

**Introduction:** Management of advanced laryngeal cancer has shown fluctuating trends during the last few decades. Though many extensive reports are available in the literature regarding survival outcomes for advanced laryngeal cancer, there is a paucity of elaborate systematic reviews giving a complete picture of facts and figures. The present analysis brings to attention the most relevant data in a focused and up-to-date format, for simpler interpretation of evidence-based inference.

**Objective:** To present trends in the treatment of T4 laryngeal cancer over the past few decades and analyze survival outcomes for different treatment modalities in the management of T4 laryngeal cancer by way of systematic review.

**Methods:** An electronic search was conducted using the terms “total laryngectomy”, “T4 laryngeal cancer”, “survival outcomes” in combination with the following search strategy: Search block Laryngeal cancer - “Laryngeal Neoplasms” [Mesh] OR (Laryngeal [tiab] OR larynx [tiab] OR “Larynx” [Mesh]) AND (“Neoplasms” [Mesh] OR neoplasm\* [tiab] OR tumor\* [tiab] OR tumour\* [tiab] OR cancer\* [tiab] OR malignancy\* [tiab] OR carcinoma\* [tiab] OR neoplasm\* [tiab] OR oncology\* [tiab]); Search block Total laryngectomy - “Laryngectomy” [Mesh] OR total laryngectomy\* [tiab] OR total laryngopharyngectomy\* [tiab] OR total pharyngolaryngectomy\* [tiab]; Search block T4–t4 [tiab]. Clinical studies were retrieved from the electronic databases of PubMed, EMBASE, SCOPUS and Cochrane Library. A total of 304 articles had been published till June 2017, which included prospective studies, randomized controlled trials, retrospective studies and smaller descriptive studies. References of the selected studies were further searched for relevant articles. Moreover, a search was conducted over Google Scholar to obtain related articles.

**Results:** Numerous studies, as mentioned in this review, provide authentic evidence in relation to the efficacy and outcome of surgical treatment for T4 laryngeal cancer. To address the problem of heterogeneity with regard to patient selection, numerous reports pertaining to T4 patients exclusively have been included.

**Conclusion:** Total laryngectomy remains the gold standard for the management of T4a laryngeal cancer. After the unparalleled oncological outcomes of more than a century, the technique has stood the test of time. An exhaustive review of literature has been presented, discussing the trends in the treatment of advanced laryngeal cancer across different continents. However, it must be specified that the purpose of the study is not to prove one treatment protocol to be superior to the other but to bring out patterns of adherence to protocols and guidelines as suggested by multidisciplinary consensus reports and the consequent outcomes.

## KEYWORDS:

Total laryngectomy, laryngeal cancer, T4 laryngeal cancer

## PURPOSE

To present the trends in the treatment of T4 laryngeal cancer over the past three decades and analyze survival outcomes for different treatment modalities in the management of T4 laryngeal cancer by way of systematic review.

## MATERIALS AND METHODS

An electronic search was conducted using the terms “total laryngectomy”, “T4 laryngeal cancer”, “survival outcomes” in combination with the following search strategy: Search block Laryngeal cancer – „Laryngeal Neoplasms” [Mesh] OR (Laryngeal[tiab] OR larynx [tiab] OR „Larynx” [Mesh]) AND (“Neoplasms” [Mesh] OR neoplasm\* [tiab] OR tumor\* [tiab] OR tumour\* [tiab] OR cancer\* [tiab] OR malignancy\* [tiab] OR carcinoma\* [tiab] OR neoplasm\* [tiab] OR oncology\* [tiab]); Search block Total laryngectomy – „Laryngectomy” [Mesh] OR total laryngectomy\* [tiab] OR total laryngopharyngectomy\* [tiab] OR total pharyngolaryngectomy – \* [tiab]; Search block T4 – t4 [tiab]. Clinical studies were retrieved

from the electronic databases of PubMed, EMBASE, SCOPUS and Cochrane Library. A total of 304 articles had been published till June 2017, which included prospective studies, randomized controlled trials, retrospective studies and smaller descriptive studies. References of the selected studies were further searched for relevant articles. Apart from this, a search was conducted over Google Scholar to obtain related articles.

## RESULTS

Numerous studies, as mentioned in this review, provide authentic evidence in relation to the efficacy and outcomes of surgical treatment for T4 laryngeal cancer. To address the problem of heterogeneity with regard to patient selection, numerous reports pertaining to T4 patients exclusively have been included. It is clear from the analysis of all available data that total laryngectomy is the best treatment option as far as T4a laryngeal cancer is concerned.

The present report makes no negative remarks in relation to any treatment modality. All institutes have their own “institutional

**Tab. I.** Survival outcomes from studies comparing Total Laryngectomy with CRT (Chemoradiotherapy).

STUDY	OVERALL SURVIVAL FOR T4		Number of Patients ( $\alpha$ - T4, $\beta$ - Stage III + Stage IV)	STATISTICAL SIGNIFICANCE
Gourin et al. <sup>a</sup> (2009)	55	25	451 <sup>a</sup>	Yes
Chen et al. <sup>b</sup> (2011)	51	48	19,326 <sup>b</sup>	Yes
Dziegielewski et al. <sup>a</sup> (2012)	49	16	258 <sup>b</sup>	Yes
Megwalu and Sikora <sup>a</sup> (2014)	40	31	5394 <sup>b</sup>	Yes
Karatzanis et al. <sup>a</sup> (2014)	41.1	16.7	384 <sup>a</sup>	Yes
Rosenthal et al. <sup>a</sup> (2015)	60	48	221 <sup>a</sup>	Yes
Timmermans et al. <sup>a</sup> (2016)	48	42	1722 <sup>a</sup>	Yes
Vengalil et al. <sup>c</sup> (2016)	70	41	107 <sup>a</sup>	Yes
Grover et al. <sup>e</sup> (2015)	61 months	39 months	969 <sup>a</sup>	Yes
Choi et al. <sup>e</sup> (2016)	87.2 months	31.3 months	89 <sup>a</sup>	Yes

a – 5-year, b – 4-year, c – 3-year, d – 2-year, e – median overall survival.

protocols” and the present study intends only to give suggestions for future research and practices.

## INTRODUCTION

Laryngeal cancer is the second most common cancer of the head and neck region. It accounts for about 2.4% of all newly diagnosed malignancies worldwide each year. Most of these cancers are squamous cell carcinoma, accounting for 85% to 95% of laryngeal malignancy [1, 2, 3]. The term “advanced laryngeal cancer” generally denotes stage 3 or 4 laryngeal cancers according to UICC/AJCC staging [4]. Cancers of the larynx would attain this staging by virtue of advanced T category (T3 or T4), N category (N1-3) or M category (M1). The guideline recommendation for the treatment of locoregionally advanced laryngeal cancer, classified as T4, has classically been surgery [5,6]. It may be followed by radiotherapy (RT) with or without chemotherapy (CT), depending on indications. This is explained by the fact that in T4 tumors, laryngeal preservation rates are much lower and often present complications which compromise laryngeal function [7]. However, some patients opt for non-surgical treatment in spite of all possible explanation. Such a treatment should only be offered when there is minimal cartilage invasion [8] and absence of vocal cord fixation, [9] otherwise, the chances of recurrence are very high, which would eventually require salvage surgery.

Recent studies have shown decline in the use of surgical management as a treatment option for T4 laryngeal cancer. Grover et al. [10] published an elaborate study revealing the selection of treatment modalities for the management of T4 laryngeal cancer in the United States. The authors highlight the lack of adherence to protocols established by multidisciplinary consensus reports and the declining incidence of total laryngectomy in a non-study, practice-based setting. Parallel to this decline in incidence of total laryngectomy, various studies witnessed a fall in survival rates for advanced laryngeal cancer. Exhaustive reports by Carvalho (2005) [11] and Hoffman (2006) [12] bring out this fact in an elegant manner.

Some studies [13–16] have compared survival after total laryngectomy (TL) versus organ preservation protocol (OPP) in advanced laryngeal cancer. However, most studies published in relation to

this topic, have included patients with different stages (T3, T4, N0, N+) of laryngeal cancer, sometimes also including cases of hypopharynx or oral cavity, which leads to inaccurate extrapolation of prognostic implications. Any study which is utilized to reflect the standard of care must be precise and reproducible, should have no major unintended consequences of the treatment studied and should not lead to unwarranted conclusions. Studies with homogeneous categories of patients should be used as benchmark reference, in order to design institutional protocols. Rosenthal et al. 2015 [17] published (2015) published the largest long-term study to exclusively include patients with T4 laryngeal cancer. The authors concluded that total laryngectomy followed by postoperative radiotherapy produced longer locoregional relapse-free intervals and better functional outcomes as compared to initial non-surgical radiation-based treatment. As many as 38% of patients treated by laryngeal preservation protocol developed locoregional failure and eventually required salvage surgery. The study emphasized that larynx preservation protocol should be reserved for the minority of highly selected patients who present with a smaller-volume disease. Also, such patients should have an intact airway protection and swallowing function, no requirement for tracheostomy or feeding tube and limited cartilage destruction. Apart from this, the selected candidates should be eligible for chemotherapy-based laryngeal preservation regimens.

## TRENDS IN TREATMENT AND SURVIVAL OUTCOMES

Over the decades, there have been noticeable changes in the treatment protocols for laryngeal cancer. The result has been a decrease in the number of advanced laryngeal cancers treated with surgery alone. Hence, the incidence of partial or total laryngectomy being performed for advanced laryngeal cancer has decreased. The major driving force for bringing out such a paradigm shift has been the publication of two studies – the Veterans Affairs Trial [13] (VA Larynx study, 1991) and the RTOG 91-11 Trial [18] (Forastiere study, 2003). Both these studies reported high rates of larynx preservation with the use of chemoradiotherapy protocols for treatment. However, it must be pointed out that in the Veterans Affairs Laryngeal study, only 85 of 332 patients (25%) included in the study had evidence of T4 disease. Of this selected group of subjects, 56%

required laryngectomy. Moreover, in this report, gross cartilage invasion and primary disease location in glottis, were also associated with poor outcomes. The resultant influence of this could be noted in the outcomes of the RTOG 91-11 study, which excluded patients with full-thickness cartilage involvement. As an inference, less than 10% of the patients in that study had T4 disease. Consequently, this prohibited any meaningful analysis of available data in relation to outcomes for advanced laryngeal cancer. Henceforth, for most T4 patients, total laryngectomy followed by radiotherapy has remained the standard treatment protocol [19].

It is pertinent to mention the results of two landmark trials by Richard et al. [20] and Li et al. [21] which were randomized controlled studies. Richard et al. (1998) presented the results of a randomized controlled trial in patients with primary advanced laryngeal cancer, in order to compare results of two treatment arms. Patients in the first group underwent total laryngectomy plus adjuvant radiotherapy. Patients in the second group underwent induction chemotherapy followed by radiotherapy in good responders and total laryngectomy plus radiotherapy in poor responders. A total of 68 patients met the inclusion criteria, 36 in the induction chemotherapy group and 32 in the no-chemotherapy group. Overall survival and disease-free survival were significantly worse in the induction chemotherapy group, as compared to the no-chemotherapy group ( $P = 0.006$  and  $P = 0.02$ , respectively). The 2-year survival rates were 69% in the induction chemotherapy group and 84% in the no-chemotherapy group. The authors recommended that larynx preservation for patients selected on the basis of response to induction chemotherapy should not be considered a standard of treatment. Li et al. (1998) [21] presented the results of a randomized controlled trial comparing the outcomes of preoperative radiation plus surgery (RS group) to surgery alone (SA group). The ages of patients were less than 75 years. A large cohort of 370 patients with laryngeal cancer was included in the study, 215 in the SA group and 155 in the RS group. The 10-year survival rate in the SA group was much better than that in the RS group (80.3% versus 68.6%). Also, the 10-year survival rates for patients with T3 and T4 supraglottic carcinomas in the SA group were better than in the RS group. The authors concluded that preoperative radiation is not a viable option for treatment of laryngeal cancer. Similarly, Morita et al. (1989) reported low control rates for T4 laryngeal cancer with radiotherapy as the treatment of choice. One of the more recent studies is that published by De Miguel et al. (2012) [23], who presented their results on functional larynx preservation. The objective was to analyze the potential association between clinical and pathological features and functional larynx preservation (FLP). The study involved 43 patients treated for squamous cell cancer of the larynx. The authors concluded that risk factors for FLP were T4 stage, lymph node status, former smoker status and stage IV. As a consequence, patients presenting with these features are not optimal candidates for organ preservation approaches.

It is relevant to bring to attention the study published by Hoffman et al. (2006) [12] which revealed a reduction in survival for laryngeal cancer over recent decades. This study enrolled a large number of 1,58,246 subjects registered with the National Cancer Database (USA) between 1985 and 2001. The authors concluded that non-surgical treatment for laryngeal cancer is associated with decreased survival outcomes. More recently, Jovic et al. (2013) [24] published a study on the role of surgery in modern treatment of laryngeal cancer. The authors concluded that most cases of ad-

vanced laryngeal cancer are indications for total laryngectomy, while near-total laryngectomy is appropriate in selected cases. Surgery after radiotherapy, particularly after chemoradiotherapy, results in complications that significantly prolong treatment and increase its costs. Surgical treatment, when offered as primary management, leads to good healing and complications are rare.

Recent studies have revived the debate on surgical management for advanced laryngeal cancer. Timmermans et al. (2016) [25] published the results of a 20-year population-based study from Netherlands, reporting the treatment and survival for advanced laryngeal cancer. This data was obtained from two combined national cancer registries. A total of 2072 T3 cases and 1722 T4 cases were identified. From 1991 to 2010, T3 disease showed similar survival rates for all primary treatment modalities. However, it was clearly evident that for T4 disease, total laryngectomy (with adjuvant RT) leads to the best survival outcomes. It is imperative to comment that T4 laryngeal cancer in the Netherlands is managed surgically.

As mentioned earlier, it is important to focus on the studies involving a large number of subjects treated exclusively for T4 laryngeal cancer (Tab. I.). Rosenthal et al. (2015) [17] presented a study evaluating the long-term disease control, survival and functional outcomes after surgical and non-surgical treatment for T4 laryngeal cancer at a single institution between 1983 and 2011 (Tab. I.). The median follow-up time was 47 months. Patients treated by laryngectomy followed by postoperative radiotherapy (161 patients) achieved better initial locoregional control (LRC) than patients treated by laryngeal preservation (LP) approach (60 patients) throughout the follow-up period. LP patients had a tracheostomy rate of 45% and any-event aspiration rate of 23%. Also, the results of high-grade dysphagia at last follow-up were worse for LP patients. More recently, similar results have been reported by Crosetti et al. (2017) [26], who recommended that TL followed by postoperative radiotherapy provides superior survival outcomes as compared to non-surgical protocols for T4 laryngeal cancer. Similarly, in one of the recent studies from France, Gorphe et al. (2016) [27] presented a review of a large series of 100 patients with T4a laryngeal cancer who were treated with primary total laryngectomy and postoperative radiotherapy, between 2001 and 2013. The 2-, 5- and 10-year overall survival (OS) rates were 65, 52.4 and 33.3% respectively, while the disease-free survival rates were 55, 42.6 and 31.8% respectively. Apart from this, the locoregional control rates were 77, 74 and 65.9% respectively. The authors concluded that in this homogeneously treated cohort, with consistent guideline application, primary surgery for T4a larynx cancer has shown good survival outcomes.

As mentioned previously, the topic of laryngeal cartilage invasion by cancer deserves special emphasis. Choi et al. (2016) [8] compared the therapeutic effects of total laryngectomy and a larynx preservation approach in patients with T4a laryngeal cancer and thyroid cartilage invasion (Tab. I.). This multicenter retrospective review included 89 patients, of whom 53 (59.6%) were initially treated with total laryngectomy (TL) and 36 (40.4%) with larynx preservation (LP) therapy. The median follow-up period was 33 months. The survival benefit of primary surgery was more striking in patients of lower N classifications. Also, the rate of distant metastases was found to be higher in the LP group (25%) compared to the TL group (9.4%). Similar results were reported by Nakayama et al. (1993) [28], who presented a study on clinical underestimation of laryngeal cancer, in

order to identify the predictive indicators. Whole-organ serial section studies were performed on 41 patients of T3 and 16 patients of T4 laryngeal cancer. All patients had undergone wild field total laryngectomy. Five risk indicators were identified for underestimation – (1) extensive cartilage ossification (risk of cartilage involvement, 73%); (2) glottic fixation (54%); (3) transglottic cancer (74%); (4) tumor length longer than the entire vocal fold length or longer than 2 cm (66%); and (5) extensive involvement of the anterior commissure (67%). The study revealed that clinical underestimation of T3 and T4 laryngeal cancer was high because thyroid cartilage involvement was not accurately diagnosed.

A highly popular and debatable study was published by Grover et al. (2015) [10], to examine practice patterns and compare survival outcomes between total laryngectomy (TL) and larynx preservation chemoradiation (LP-CRT) in the setting of T4a larynx cancer (Tab. I.), using the National Cancer Database (USA). The authors pointed out that the use of total laryngectomy as the primary treatment modality for T4 laryngeal cancer had shown a decline in the United States of America, which is actually against the guidelines. A total of 616 patients (64%) received LP-CRT and 353 patients (36%) received TL. The authors proposed TL as the preferred initial approach for patients with T4a larynx cancer. Karatzanis et al. (2014) [29] published the results of a retrospective analysis of a large group of 384 subjects, primarily treated for T4a squamous cell carcinoma of the larynx (Tab. I.). Two major groups of patients were defined. One group was treated by primary surgery with or without adjuvant CRT (321 cases). The other group received radiotherapy with or without chemotherapy as primary treatment (CRT group) and, if needed, salvage surgery (63 cases). Patients treated with primary surgery were found to have superior prognosis. Disease-specific survival rate was found to be 62.2% for the primary surgery group and 24.5% for the CRT group. Francis et al. (2013) [30] conducted a study to assess the survival outcomes of T4a laryngeal cancer patients treated at their institution by primary total laryngectomy and neck dissection with adjuvant therapy, when indicated. Thirty patients met the inclusion criteria. Overall survival at 2 years ranged from 30% to 100% with surgery, <30% to 65% with chemoradiotherapy and from 12% to 21.2% with radiotherapy. The authors concluded that primary total laryngectomy provides a high survival rate of T4a laryngeal cancer. It would be overemphasizing to repeat that the above mentioned studies were focused exclusively on T4 laryngeal cancer patients.

For addressing the concern about the level of evidence reported in various studies, it is important to discuss the meta-analysis presented by Fu et al. (2016) [31], to compare the efficacy of total laryngectomy to that of non-surgical organ-preservation in the treatment of advanced laryngeal cancer. A total of 8308 patients (4478 in the TL group and 3701 in the nonsurgical group) were included in this study from an analysis of 16 studies. Overall survival (OS) and disease-specific survival (DSS) were clearly better in the TL group as compared to the non-surgical group. Among the articles reporting the results of a large study cohort, Harris et al. (2016) [32] presented a study that retrospectively analyzed patients in the Surveillance, Epidemiology and End Results (SEER) database with advanced-stage laryngeal squamous cell cancer, treated between 2004 and 2012. On the whole, a total of 6797 patients met the inclusion criteria, with 2051 patients undergoing primary surgery and 4746 patients undergoing primary radiotherapy (RT) or chemoradiotherapy (CRT). Disease-specific survival (DSS) and

overall survival (OS) were significantly better for patients treated with primary surgery. When the same patients were analyzed after stratification by T category, N category and subsite, OS and DSS benefits were observed for patients with T3 and T4a tumors, N0 neck disease or supraglottic primaries. With an extremely large sample size (Tab. I.), Chen et al. (2010) [33] reported a study analyzing the survival outcomes for patients with advanced laryngeal cancer (stage III and IV) who received treatment between 1996 and 2002. Patient records were retrieved from the National Cancer Database (USA). Treatment included total laryngectomy (TL – 37.6%), chemoradiotherapy (CRT – 29.4%) and RT alone (33%). The authors observed that treatment with non-surgical therapy (CRT or RT) was associated with a higher risk of death, while total laryngectomy was associated with improved survival outcome. Rodrigo et al. (2014) [34] presented a study that analyzed the oncological outcomes of total laryngectomy (TL) as treatment for T3 and T4a laryngeal cancer. Eighty patients met the inclusion criteria (29 of T4a and 51 of T3). Bilateral neck dissection was performed in 54 patients, unilateral in 11 and central in 4. Twenty patients (25%) received postoperative radiotherapy. The 5-year disease-specific survival was 72% and 5-year overall survival was 55%. The authors emphasized that TL is an effective treatment for the management of patients with locally advanced laryngeal cancer. In a study from Canada, Dziegielewski et al. (2012) [35] presented their results for analysis of survival outcomes of primary total laryngectomy versus organ preservation for T3/T4a laryngeal cancer (Tab. I.). A large cohort of patients registered with the Alberta Cancer Registry was included. The mean follow-up was 3.43 years. The overall survival (OS) for T4a cancers at 2 years and 5 years for total laryngectomy, with or without adjuvant therapy (TL-R/LT) was 60% and 49% respectively. The OS for RT was 12% and 5% respectively, while that for CRT was 32% and 16% respectively. The authors concluded that TL-R/CT provides superior survival for T3 and T4a laryngeal cancers versus RT or CRT. Van Dijk et al. (2013) [36] presented an analysis of patients treated for laryngeal cancer between 1989 and 2010. The treatment for T4 laryngeal cancer in Netherlands is total laryngectomy, which may be followed by adjuvant therapy. This is in accordance with the guidelines of Dutch Head and Neck Society. The results of the study revealed declining incidence and mortality rates for men, while the incidence and mortality for women were stable. These findings are in marked contrast to the patterns in the USA, where the survival rates have been reported to be declining.

To evaluate the complications associated with various treatment modalities, Lin et al. (2016) [37] conducted a study involving a large cohort of 3212 patients, to compare the effectiveness of surgical and non-surgical therapy for advanced laryngeal cancer (stage III and stage IVa). As many as 42% of the patients underwent surgery while 18% underwent CRT. The remaining patients received other non-standard treatment (861 patients) or were not treated (416 patients). Only 24% of the patients treated with concurrent CRT completed the full courses. Among patients with incomplete CRT, 277 (63.8%) patients suffered from dysphagia, 152 (35%) had percutaneous endoscopic gastrostomy tube placement, 40 (9.2%) had xerostomia, 58 (13.4%) had mucositis and 37 (27%) had neutropenic fever. Equivalent results were reported by Lavo et al. [38]. This study involved a retrospective chart review of 28 laryngeal cancer patients from 2005 to 2008 who had been treated with radiation +/- chemotherapy. Videolaryngoscopies were performed 6 months later. The videos were evaluated on the basis of the Laryngeal Ede-



ma Scale (LES) and Reflux Finding Score (RFS). Tracheostomy and feeding tube outcomes were then correlated with the two scales. The results revealed that feeding tube and tracheostomy dependence were associated with pre-treatment vocal-cord paralysis, advanced T-stage and chemoradiation. Eight categories from the LES and RFS scales exhibited significant association with a need for a feeding tube. Apart from laryngeal cartilage invasion, vocal cord fixation is an important criterion for patient selection. Staton et al. (2002) [9] reported a study to analyze factors predictive of poor functional outcome after chemoradiation for advanced laryngeal cancer. As many as 45 patients met the inclusion criteria. The main outcome measure was persistent use of gastrostomy tube feedings and/or tracheostomy at 6 months after the completion of therapy. Vocal cord fixation was found to be the strongest predictor of a poor functional outcome. As many as 56% of patients exhibiting vocal cord fixation demonstrated poor functional outcome, in contrast to only 6% of patients without vocal cord fixation. Correspondingly, Janot et al. (2002) [39] presented their retrospective study on laryngeal preservation with induction chemotherapy and radiotherapy for good responders. This study involved a large cohort of 104 patients. The overall survival for the entire cohort was 76% at 3 years and 69% at 5 years, with a laryngeal preservation rate of 36%. The results revealed that the single prognostic factor affecting survival was arytenoid mobility before treatment ( $P < 0.004$ ). Locoregional failures were higher (33% vs. 15%,  $P < 0.03$ ) and laryngeal preservation was lower (18% vs. 51%) in patients with a fixed arytenoid (49 cases), when compared to cases with non-fixed arytenoid (55 patients). Other studies, by McCoul et al. [40] and Spaulding et al. [41] have confirmed these findings with similar results.

Teymoortash et al. (2016) [42] reported their results on oncological and surgical outcome of total laryngectomy in combination with neck dissection in the elderly. A total of 58 patients separated into two age groups (28 < 65 versus 30 ≥ 65 years) with laryngeal and hypopharyngeal cancer who underwent total laryngectomy and neck dissection were enrolled. Disease-free and overall survival showed no significant differences for the two age groups. The authors concluded that total laryngectomy in combination with neck dissection is a good option for elderly patients. This is in contrast to the fact that chemoradiotherapy is not preferred in patients of age over 70 years. Further discussion will focus on the studies describing survival outcomes for supraglottic, glottic and subglottic laryngeal cancer as separate entities. Kowalski et al. (1998) [43] presented a comparison of outcomes for patients with supraglottic carcinoma treated by radiotherapy with those treated by surgery. A large cohort of 164 cases was included. The 5-year actuarial survival rates were 58.5% for patients in the surgery group versus 16.3% in the radiotherapy group. Similar results were reported by Wang et al. (1991) [44] who recommended total laryngectomy for T3 and T4 supraglottic tumors because of poor locoregional control with radiotherapy. Johnson et al. (1993) [45] presented a retrospective review of 270 patients with glottic carcinoma of the larynx. Patients treated for T3 and T4 disease underwent total laryngectomy with or without neck dissection. Cervical nodes were involved in 22% of T3 and 41% of T4 patients at the time of treatment. The results revealed that patients treated for T4 glottic cancer with neck dissection had improved survival compared with patients treated with laryngectomy alone ( $P = 0.006$ ). Similar findings were reported by Razack et al. (1989) [46] who presented results of a large cohort of 128 patients with T3 or T4 glottic carci-

noma. This study proved that initial total laryngectomy gave better results for advanced glottic carcinoma. The results of these studies on advanced supraglottic and glottic carcinoma of the larynx were in confirmation with the studies published by Fuji et al. (1997) [47], Ikarashi et al. (1990) [48] and Hirano et al. (1976) [49], who recommended surgical treatment for T4 carcinoma of the larynx, involving all three subsites, i.e. supraglottis or glottis or subglottis. It is pertinent to mention that the study by Fuji et al. involved a large sample size of 1079 patients. These patients included 64% with glottic cancer, 35% with supraglottic cancer and 12 patients with subglottic carcinoma. Total laryngectomy was performed for all T4 lesions. The 5-year relative survival rates for stage IV were 52% for glottic carcinoma and also 52% for supraglottic carcinoma. The study by Ikarashi involved 131 patients with 87 cases of glottic type, 42 of supraglottic type and 2 of subglottic type. The authors recommended total laryngectomy as an initial treatment for T3 and T4 cancers. Hirano et al. presented a retrospective analysis of 158 cases of which glottic cancer was most frequent and subglottic type was rare. The authors suggested total laryngectomy as initial treatment for T4 cancer of supraglottic, glottic and subglottic type. Furthermore, they recommended an elective neck dissection for supraglottic T2, T3 and T4 cases and subglottic T3 and T4 cases.

## DISCUSSION

Management of laryngeal cancer has shown fluctuating trends during the last few decades. This was elaborated in the study by Carvalho et al. (2005) [11], who reported a site-specific analysis of the SEER database (Surveillance, Epidemiology and End Results, USA) in relation to trends and prognosis for head and neck cancer in the United States. A large cohort of 96,232 cases was evaluated for trend analysis in incidence, clinical stage, treatment and 5-year survival. These patients were registered with the SEER database from 1974 to 1997. On site-specific analysis for laryngeal cancer, the study revealed a significant decrease in the 5-year overall survival rate from 65.2% (1974–1976) to 62.0% (1995–1997) over the time period. These results were further confirmed by Hoffman et al. (2006) [12], who presented a study involving a large number of 1,58,426 cases of laryngeal cancer, registered with the National Cancer Data Base (NCDB, USA). The authors reported a decrease in the 5-year survival rates from 1985 to 1996. This increase in mortality was parallel to the increase in non-surgical management for laryngeal cancer, over the same time period. Olsen (2016) [50] has brought to attention another important factor in relation to the treatment of advanced laryngeal cancer. His study revealed that most of the results in relation to effectiveness of non-surgical treatment modalities are obtained from randomized controlled trials which were based on specific inclusion criteria for patient selection, followed by treatment in accordance with a specified protocol. These protocol results, in reality, do not correctly extrapolate to outcomes in daily practice. A direct inference of the study is that results of these randomized controlled trials cannot be applied to every patient population. Total laryngectomy remains the gold standard for management of T4a laryngeal cancer [18]. Numerous studies, as mentioned earlier in this review, provide authentic evidence in relation to the efficacy and outcome of surgical treatment for T4 laryngeal cancer. Though in some parts of the world, as pointed out by Grover et al. [10], the incidence of the use of surgical treatment modalities for management of T4 laryngeal carcinoma has shown a decline, it was clearly proved to provide better survival outcomes, by many studies men-

tioned in the preceding descriptive analysis. To address the problem of heterogeneity with regard to patient selection, numerous reports pertaining to T4 patients exclusively have been included, so as to address undue criticism. Due weightage has been given to the importance of postoperative adjuvant radiotherapy, as well as the complication rates of various treatment modalities. Treatment guidelines have been elucidated for effective selection of patients and interpretation of the available data.

## CONCLUSION

Total laryngectomy remains the gold standard for the management of T4a laryngeal cancer. Numerous studies, as mentioned earlier in this review, provide authentic evidence in relation to the effi-

cacy and outcomes of surgical treatment for T4 laryngeal cancer. Though many extensive reports are available in the literature regarding survival outcomes for advanced laryngeal cancer, there is a paucity of elaborate systematic reviews giving a complete picture of facts and figures. The present analysis brings to attention the most relevant data in a focused and up-to-date format, for simpler interpretation of evidence-based inference. Also, it must be specified that the purpose of the study is not to prove one treatment protocol to be superior to the other but to bring out patterns of adherence to protocols and guidelines as suggested by multidisciplinary consensus reports and the consequent outcomes. Nonetheless, it is important to remember that the goal of every cancer specialist, no matter from either surgical or non-surgical disciplines, is to fight against cancer and not against a specific treatment modality. The battle is against the disease and we are all on the same side.

## REFERENCES

- Jemal A., Siegel R., Ward E., Murray T., Xu J., Thun M.J.: Cancer statistics, 2007. *CA Cancer J Clin.*, 2007; 57: 43–66.
- Lin H.W., Bhattacharyya N.: Staging and survival analysis for nonsquamous cell carcinomas of the larynx. *Laryngoscope*, 2008; 118: 1003–1013.
- Barnes L., Tse L.Y., Hunt J.L., Brandwein-Gensler M., Urken M., Slootweg P. et al.: Tumours of the hypopharynx, larynx and trachea: introduction. W: World Health Organization Classification of Tumours: Pathology and Genetics of Head and Neck Tumours, red.: L. Barnes, J. Eveson, P. Reichart, D. Sidransky, Lyon, France: IARC Press; 2005: 111–117.
- Edge S.B., Byrd D.R., Compton C.C., Fritz A.G., Greene F.L., Trotti A.: *Larynx AJCC Cancer Staging Manual*. 7th ed., Springer, New York 2010: 57–62.
- Forastiere A.A., Ang K.K., Brizel D., Brockstein B.E., Burtneiss B.A., Cmelak A.J. et al.: Head and neck cancers. *J Natl Compr Canc Netw.*, 2008; 6: 646–695.
- Pfister D.G., Spencer S., Brizel D.M., Burtneiss B., Busse P.M., Caudell J.J. et al.: Head and neck cancers, Version 2.2014. Clinical practice guidelines in oncology. *J Natl Compr Canc Netw.*, 2014; 12: 1454–1487.
- Weber R.S., Berkey B.A., Forastiere A., Cooper J., Maor M., Goepfert H. et al.: Outcome of salvage total laryngectomy following organ preservation therapy: The Radiation Therapy Oncology Group trial 91–11. *Arch Otolaryngol Head Neck Surg.*, 2003; 129: 44–49.
- Choi Y.S., Park S.G., Song E.K., Cho S.H., Park M.R., Park K.U. et al.: Korean South West Oncology Group (KSWOG) Investigators. Comparison of the therapeutic effects of total laryngectomy and a larynx-preservation approach in patients with T4a laryngeal cancer and thyroid cartilage invasion: A multicenter retrospective review. *Head Neck*, 2016; 38: 1271–1277.
- Staton J., Robbins K.T., Newman L., Samant S., Sebelik M., Vieira F.: Factors Predictive of Poor Functional Outcome after Chemoradiation for Advanced Laryngeal Cancer. *Otolaryngology Head and Neck Surgery*, 2016; 127: 43
- Grover S., Swisher-McClure S., Mitra N., Li J., Cohen R.B., Ahn P.H. et al.: Total Laryngectomy Versus Larynx Preservation for T4a Larynx Cancer: Patterns of Care and Survival Outcomes. *Int J Radiat Oncol Biol Phys.*, 2015; 92: 594–601.
- Carvalho A.L., Nishimoto I.N., Califano J.A., Kowalski L.P.: Trends in incidence and prognosis for head and neck cancer in the United States: a site-specific analysis of the SEER database. *Int J Cancer*, 2005; 114: 806–816.
- Hoffman H.T., Porter K., Karnell L.H., Cooper J.S., Weber R.S., Langer C.J. et al.: Laryngeal cancer in the United States: changes in demographics, patterns of care, and survival. *Laryngoscope*, 2006; 116: 1–13.
- Department of Veterans Affairs Laryngeal Cancer Study Group, Wolf G.T., Fisher S.G., Hong W.K., Hillman R., Spaulding M. et al.: Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. *N Engl J Med.*, 1991; 324: 1685–1690.
- Do L., Puthawala A., Syed N., Azawi S., Williams R., Vora N.: Treatment outcomes of T4 locally advanced head and neck cancers with soft tissue invasion or bone and cartilage invasion. *Am J Clin Oncol.*, 2009; 32: 477–482.
- Semrau S., Waldfahrer F., Lell M., Linke R., Klautke G., Kuwert T. et al.: Feasibility, toxicity, and efficacy of short induction chemotherapy of docetaxel plus cisplatin or carboplatin (TP) followed by concurrent chemoradiotherapy for organ preservation in advanced cancer of the hypopharynx, larynx, and base of tongue. Early results. *Strahlenther Onkol.*, 2011; 187: 15–22.
- Wanebo H.J., Rathore R., Chougule P., DiSiena M.R., Koness R.J., McRae R.G. et al.: Selective organ preservation in operable locally advanced head and neck squamous cell carcinomas guided by primary site restaging biopsy: long-term results of two sequential brown university oncology group chemoradiotherapy studies. *Ann Surg Oncol.*, 2011; 18: 3479–3485.
- Rosenthal D.I., Mohamed A.S.R., Weber R.S., Garden A.S., Sevak P.R., Kies M.S. et al.: Long-term Outcomes after Surgical or Nonsurgical Initial Therapy for T4 Squamous Cell Carcinoma of the Larynx: A Three Decades Survey. *Cancer*, 2015; 121: 1608–1619.
- Forastiere A.A., Goepfert H., Maor M., Pajak T.F., Weber R., Morrison W. et al.: Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. *N Engl J Med.*, 2003; 349: 2091–2098.
- Sheahan P.: Management of Advanced Laryngeal Cancer. *Rambam Maimonides. Med J.*, 2014; 5: e0015.
- Richard J.M., Sancho-Garnier H., Pessey J.J., Luboinski B., Lefebvre J.L., Deshesdin D. et al.: Randomized trial of induction chemotherapy in larynx carcinoma. *Oral Oncol.*, 1998; 34: 224–228.
- Li Q., Tu G., Tang P.: Preoperative radiation plus surgery vs. operation alone for laryngeal carcinoma. *Zhonghua Er Bi Yan Hou Ke Za Zhi.*, 1998; 33: 364–367.
- Morita K., Ito Y., Kato E., Kawabe Y., Kondo T.: Results of radiotherapy in carcinoma of the larynx. *Gan No Rinsho*, 1989; 35: 1387–1393.
- De Miguel Luken M.J., Pena E.D., Manuel C.C., De Miguel Luken V., Espino D.C., Moya A.C. et al.: Functional organ preservation in larynx cancer: Correlation with baseline clinical and pathological features. *Journal of Clinical Oncology*, 2012; 30: e16037.
- Jović R.M.: Role of surgery in modern treatment of laryngeal carcinoma. *Med Przegł.*, 2013; 66: 349–356.
- Timmermans A.J., van Dijk B.A., Overbeek L.I., van Velthuisen M.L., van Tinteren H., Hilgers F.J. et al.: Trends in treatment and survival for advanced laryngeal cancer: A 20-year population-based study in The Netherlands. *Head Neck.*, 2016; 38: E1247–E1255.
- Crosetti E., Caracciolo A., Arrigoni G., Fantini M., Sprio A., Berta G.N. et al.: Management of T4a Laryngeal Cancer. *Current Otorhinolaryngology Reports*, 2017; 5: 69–82.
- Gorphe P., Matias M., Moya-Plana A., Tabarino F., Blanchard P., Tao Y. et al.: Results and Survival of Locally Advanced AJCC 7th Edition T4a Laryngeal Squamous Cell Carcinoma Treated with Primary Total Laryngectomy and Postoperative Radiotherapy. *Annals of Surgical Oncology*, 2016; 23: 2596–2601.
- Nakayama M., Brandenburg J.H.: Clinical underestimation of laryngeal cancer. Predictive indicators. *Arch Otolaryngol Head Neck Surg.*, 1993; 119: 950–957.
- Karatzanis A.D., Psychogios G., Waldfahrer F., Kapsreiter M., Zenk J., Velegrakis G.A. et al.: Management of locally advanced laryngeal cancer. *J Otolaryngol Head Neck Surg.*, 2014; 43: 4.
- Francis E., Matar N., Khoueir N., Nassif C., Farah C., Haddad A.: T4a laryngeal cancer survival: retrospective institutional analysis and systematic review. *Laryngoscope*, 2014; 124: 1618–1623.
- Fu X., Zhou Q., Zhang X.: Efficacy Comparison Between Total Laryngectomy and Nonsurgical Organ-Preservation Modalities in Treatment of Advanced Stage Laryngeal Cancer: A Meta-Analysis. *Medicine (Baltimore)*, 2016; 95: e3142.

32. Harris B.N., Bhaskute A.A., Rao S., Farwell D.G., Bewley A.F.: Primary surgery for advanced-stage laryngeal cancer: A stage and subsite-specific survival analysis. *Head Neck*, 2016; 38: 1380–1386.
33. Chen A.Y., Fedewa S., Pavluck A., Ward E.M.: Improved survival is associated with treatment at high-volume teaching facilities for patients with advanced stage laryngeal cancer. *Cancer*, 2010; 116: 4744–4752.
34. Rodrigo J.P., Lopez F., Llorente J.L., Alvarez-Marcos C., Suarez C.: Results of total laryngectomy as treatment for locally advanced laryngeal cancer in the organ-preservation era. *Acta Otorrinolaringol Esp.*, 2015; 66: 132–138.
35. Dziegielewski P.T., O'Connell D.A., Klein M., Fung C., Singh P., Alex Mlynarek M. et al.: Primary total laryngectomy versus organ preservation for T3/T4a laryngeal cancer: a population-based analysis of survival. *J Otolaryngol Head Neck Surg.*, 2012; 41: S56–S64.
36. van Dijk B.A., Karim-Kos H.E., Coebergh J.W., Marres H.A., de Vries E.: Progress against laryngeal cancer in The Netherlands between 1989 and 2010. *Int J Cancer*, 2013; 134: 674–681.
37. Lin C.C., Fedewa S.A., Prickett K.K., Higgins K.A., Chen A.Y.: Comparative effectiveness of surgical and nonsurgical therapy for advanced laryngeal cancer. *Cancer*, 2016; 122: 2845–2856.
38. Lavo J.P., Ludlow D., Morgan M., Caldito G., Nathan C.: Predicting feeding tube and tracheotomy dependence in laryngeal cancer patients. *Acta Oto-Laryngologica*, 2017; 137: 326–330.
39. Janot F., Rhein B., Koka V.N., Wibault P., Domenge C., Bessede J.P. et al.: Laryngeal Preservation with Induction Chemotherapy. Experience of two GETTEC Centers, Between 1985 and 1995. *Annales d'oto-laryngologie et de chirurgie cervico faciale*. 2002; 119: 12–20.
40. McCoul E.D., Har-El G.: Meta-analysis of impaired vocal cord mobility as a prognostic factor in T2 glottic carcinoma. *Arch Otolaryngol Head Neck Surg.*, 2009; 135: 479–486.
41. Spaulding C.A., Gillenwater A., Constable W.C., Hahn S.S., Kersh C.R.: Prognostic value of vocal cord fixation with respect to treatment in cancers of the supraglottis and pyriform sinus. *Laryngoscope*, 1987; 97: 1450–1453.
42. Teymoortash A., Bohne F., Kissing L., Daniel H., Kurt B., Wilhelm T. et al.: On-cological and surgical outcome of total laryngectomy in combination with neck dissection in the elderly. *Eur Arch Otorhinolaryngol.*, 2016; 273: 1825–1833.
43. Kowalski L.P., Santos J.C.R., Santos C.R., Magrin J., Saboia M.V., Fogaroli R.C. et al.: Prognostic factors in supraglottic carcinoma patients treated by surgery or radiotherapy. *Annals of Otology, Rhinology and Laryngology*, 1998; 107: 697–702.
44. Wang C.C., Montgomery W.W.: Deciding on optimal management of supraglottic carcinoma. *Oncology (Williston Park)*, 1991; 5: 41–46.
45. Johnson J.T., Myers E.N., Hao S.P., Wagner R.L.: Outcome of open surgical therapy for glottic carcinoma. *Ann Otol Rhinol Laryngol.*, 1993; 102: 752–755.
46. Razack M.S., Maipang T., Sako K., Bakamjian V., Shedd D.P.: Management of advanced glottic carcinomas. *Am J Surg.*, 1989; 158: 318–320.
47. Fujii T., Sato T., Yoshino K., Inakami K., Nagahara M., Okita J.: A clinical study of 1079 patients with laryngeal cancer. *Nihon Jibiinkoka Gakkai Kaiho*, 1997; 100: 856–863.
48. Ikarashi F., Nonomura N., Nakano Y.: Clinical study on laryngeal cancer. *Nihon Jibiinkoka Gakkai Kaiho*, 1990; 93: 772–778.
49. Hirano M., Shin T., Mihashi S.: Long term results of treatments for carcinoma of the larynx. *Otologia Fukuoka*, 1976; 22: 748–759.
50. Olsen K.D.: Reexamining the treatment of advanced laryngeal cancer. *Head Neck*, 2010; 32: 1–7.
51. Dang Y., Wang Y., Ouyang X., Wang L., Huang Q.: High Expression of IncRNA-PCNA-AS1 in Human Gastric Cancer and its Clinical Significances. *Clin Lab.*, 2015; 61(11): 1679–1685.

Word count: 6290

Page count: 7

Tables: 1

Figures: -

References: 51

DOI: 10.5604/01.3001.0012.2307

Table of content: <https://ppch.pl/issue/11974>

Copyright: Copyright © 2019 Fundacja Polski Przegląd Chirurgiczny. Published by Index Copernicus Sp. z o.o. All rights reserved.

Competing interests: The authors declare that they have no competing interests.



The content of the journal „Polish Journal of Surgery” is circulated on the basis of the Open Access which means free and limitless access to scientific data.



This material is available under the Creative Commons - Attribution 4.0 GB. The full terms of this license are available on: <http://creativecommons.org/licenses/by-nc-sa/4.0/legalcode>

Corresponding author: Dr. Jaspreet Singh Badwal; No. 4 Phulkian Enclave, Jail Road, Patiala – 147001, Punjab, India;  
E-mail: [badwaljaspreetsingh17@gmail.com](mailto:badwaljaspreetsingh17@gmail.com)

Cite this article as: Badwal J., S.: Total Laryngectomy for Treatment of T4 Laryngeal Cancer: Trends and Survival Outcomes; *Pol Przegl Chir* 2019; 91 (3): 30–37

