Efficacy comparison between primary total laryngectomy and nonsurgical organ-preservation strategies in treatment of advanced stage laryngeal cancer
A meta-analysis
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Abstract
Background: We aimed to provide a pooled analysis of controlled trials comparing long-term survival after primary laryngectomy and primary organ preservation methods in patients with T3-4 laryngeal cancer.

Methods: We performed random-effects meta-analyses on overall survival (OS), disease-free survival (DFS), disease-specific survival (DSS), and locoregional control (LRC).

Results: Fifteen studies met the selection criteria including 6288 patients (2696 patients who underwent primary laryngectomy and 3592 patients who underwent primary nonsurgical organ preservation therapy). There was a significant difference between the groups with respect to OS (HR 0.71, 95% CI 0.57–0.89, P = .003). However, a subgroup analysis found OS was not significantly worse for patients with T3 laryngeal cancer who received primary organ preservation compared with patients who underwent primary laryngectomy (HR 0.96, 95% CI 0.45–2.03, P = .91). There was no significant difference for DFS (HR 0.63, 95% CI 0.39–1.04, P = .07) in two groups. Patients with laryngeal cancer who underwent primary organ preservation had a better DSS (HR 0.47, 95% CI 0.25–0.88, P = .02) and LRC (HR 0.56, 95% CI 0.39–0.80, P = .001) than patients who underwent primary nonsurgical organ preservation therapy.

Conclusion: Our results support total laryngectomy for patients with T4 laryngeal cancer and show that primary organ preservation for laryngeal cancer has no advantage and also did not decrease the rate of OS in patients with T3 laryngeal cancer when compared with primary total laryngectomy.

Abbreviations: CIs = confidence intervals, CRT = combination of these, CT = chemotherapy, DFS = disease-free survival, DSS = disease-specific survival, HRs = hazard ratios, LRC = locoregional control, OS = overall survival, RT = radiotherapy, SCC = squamous cell carcinoma, SEs = standard errors.

Keywords: chemotherapy, disease-free survival, laryngeal cancer, laryngectomy, organ preservation, radiotherapy

1. Introduction
Laryngeal cancer represents one of the most common head and neck malignancies, accounting for approximately 20% of all cases, and up to 40% of patients present with advanced disease at the time of diagnosis.[1,2] In 2014, the estimated incidence of laryngeal cancer in the United States was 12,630, with 3610 deaths.[3] The proper treatment for locally advanced laryngeal cancer (T3-4) is controversial and includes surgery, chemothera-py (CT), radiotherapy (RT), or some combination of these (CRT). Among these treatments, total laryngectomy remains the primary treatment for T3-4 laryngeal cancers in many centers across the world; however, organ-sacrificing surgical resection of the larynx can result in a severely reduced quality of life. Other treatment options for organ preservation by nonsurgical means (e.g., CRT and RT) have therefore gained in popularity. Initially, the 1991 landmark Veterans Affairs Laryngeal Cancer Study Group[4] results demonstrated organ preservation therapies were shown no worse survival than total laryngectomy in advanced laryngeal cancer patients.

Despite lots of laryngeal preservation studies have been successfully reported, a study from 1985 to 2001 based on a national registration database of the United States found a reduced survival and revealed that this result may be associated with the option of initial treatment strategy for advanced-stage laryngeal cancer.[5] Chen and Halpern’s[6] research based on the National hospital-based cancer registry has reported that the
concurrent CRT has a worse survival outcome than total laryngectomy for stage IV laryngeal cancer patients. Other researches have also suggested there are advantages in therapy strategies that choosing total laryngectomy in tumor control, especially in T4 cases[7,8] However, so far it still unclear which T4-3 laryngeal cancer patients are suitable for CRT and organ preservation. Because of the controversies involved in the management of advanced laryngeal carcinoma, this meta-analysis aimed to investigate the patients with locally advanced laryngeal cancer (T3-4) and determine whether survival was compromised because a laryngeal preservation protocol was chosen instead of total laryngectomy. Clinical outcomes as well as overall survival (OS), disease-free survival (DFS), disease-specific survival (DSS), and locoregional control (LRC) were all considered. The results of this meta-analysis might provide answers to surgeons' concerns by providing statistically greater power and better-quality analyses.

2. Methods

On the basis of the recommendations of the Cochrane Collaboration, a rigorous analysis protocol was established. Eligible literatures were filtered primarily through reading abstracts by two observers. We conducted a systematic review and meta-analysis on patients with laryngeal cancer who received surgery as the only mode of therapy in the initial management of their disease compared with patients who were treated with primary RT or CRT.

2.1. Selection criteria

This meta-analysis included all studies meeting the following criteria: clinic trials compared the curative effects between primary TL and primary RT or CRT; patients with local advanced laryngeal squamous cell carcinoma (SCC) that was biopsy-proven and untreated previously; laryngeal cancer included any supraglottic, glottic, or subglottic lesions; the original articles provided sufficient information for meta-analysis; and the papers were published in the English language. The study does not involve patient consent, so ethical approval is not necessary for this study.

2.2. Quality assessment

A systematic electronic search was independently performed by 2 investigators using MEDLINE, EMBASE, and the Cochrane Library database CENTRAL, from their dates of inception through October 2016. We included studies that evaluated the associations between preoperative anaemia and OS, DFS, DSS, and/or LRC of patients with resected laryngeal cancer.

We identified 15 published studies that reported the comparative survival of laryngeal cancer patients who underwent primary total laryngectomy versus nonsurgical organ preservation strategies. The search terms were “laryngeal cancer”, “laryngectomy”, “chemotherapy”, “radiotherapy”, “chemoradiotherapy” and “organ preservation”, and MeSH headings “laryngeal cancer” (MeSH), “laryngectomy” (MeSH), “chemotherapy” (MeSH), “radiotherapy” (MeSH), “chemoradiotherapy” (MeSH), “organ preservation” (MeSH) were used in combination with the Boolean operators AND or OR. We also checked reference lists of relevant articles and review articles. No language restrictions or time limits were applied to the initial search.

2.3. Statistical analysis

Synchronized extraction results were pooled statistically as effect estimates in meta-analyses. We used combined hazard ratios (HRs) with 95% confidence intervals (CIs) to measure the effect of primary organ preservation strategies on OS, DFS, DSS, and LRC. The HRs and 95% CIs were directly provided in some studies, while for other studies they were acquired by calculating the following parameters: the number of patients at risk in each group, the total number of events, and the log-rank statistic or its P-value. Then, we calculated the log (HRs) and the corresponding standard errors (SEs) according to the methods described by Tierney [15]. We used the Cochran Q statistic (if it had a P-value > .10 it was defined as significant for heterogeneity) and the I² value to assess heterogeneity among the studies. I² > 50% was considered to indicate significant heterogeneity. A fixed-effects model was used first to calculate the pooled HR, but if the assumption of homogeneity had to be rejected, a random-effects model was used. If the 95% CI for overall HR overlapped 1, it was not considered to be significant. All statistical analyses were performed with Review manager 5.0 (http://www.cochrane.org).

3. Results

3.1. Characteristics of included trials

A total of 15 studies were included[1,9–23]. All eligible studies were published between 1995 and 2016. Table 1 shows details for each trial, including baseline characteristics, primary method, publication year, tumor stages and reported outcomes of each trial. A PRISMA flowchart (Fig. 1) shows the details of the literature search for this systematic review.

3.2. Meta-analysis

3.2.1. Overall survival. The OS rate was evaluated for all 11 studies. There was a significant statistical difference between the groups with respect to OS (HR 0.71, 95% CI 0.57–0.89, P = .003), but the heterogeneity was found to be significant (I² = 67%, χ² = 30.20, df = 10, P = .0008) (Fig. 2). Subgroup analysis found that the difference in the T4 subgroup was more significant (HR 0.64, 95% CI 0.51–0.81, P = .0001). The degree of heterogeneity was found to be significant (I² = 54%, χ² = 19.75, df = 9, P = .02) (Fig. 3). However, the subgroup analysis of studies found OS was not significantly worse for patients with T3 laryngeal cancer who received primary organ preservation compared with patients who underwent primary laryngectomy (HR 0.96, 95% CI 0.45–2.03, P = .91). Heterogeneity was found to be significant (I² = 77%, χ² = 12.79, df = 3, P = .005) (Fig. 4).

3.2.2. Disease-free survival. Five studies reported the rate of DFS. There was no significant difference for DFS (HR 0.63, 95% CI 0.39–1.04, P = .07) between patients with advanced laryngeal cancer who were treated with primary laryngectomy and those who underwent primary nonsurgical organ preservation therapy; however, the heterogeneity was found to be significant (I² = 69%, χ² = 12.98, df = 4, P = .01) (Fig. 5).

3.2.3. Disease-specific survival. Four studies reported the rate of DSS. Our results showed that the patients with laryngeal cancer who underwent primary laryngectomy had a better DSS (HR 0.47, 95% CI 0.25–0.88, P = .02) than the patients who underwent primary nonsurgical organ preservation therapy, but the heterogeneity was found to be significant (I² = 60%, χ² = 7.41, df = 3, P = .06) (Fig. 6).
3.2.4. Locoregional control. Five studies reported the rate of LRC. Our results showed that the patients with laryngeal cancer who underwent primary laryngectomy had a better LRC (HR 0.56, 95% CI 0.39–0.80, \( P = 0.001 \)) than the patients who underwent primary nonsurgical organ preservation therapy, and heterogeneity was not found to be significant (\( I^2 = 20\% \), \( x^2 = 4.99, df = 4, P = 0.29 \)) (Fig. 7).

4. Discussion

Among head and neck squamous cell carcinomas, laryngeal tumors are characterized by several unique features. The larynx plays a fundamental role in breathing, the sphincteric functions of the upper digestive tract, and voice production.[24] These facts must always be given consideration when a decision has to be made about maximizing functional preservation of the larynx without affecting tumor control. Organ-preservation strategies, including surgical or nonsurgical, have dominated the approach of laryngeal cancer in recent years. Recent nonsurgical organ-preservation strategies, including CT, RT, or concomitant CRT, have changed the field of local advanced laryngeal cancer treatment.[25]

Lots of prospective studies that have assessed the efficacy of organ-preservation protocols for stage III to IV laryngeal cancer.[26,27] Whereas, no studies have been exclusive for T3-4 lesions and less studies about direct comparisons with total laryngectomy have also been reported. A recent randomized trial of 332 patients with stage III/IV laryngeal cancer was reported by The Veterans Affairs Laryngeal Cancer Study Group,[28] who prospectively compared the outcomes of chemotherapy and laryngectomy, both followed by radiotherapy and suggested that nonsurgical organ-preservation strategies can be as effective in preserving the larynx without compromising overall survival. In contrast to this study that supported the nonsurgical organ-preservation approach, another randomized trials of 68 laryngeal cancer patients with T3 stage demonstrated that OS could be worse among patients accepted chemotherapy plus radiotherapy than those receiving total laryngectomy followed by radiotherapy.[15] However, no randomized studies that compared surgery followed by radiotherapy to concurrent chemoradiotherapy have been reported so far.

Because of investigator biases in terms of choice of therapy, definitive trials with a small number of patients may be difficult to perform. In an attempt to overcome the statistical limitations of the small, individual publications on this topic, and to add a quantitative measurement, in this review, recurrence data from individual studies were pooled and a meta-analysis was performed. The primary purpose of this meta-analysis was to include a large enough sample from published literature to reveal a possible significant difference between primary total laryngectomy and nonsurgical organ preservation methods in terms of OS, DFS, DSS, and LRC. A meta-analysis comparing these two treatment regimens, particularly in patients with laryngeal cancer, has not yet been published. For this study, attempts

| Table 1 | Demographic data. |
|---|---|
| References | Publication year | Source of patients | Follow-up, months | Patients | Outcomes reported | Multivariate Analysis |
| Bryant et al[23] | 1995 | Australia | NR | 1–60 | 42 | 55 | DFS/DSS | Yes |
| Porter et al[22] | 1998 | New Zealand | 24 | 12–49 | 46 | 25 | DSS | Yes |
| Nguyen-Tan et al[21] | 2001 | Canada | 41 | 2–367 | 161 | 62 | LRC | Yes |
| Patel and Howell[19] | 2011 | America | 12 | 1–40 | 13 | 21 | OS | Yes |
| Rades et al[20] | 2011 | Germany | NR | 1–60 | 88 | 44 | OS/DFS/LRC | Yes |
| Dziegielewski et al[18] | 2012 | Canada | 41 | 1–60 | 116 | 142 | OS/DFS | Yes |
| Bussu et al[17] | 2013 | Italy | 26 | NR | 89 | 34 | OS/DFS | Yes |
| Hein et al[15] | 2014 | America | 34 | 2–100 | 14 | 48 | OS/DFS/LRC | Yes |
| Karatzanis et al[17] | 2014 | Germany | 56 | 2–199 | 32 | 63 | DSS | Yes |
| Grover et al[12] | 2015 | America | NR | 1–120 | 353 | 616 | OS | Yes |
| Rosenhal et al[14] | 2015 | America | 47 | 6–293 | 161 | 60 | OS/DFS/LRC | Yes |
| Timme et al[13] | 2015 | America | 40 | 15–93 | 37 | 34 | OS | Yes |
| Timmermans et al[11] | 2015 | Netherlands | NR | NR | 60 | 122 | OS | Yes |
| Vengali et al[8] | 2016 | Canada | 53 | 9–117 | 42 | 65 | OS/LRC | Yes |
| Timmermans et al[10] | 2016 | Netherlands | NR | NR | 1172 | 2281 | OS | Yes |

DFS = disease-free survival, DSS = disease-specific survival, NR = not reported, NSOP = nonsurgical organ preservation, OS = overall survival, TL = total laryngectomy.
were made wherever possible to closely follow the Cochrane Collaboration recommendations. We prespecified a rigorous study protocol and searched several electronic databases, identified international conference abstracts, and searched the study reference lists for relevant trials.

Surprisingly, although the efficacy and safety of organ preservation in the treatment of locally advanced laryngeal cancer has been well established, pooling data from a large number of patients in this meta-analysis suggests that the addition of primary organ preservation strategies reduces OS, DSS, and LRC in all patients grouped together regardless of stage. When analyzed in subgroups by stage, for T4 laryngeal cancer, patients treated with primary organ preservation strategies have poorer survival compared with patients treated with primary total laryngectomy. However, OS was not significantly worse for patients with T3 laryngeal cancer who received primary organ preservation strategies.

Figure 2. Comparison of overall survival between total laryngectomy and nonsurgical organ-preservation modalities in all patients with T3-4 laryngeal cancer.

Figure 3. Comparison of overall survival between total laryngectomy and nonsurgical organ-preservation modalities in patients with T4 laryngeal cancer.

Figure 4. Comparison of overall survival between total laryngectomy and nonsurgical organ-preservation modalities in patients with T3 laryngeal cancer.
preservation compared with the patients who underwent primary laryngectomy.

The first total laryngectomy for laryngeal cancer was performed by Billroth in 1873, and this has been the standard treatment for advanced laryngeal cancer for many years. However, the application of total laryngectomy as initial treatment has decreased remarkably in many areas. It is now mostly applied to salvage treatment after failure of nonsurgical organ preservation strategies. In the present review, however, primary nonsurgical organ preservation strategies were shown to result in significantly worse survival outcomes when compared to primary laryngectomy for T4 laryngeal cancer. In addition, the NCCN guidelines suggested that total laryngectomy as the preferred treatment for the patients with laryngeal cancer, particularly for patients with T4a disease. Therefore, for most patients with T4 disease, primary laryngectomy still plays an important role as primary therapy for laryngeal cancer. Historically, survival of patients with T3 laryngeal cancer has been better than that of patients with T4 laryngeal cancer. In this review, the OS curves for each treatment method (primary laryngectomy or primary organ preservation) were similar for T3 laryngeal cancer in the included trials. Moreover, our data demonstrate that primary organ preservation does not seem to increase long-term survival for T3 laryngeal cancer, which led us to consider whether this treatment should be routine.

Several potential limitations of this study still exist. First, only literature articles published in English language were including for analysis. If the search range had been extended to include other languages literature, some additional related trials might have been included and the results of this meta-analysis could be more accurate. Second, there is a potential interaction and crossover between several evaluated factors, which could not be controlled in this meta-analysis. In addition, number of trials included in the subgroup analysis is too a small, this may have a potential effect on our results.

5. Conclusion

In conclusion, total laryngectomy is the cornerstone of treatment for patients with T4 laryngeal cancer. Our results showed that primary organ preservation for laryngeal cancer had no advantage for all stages of patients, but it did not decrease the rate of OS in patients with T3 laryngeal cancer when compared with primary total laryngectomy. Based on these results, primary
organ preservation methods may be beneficial in a clinical setting, especially in T3 laryngeal cancer patients. Our results give physicians a partial guideline for selecting laryngeal cancer treatment.

Author contributions

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References

[1] Hoffman HT, Karnell LH, Funk GF, et al. The National Cancer Data Base report on cancer of the head and neck. Arch Otolaryngol Head Neck Surg 1998;124:951–62.
[2] Chu EA, Kim YJ. Laryngeal cancer: diagnosis and preoperative work-up. Otolaryngol Clin North Am 2008;41:673–95.
[3] Siegel R, Ma J, Zou Z, et al. Cancer statistics, 2014. CA Cancer J Clin 2014;64:9–29.
[4] The Department of Veterans Affairs Laryngeal Cancer Study Group. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. N Engl J Med 1991;324:1685–90.
[5] Hoffman HT, Porter K, Karmell LH, et al. Laryngeal cancer in the United States: changes in demographics, patterns of care, and survival. Laryngoscope 2006;116:1–3.
[6] Chen AY, Halpern M. Factors predictive of survival in advanced laryngeal cancer. Arch Otolaryngol Head Neck Surg 2007;133:1270–6.
[7] Bussu F, Micciche F, Rigeante M, et al. Oncologic outcomes in advanced laryngeal squamous cell carcinomas treated with different modalities in a single institution: a retrospective analysis of 65 cases. Head Neck 2012;34:573–9.
[8] Gourin CG, Conger BT, Sheils WC, et al. The effect of treatment on survival in patients with advanced laryngeal carcinoma. Laryngoscope 2009;119:1112–7.
[9] Vengalil S, Giuliani ME, Huang SH, et al. Clinical outcomes in patients with T4 cancer treated with primary radiotherapy versus primary laryngectomy. Head Neck 2016;38(suppl 1):E2035–40.
[10] Timmermans AJ, van Dijk BA, Overbeek LI, et al. Trends in treatment and survival for advanced laryngeal cancer: a 20-year population-based study in The Netherlands. Head Neck 2016;38(suppl 1):E1247–55.
[11] Timmermans AJ, de Gooyer CJ, Hamming-Vrieze O, et al. T3-T4 laryngeal cancer in The Netherlands Cancer Institute; 10-year results of the consistent application of an organ-preserving/sacrificing protocol. Head Neck 2015;37:1495–503.
[12] Grover S, Swisher-McClure S, Mitra N, 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.
[13] Timme DW, Jonnalagadda S, Patel R, et al. Treatment selection for T3/ T4a laryngeal cancer: chemoradiation versus primary surgery. Ann Otol Rhinol Laryngol 2015;124:845–51.
[14] Rosenthal DI, Mohamed AS, Weber RS, et al. Long-term outcomes after surgical or nonsurgical initial therapy for patients with T4 squamous cell carcinoma of the larynx: a 3-decade survey. Cancer 2015;121:1608–19.
[15] Hsu LJ, Fung TJ, Tsang NM, et al. Tumor volumetry as a prognostic factor in the management of T4a laryngeal cancer. Laryngoscope 2014;124:1134–40.
[16] Karatzanis AD, Psychogios G, Waldhaffer F, et al. Management of locally advanced laryngeal cancer. J Otolaryngol Head Neck Surg 2014;43:4.
[17] Bussu F, Paludetti G, Almodori G, et al. Comparison of total laryngectomy with surgical (cricohyoidopexy) and nonsurgical organ-preservation modalities in advanced laryngeal squamous cell carcinomas: a multicenter retrospective analysis. Head Neck 2013;35:554–61.
[18] Drzgulewski PT, O’Connell DA, Klein 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(Suppl 1):S56–64.
[19] Patel UA, Howell JK. Local response to chemoradiation in T4 larynx cancer with cartilage invasion. Laryngoscope 2013;121:106–10.
[20] Rades D, Schroeder U, Bajrovic A, et al. Radiochemotherapy versus surgery plus radio(chemo)therapy for stage T3/T4 larynx and hypopharynx cancer—results of a matched-pair analysis. Eur J Cancer 2011;47:2729–34.
[21] Nguyen-Tan PF, Le QT, Quvey JM, et al. Treatment results and prognostic factors of advanced T3–4 laryngeal carcinoma: the University of California, San Francisco (UCSF) and Stanford University Hospital (SUH) experience. Int J Radiat Oncol Biol Phys 2001;50:1172–80.
[22] Porter MJ, Mclvor NP, Morton RP, et al. Audit in the management of T3 fixed-cord laryngeal cancer. Am J Otolaryngol 1998;19:360–4.
[23] Bryant GP, Poulsen MG, Tripcony L, et al. Treatment decisions in T3N0M0 glottic carcinoma. Int J Radiat Oncol Biol Phys 1995;31:285–93.
[24] Forastiere AA, Goepfert H, Maor M, et al. Concurrent chemoradiotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. N Engl J Med 2003;349:2091–8.
[25] Li B, Bohinski M, Gandour-Edwards R, et al. Overstaging of cartilage invasion by multidetector CT scan for laryngeal cancer and its potential effect on the use of organ preservation with chemoradiation. Br J Radiol 2011;84:64–9.
[26] Karp DD, Vaughan CW, Carter R, et al. Larynx preservation using induction chemotherapy plus radiation therapy as an alternative to laryngectomy in advanced head and neck cancer. A long-term follow-up report. Am J Clin Oncol 1999;14:273–9.
[27] Eskizmir G, Tanyeri TG, Celik O, et al. Predictive and prognostic factors for patients with locoregionally advanced laryngeal carcinoma treated with surgical multimodality protocol. Eur Arch Otorhinolaryngol 2012;274:1701–11.
[28] Wolf GT, Fisher SG, Hong WK, et al. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. N Engl J Med 1991;324:1685–90.