

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 laryngectomy 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, chemotherapy (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

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concurrent CRT has a worse survival outcome than total laryngectomy for stage IV laryngeal cancer patients. Other researches have also suggests 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 T3-4 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 choosed 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 anemia 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 I^2 value to assess heterogeneity among the studies. $I^2 > 50\%$ 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 ($I^2 = 67\%$, $\chi^2 = 30.20$, $df = 10$, $P = .0008$) (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 ($I^2 = 54\%$, $\chi^2 = 19.75$, $df = 9$, $P = .02$) (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 ($I^2 = 77\%$, $\chi^2 = 12.79$, $df = 3$, $P = .005$) (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 ($I^2 = 69\%$, $\chi^2 = 12.98$, $df = 4$, $P = .01$) (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 ($I^2 = 60\%$, $\chi^2 = 7.41$, $df = 3$, $P = .06$) (Fig. 6).

Table 1
Demographic data.

References	Publication year	Source of patients	Follow-up, months		Patients			Outcomes Reported	Multivariate Analysis	Tumor Stages
			Median	Range	TL	NSOP	OS			
Bryant et al ^[23]	1995	Australia	NR	1–60	42	55	DFS/DSS	Yes	T3	
Porter et al ^[22]	1998	New Zealand	24	12–49	46	25	DSS	Yes	T3	
Nguyen-Tan et al ^[21]	2001	Canada	41	2–367	161	62	LRC	Yes	T3/T4	
Patel and Howell ^[19]	2011	America	12	1–40	13	21	OS	Yes	T4	
Rades et al ^[20]	2011	Germany	NR	1–60	88	44	OS/DFS/LRC	Yes	T3/T4	
Dziegielewski et al ^[18]	2012	Canada	41	1–60	116	142	OS/DFS	Yes	T3/T4	
Bussu et al ^[17]	2013	Italy	26	NR	89	34	OS/DSS	Yes	T3/T4	
Hsin et al ^[15]	2014	America	34	2–100	14	48	OS/DFS/LRC	Yes	T4	
Karatzanis et al ^[17]	2014	Germany	56	2–199	321	63	DSS	Yes	T3/T4	
Grover et al ^[12]	2015	America	NR	1–120	353	616	OS	Yes	T4	
Rosenthal et al ^[14]	2015	America	47	6–293	161	60	OS/DFS/LRC	Yes	T4	
Timme et al ^[13]	2015	America	40	15–93	37	34	OS	Yes	T3/T4	
Timmermans et al ^[11]	2015	Netherlands	NR	NR	60	122	OS	Yes	T3/T4	
Vengalil et al ^[9]	2016	Canada	53	9–117	42	65	OS/LRC	Yes	T4	
Timmermans et al ^[10]	2016	Netherlands	NR	NR	1172	2281	OS	Yes	T3/T4	

DFS = disease-free survival, DSS = disease-specific survival, NR = not reported, NSOP = nonsurgical organ preservation, OS = overall survival, TL = total laryngectomy.

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, $P = .001$) than the patients who underwent primary nonsurgical organ preservation therapy, and heterogeneity was not found to be significant ($I^2 = 20\%$, $\chi^2 = 4.99$, $df = 4$, $P = .29$) (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 laryngeal 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

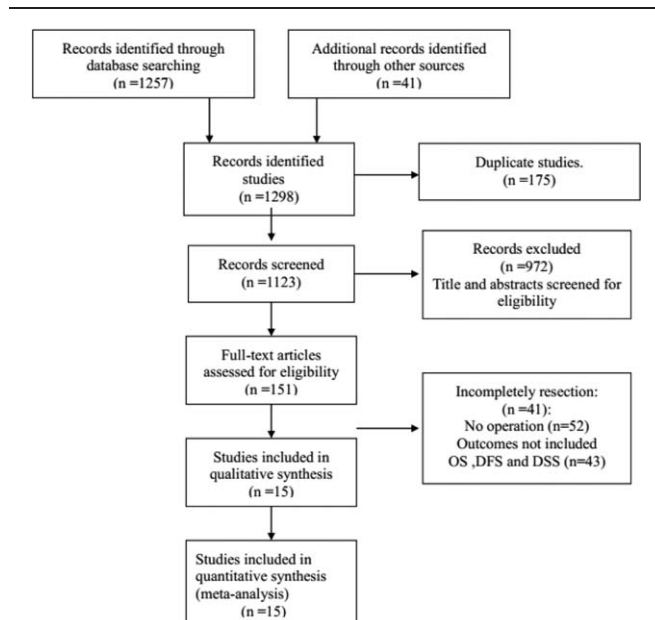


Figure 1. Flow chart of the study selection process for eligible studies in the systematic review.

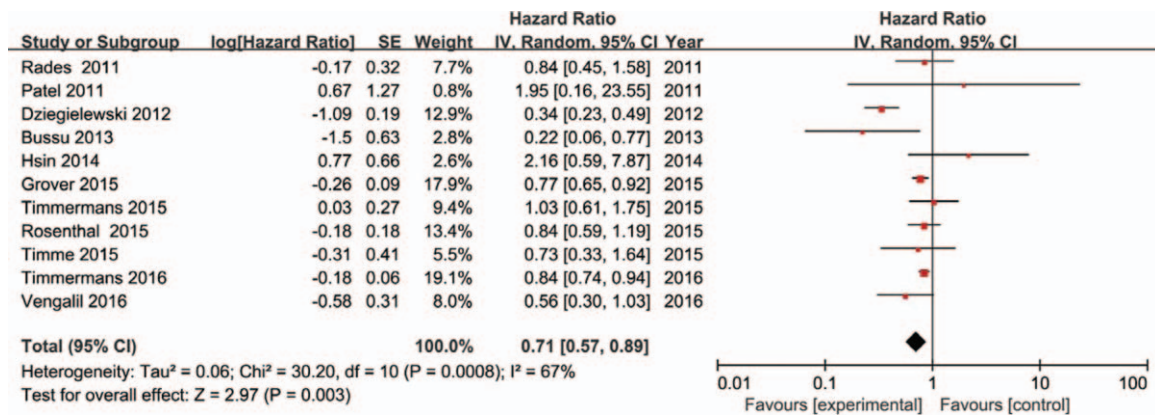


Figure 2. Comparison of overall survival between total laryngectomy and nonsurgical organ-preservation modalities in all patients with T3-4 laryngeal cancer.

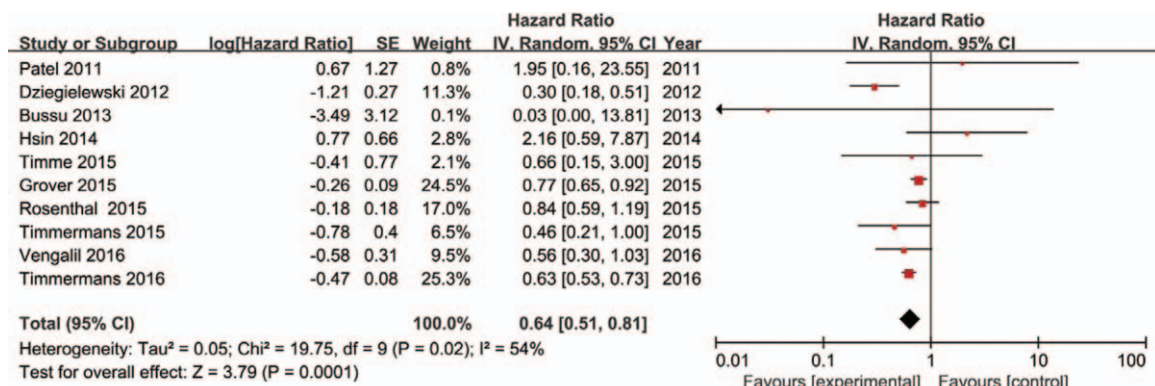


Figure 3. Comparison of overall survival between total laryngectomy and nonsurgical organ-preservation modalities in patients with T4 laryngeal cancer.

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

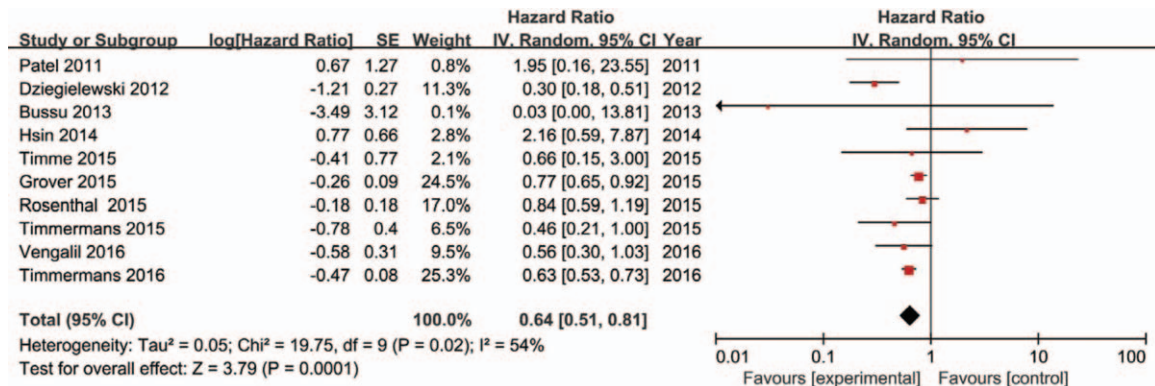


Figure 4. Comparison of overall survival between total laryngectomy and nonsurgical organ-preservation modalities in patients with T3 laryngeal cancer.

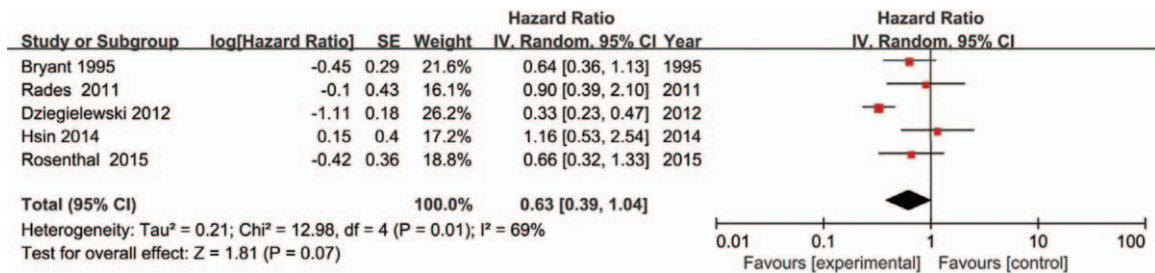


Figure 5. Comparison of disease-free survival between total laryngectomy and nonsurgical organ-preservation modalities in all patients with T3-4 laryngeal cancer.

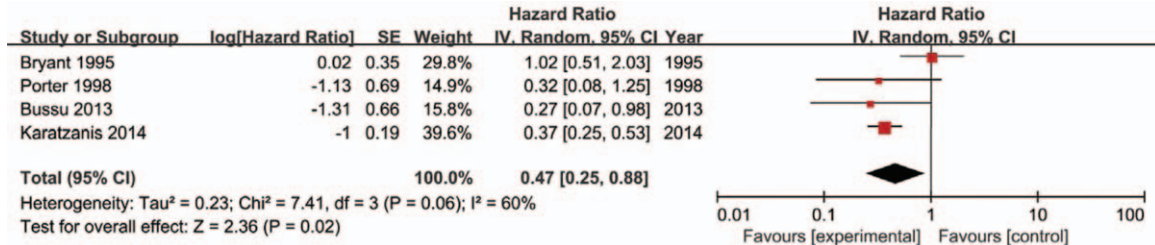


Figure 6. Comparison of disease-specific survival between total laryngectomy and nonsurgical organ-preservation modalities in all patients with T3-4 laryngeal cancer.

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 included 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

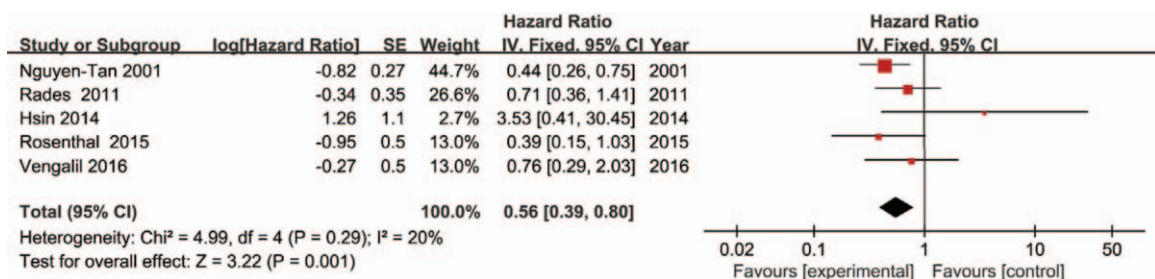


Figure 7. Comparison of locoregional control between total laryngectomy and nonsurgical organ-preservation modalities in all patients with T3-4 laryngeal cancer.

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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Writing – original draft: Jing-Lin Gong, Zhen-Hua Li, Yun He, Xiao-Hong Zhou.

Writing – review & editing: Zhen-Hua Li.

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