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Original Article

Oncologic outcomes of transoral laser microsurgery for T3 laryngeal carcinoma: a meta-analysis

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Abstract: Laryngeal carcinomas are the second most common type of head and neck tumors, most of which are squamous cell carcinomas. The specific choice of treatment of T3 laryngeal (glottic or supraglottic) squamous cell carcinoma has been rather controversial. The aim of this study was to evaluate the efficacy and oncologic outcomes of transoral laser microsurgery (TLM) for untreated T3 laryngeal carcinoma. This study searched and screened all publications about TLM for untreated T3 laryngeal carcinoma in PubMed, EMBASE, Cochrane Library, and clinical trials. Retrieval cut-off date was May 31, 2017. Quality of studies was assessed and relevant data were extracted through inclusion and exclusion criteria. Seven studies were included in this meta-analysis. Pooled oncologic outcomes of patients with T3 glottic carcinoma, including 5-year overall survival (OS), 5-year disease-specific survival (DSS), and 5-year laryngectomy-free survival (LFS) rates, were 63% (95% confidence internal [CI], 57-69), 80% (95% CI, 65-92), and 77% (95% CI, 63-88), respectively. Pooled oncologic outcomes of patients with T3 supraglottic carcinoma, including 5-year OS, DSS, and LFS rates, were 68% (95% CI, 52-82), 80% (95% CI, 65-92), and 90% (95% CI, 79-97), respectively. Pooled ORs for 5-year OS, DSS, and LFS between glottic carcinoma and supraglottic carcinoma were 0.84 (95% CI, 0.35-2.01), 0.88 (95% CI, 0.27-2.85), and 0.33 (95% CI, 0.20-0.56), respectively. In conclusion, TLM offers patients with T3 glottic or supraglottic carcinomas better oncologic outcomes. TLM may be a valid option for organ-preserving surgery. However, its efficacy should be confirmed by more prospective clinical trials.

Keywords: Laryngeal carcinoma, transoral laser microsurgery, overall survival, disease-specific survival, laryngectomy-free survival, meta-analysis

Introduction

Laryngeal carcinoma is the second most common type of head and neck tumors, most of which are squamous cell carcinomas [1]. For patients with T3 laryngeal carcinoma, main treatment methods for preserving laryngeal function are radiation therapy alone or combined with chemotherapy, open partial laryngectomy (OPL), and transoral laser microsurgery (TLM). The specific choice of treatment for T3 laryngeal (glottic or supraglottic) squamous cell carcinoma has been rather controversial. Some experts have considered OPL as a treatment alternative to non-surgical treatment or total laryngectomy because patients could preserve laryngeal function and have better oncologic outcomes [2, 3]. However, Wilkie MD et al. considered TLM as a valid therapeutic option for selected moderately advanced glottic and supraglottic laryngeal carcinoma [4, 5]. TLM, a treatment modality for laryngeal carcinoma, has been considered a substitute for chemoradiotherapy [2, 6-10] and OPL for treatment of early laryngeal carcinoma [11, 12]. For patients with laryngeal carcinoma, TLM treatment confers the advantages of short hospital stays, less complications, and lower costs [13-15]. In recent years, TLM has been used for treatment of locally advanced laryngeal carcinoma [16]. Patients with T3 glottic or supraglottic carcinomas are more willing to choose TLM therapy. Thus, the aim of this study was to systematically review publications using meta-analysis and to analyze oncologic outcomes of patients undergoing TLM for T3 glottic or supraglottic carcinomas. Primary endpoints of this study included 5-year overall survival (OS), disease-

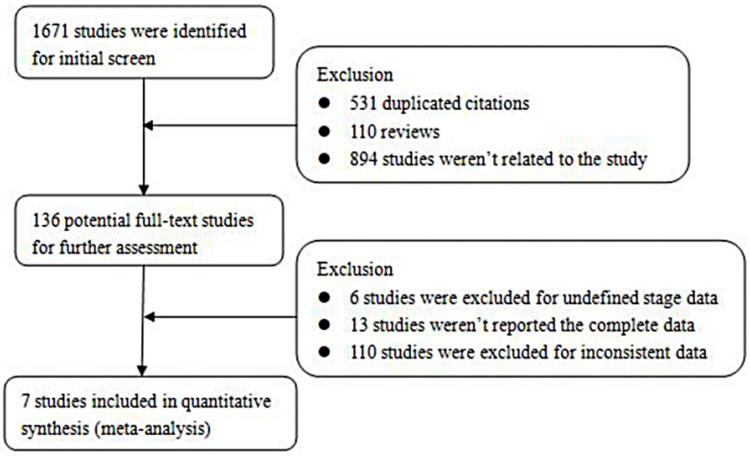

Figure 1. Flowchart of screening and selection process of included literature.

specific survival (DSS), and laryngectomy-free survival (LFS) rates.

Materials and methods

Data sources and search

This study aimed to identify all studies including oncologic outcomes of patients treated first with TLM for T3 laryngeal carcinoma. Searched databases included PubMed, EMBASE, Cochrane Library, and clinical trials. The search was updated to May 31, 2017. Retrieval terms used were "laryngeal carcinoma", "glottic carcinoma", "supraglottic carcinoma", "transoral laser microsurgery", "TLM", "laser surgery", and related entry terms. Terms were searched in different combinations. Language was limited to English only.

Inclusion and exclusion criteria

Qualified references were selected carefully based on the following rules: (1) First treatment of T3 laryngeal carcinoma with TLM; (2) One or more oncologic outcomes including 5-year OS, 5-year DSS, and 5-year LFS; and (3) More than 10 patients were reported in each study. Exclusion criteria were as follows: (1) Studies reporting on T3 laryngeal carcinoma in general without specifying the location of the tumor; (2) Studies reporting only on functional results; and (3) Studies with incomplete or similar data of outcomes. When included studies referred to the same enrolled patients, the most recently published papers were chosen.

Data extraction

Studies were carefully assessed, independently, by two reviewers according to inclusion and exclusion criteria. Disagreements were resolved by consensus. Full texts of eligible studies were obtained and the following information was collected from each study: first author, year of publication, patient data (such as number of enrolled patients and location of T3 laryngeal carcinoma), and oncologic outcomes.

Quality assessment

Included studies were assessed and scored for randomization (0-2 points), double-blind (0-2 points), and follow-up (0-1 points). Based on these, total scores ranged from 0 to 5. Scores of 0 to 2 indicated lower quality, while scores over 3 suggested higher quality [17, 18].

Statistical analysis

Meta-analysis was performed by pooling oncologic outcomes of patients undergoing first treatment with TLM. Statistical analysis of data was carried out using statistical packages (RevMan 5.2, Meta package of R software, and STATA 12.0). Pooled estimate and pooled odds ratio (OR) with 95% confidence interval (CI) were determined, along with the generation of forest plots using fixed or random effects. Significant heterogeneities between studies were examined using Chi-squared Q-test. When P value of the Q-test is <0.1, or when I^2 is >50%, heterogeneity exists between studies. Overall effect was tested using z scores with significance set at P <0.05. Egger's test was used to test publication bias.

Results

Study selection and description

After searching several databases, a total of 1,671 studies were retrieved. Two reviewers reviewed and assessed whether these studies met inclusion criteria. Finally, seven studies concerning evaluation of oncologic outcomes of TLM for T3 glottic and supraglottic carcino-

Table 1. Characteristics of included studies.

Author (publication year)	Quality score	Tumor site	Patients (n)	5-year OS (%)	5-year DSS (%)	5-year LFS (%)	Cases of local and locoregional recurrence (n)	Total cases of laryngectomy after local recurrence (n)
Motta G, 2005	3	G	51	64	72	80.5	26	7
Vilaseca I, 2010	3	G	51	73.1	86.3	51	NA	NA
Canis M, 2014	3	G	122	58.6	84.1	83	39	10
Pantazis D, 2015	3	G	19	63.2	63.2	NA	9	5
Peretti G, 2015	3	G	34	65.2	NA	85.3	10	5
Day AT, 2017	2	G	12	46	60	83	NA	NA
Motta G, 2004	2	S	18	81	81	93.7	3	1
Vilaseca I, 2010	3	S	96	45.8	61.8	76.6	NA	NA
Canis M, 2014	3	S	104	66.5	84.2	92	22	5
Peretti G, 2015	3	S	22	59.3	NA	95.5	1	1
Pantazis D, 2015	3	S	24	87.5	91.7	NA	3	2

OS: overall survival; DSS: disease-specific survival; LFS: laryngectomy-free survival; G: glottic; S: supraglottic; NA: not available.

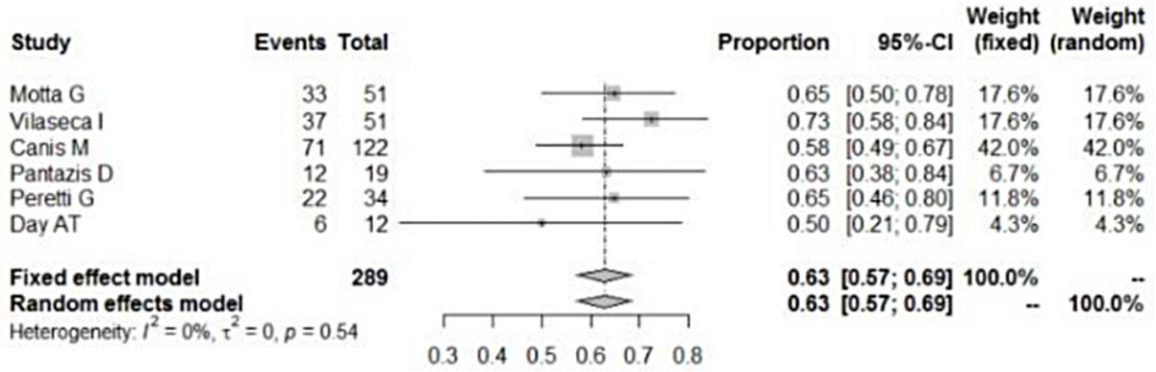

Figure 2. Forest plot of 5-year overall survival for patients with glottic carcinoma.

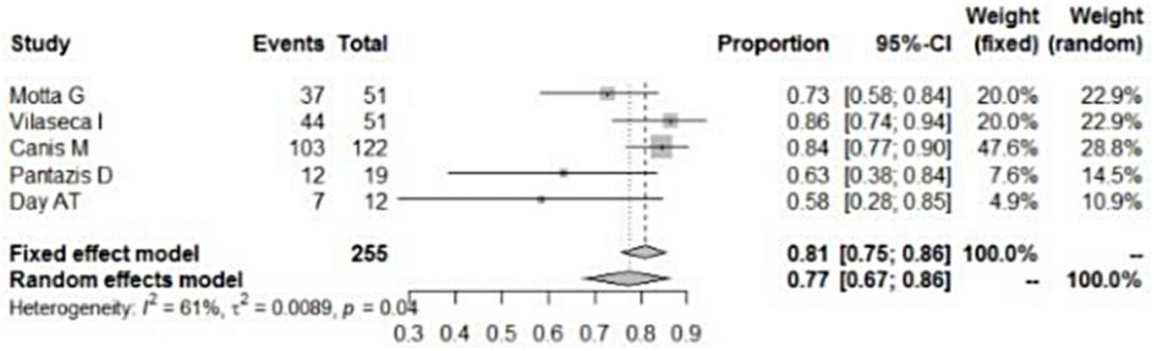

Figure 3. Forest plot of 5-year disease-specific survival for patients with glottic carcinoma.

mas, with previously untreated treatments, were included in this meta-analysis [6, 19-24]. **Figure 1** displays the selection process.

Seven studies, involving 453 adult patients (189 glottic carcinoma cases and 264 supraglottic carcinoma cases), were included in this meta-analysis. From studies conducted by Vilaseca I et al., Pantazis D et al., Canis M et al., and Peretti G et al., data were extracted, respectively. Motta G et al. reported oncologic outcomes of TLM in the treatment of glottic carcinoma and supraglottic carcinoma in 2005 and 2004, respectively. Day AT et al. reported

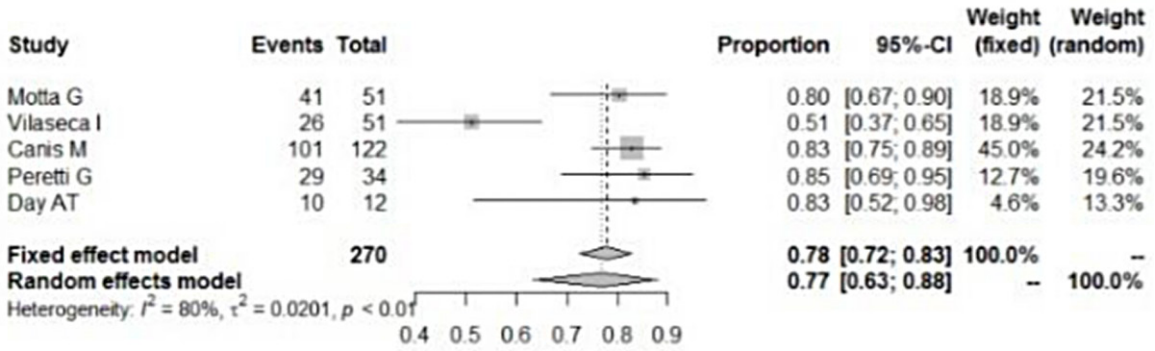

Figure 4. Forest plot of 5-year laryngectomy-free survival for patients.

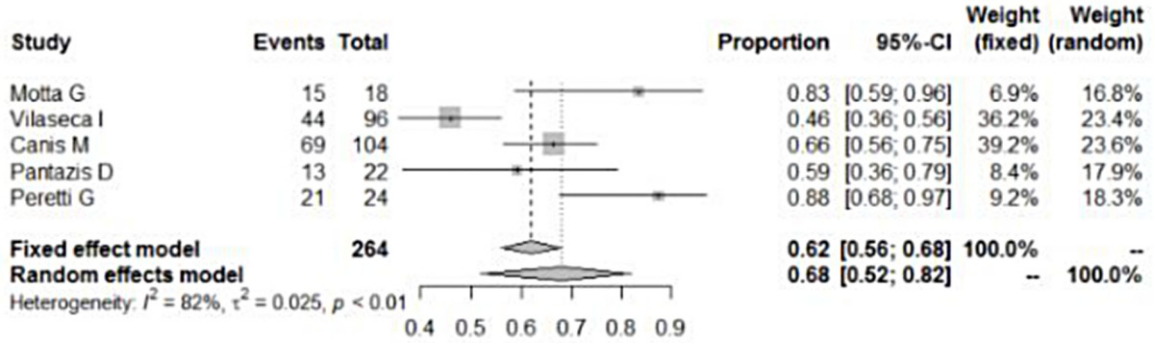

Figure 5. Forest plot of 5-year overall survival for patients with supraglottic carcinoma.

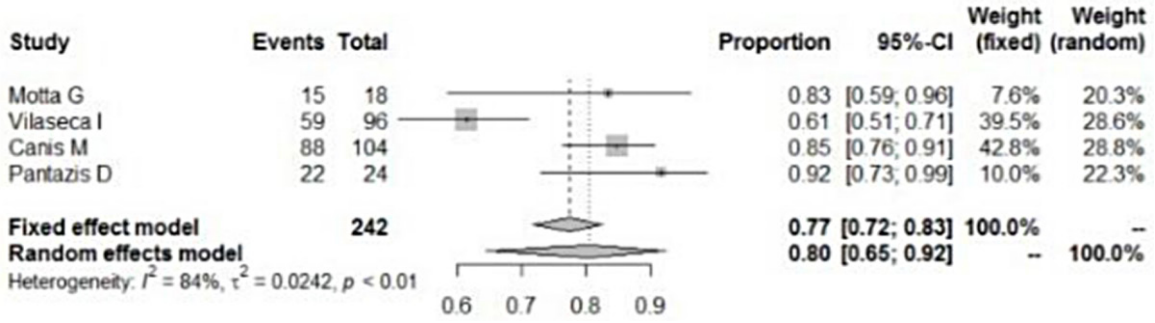

Figure 6. Forest plot of 5-year disease-specific survival for patients with supraglottic carcinoma.

oncologic outcomes of TLM in the treatment of glottic carcinoma in 2016. Characteristics of included studies are reported in **Table 1**.

Overall survival rate

A total of six studies reported 5-year OS rates of patients with T3 glottic carcinoma. Pooled 5-year OS was 63% (95% CI, 57-69) (**Figure 2**), whereas pooled 5-year OS of patients with T3 supraglottic carcinoma was 68% (95% CI, 52-82), based on five studies (**Figure 5**). I^2 values for OS were 0% and 82%, respectively, and a random effects model was used.

Of the five studies comparing T3 glottic carcinoma with supraglottic carcinoma, pooled OR for 5-year OS was 0.84 (95% CI, 0.35-2.01). No statistically significant differences were founded between T3 glottic carcinoma and supraglottic carcinoma (P = 0.69). I^2 values for OR were 76% and a random effect models was used (**Figure 8**).

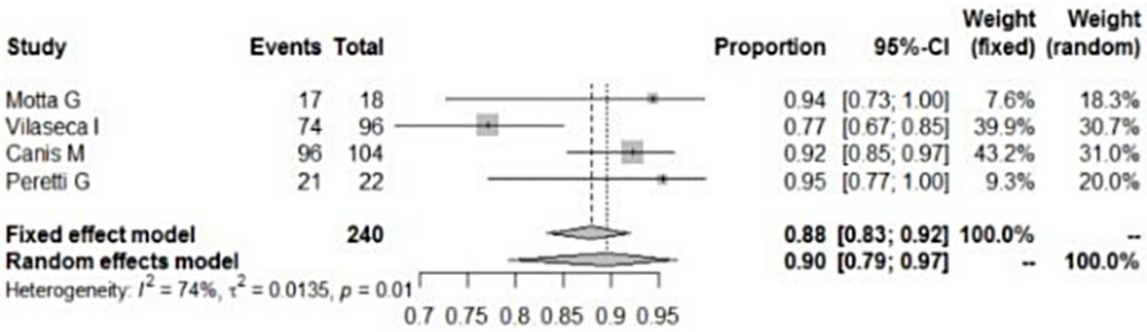

Figure 7. Forest plot of 5-year laryngectomy-free survival for patients with supraglottic carcinoma.

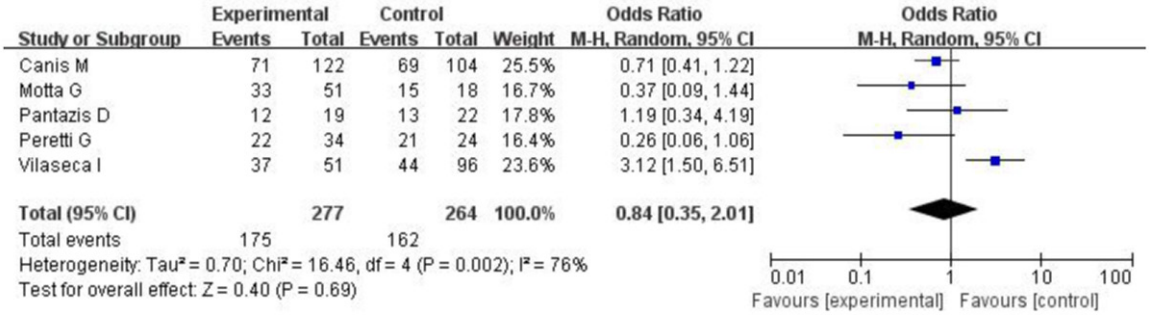

Figure 8. Forest plot for odds ratio of 5-year overall survival between glottic carcinoma and supraglottic carcinoma.

Disease-specific survival rate

A total of five studies exhibited 5-year DSS rates of patients with T3 glottic carcinoma. Pooled 5-year DSS was 77% (95% CI, 67-86) (**Figure 3**). Four studies reported 5-year DSS rate of patients with T3 supraglottic carcinoma. Pooled 5-year DSS was 80% (95% CI, 65-92) (**Figure 6**). Both I^2 values for DSS (61% and 84%, respectively) were high, suggesting great heterogeneity across studies. A random model was selected.

Pooled OR for 5-year DSS was 0.88 (95% CI, 0.27-2.85), according to the four studies comparing T3 glottic carcinoma with supraglottic carcinoma. No statistically significant differences were found between T3 glottic carcinoma and supraglottic carcinoma (P = 0.83). I^2 values for OR were 78% and a random effects model was used (**Figure 9**).

Laryngectomy-free survival rate

Figures 4 and **7**, respectively, show forest plots for 5-year LFS rates of patients with T3 glottic carcinoma and supraglottic carcinoma. Pooled 5-year LFS were 77% (95% CI, 63-88) and 90% (95% CI, 79-97), respectively, and a random model was used (I^2: 80% and 74%).

Figure 10 displays the forest plot for 5-year LFS rates based on four studies comparing T3 glottic carcinoma with supraglottic carcinoma. Pooled OR for 5-year LFS were 0.33 (95% CI, 0.20-0.56) and a fixed model was used (I^2: 0%). Results of pooled analysis were statistically significant (P<0.0001).

Other follow-up results

Five studies reported numbers of local, locoregional, and total laryngectomy after local recurrence. There were certain proportions in both glottic and supraglottic carcinomas. Detailed data of included studies are reported in **Table 1**.

Publication bias

According to Begg's test (**Figure 11**), there was no publication bias by REML method (P>0.05).

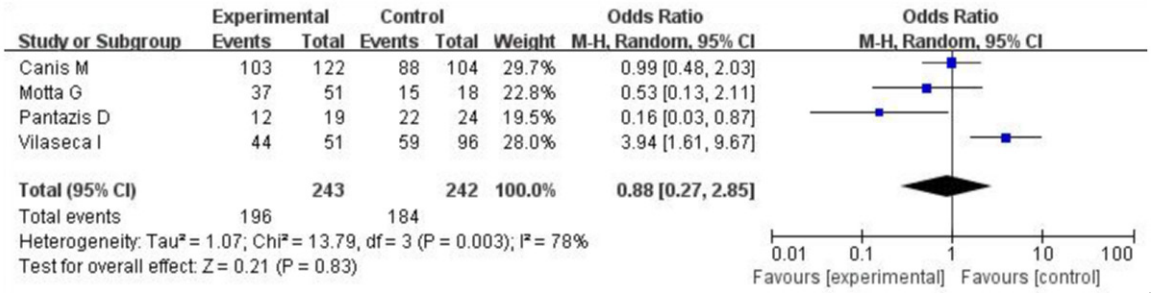

Figure 9. Forest plot for odds ratio of 5-year disease-specific survival between glottic carcinoma and supraglottic carcinoma.

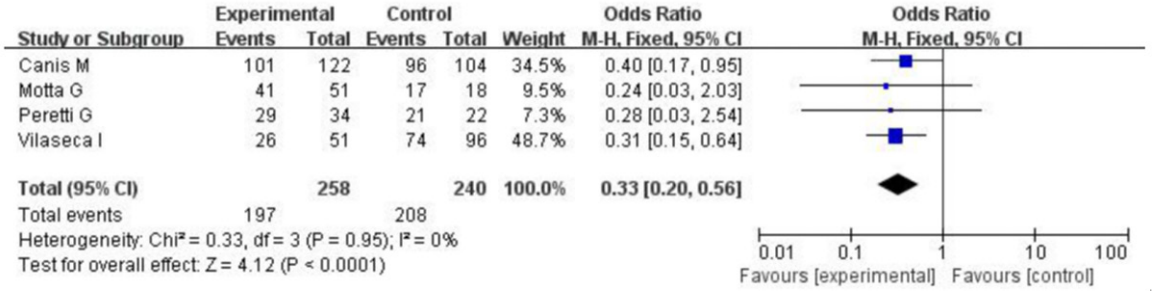

Figure 10. Forest plot for odds ratio of 5-year laryngectomy-free survival between glottic carcinoma and supraglottic carcinoma.

Discussion

Regarding T3 laryngeal (glottic or supraglottic) carcinomas, there remains much debate about which treatment to choose. The United Kingdom National Multidisciplinary Guidelines recommended that concurrent chemoradiotherapy, TLM, and open partial surgery are reasonable treatment options for T3 laryngeal (glottic or supraglottic) carcinomas [25]. Since TLM was introduced in 1972 [26], it has been proven to be a modality to treat laryngeal carcinomas. Based on present inclusion criteria, seven studies were included in this meta-analysis. To the best of our knowledge, this is the first meta-analysis to assess oncologic outcomes of TLM in the treatment of T3 glottic and supraglottic carcinomas.

According to analysis, pooled 5-year OS, DSS, and LFS rates of main oncologic outcomes were calculated based on extracted information from seven included studies. Pooled 5-year OS, DSS, and LFS for patientswith T3 laryngeal carcinoma were 63% vs 68%, 77% vs 80%, and 77% vs 90% (glottic vs supraglottic), respectively. Results showed that TLM could be an effective treatment for T3 laryngeal carcinomas. Many patients with T3 laryngeal carcinoma have selected chemoradiation therapy attempting to preserve laryngeal function. Al-Mamgai A et al. observed 5-year OS of 49%, DSS of 60%, and LFS of 50% for T3 laryngeal carcimoma [27]. Nakata Y et al. investigated 28 patients with advanced laryngeal carcinoma after alternating chemoradiotherapy. 5-year OS was 77.4% and LFS was 59.4% [28]. Jørgensen K et al. achieved a 5-year DSS rate of 59% and a 5-year LFS of 50% for patients with T3 glottic carcinoma [29]. Hinerman et al. were able to preserve the larynx in 68% of their patients treated with (chemo) radiotherapy for T3 supraglottic carcinoma [30]. Pooled survival rates of oncologic outcomes, in this study, were higher than in above studies. Furthermore, chemoradiotherapy may permanently affect patient quality of life through different ways, including cardiac and renal failure, atherosclerosis of the carotid vessels, and sensorineural hearing loss. It should be considered that better survival results can be obtained by choosing suitable patients for TLM.

OPL is another option for patients with T3 laryngeal carcinoma. According to a study by Riga M et al., both TLM and OPL seemed to be very

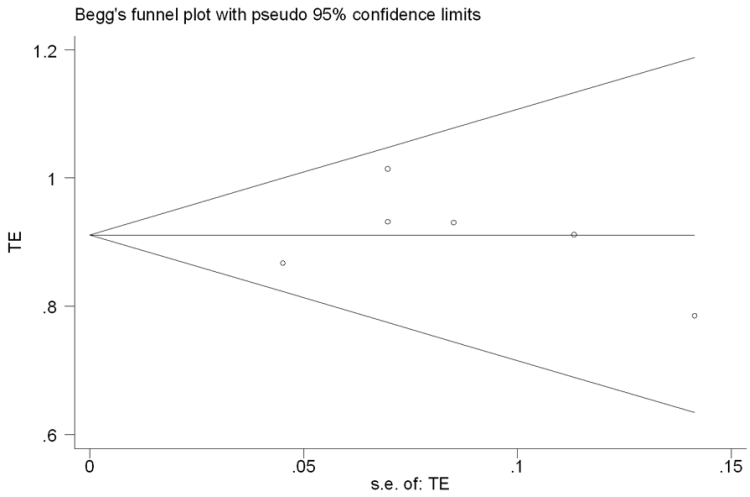

Figure 11. Funnel plot for analysis of publication bias.

effective in terms of OS, DSS, and local control rates [31]. Sperry S et al. reported 5-year OS of 78%, DSS of 81%, and LFS of 91% for T3 laryngeal carcinoma without prior radiotherapy [2]. Megwalu UC et al. found patients that with T3N0 that received surgical therapy had better 5-year DSS (69% vs 63%) and 5-year OS (59% vs 48%) than patients receiving nonsurgical therapy [32]. Mantsopoulos K et al. achieved a 5-year of DSS 78.3% and LFS of 90.1% for 120 patients with glottic carcinoma [33]. However, Al-Gilani et al. achieved the lower 5-year OS (41%) for surgical T3 glottic carcinoma [34]. Most patients whose primary management was surgery showed better oncologic outcomes. However, OPL requires surgical skills and expertise. In most patients, feeding tubes can be removed within a month after surgery. Furthermore, OPL causes a permanent change in voice that can significantly affect quality of life.

The present study revealed similar oncologic outcomes of TLM for T3 glottic and supraglottic carcinoma in terms of pooled OR for 5-year OS and DSS. This study found better LFS rates for T3 supraglottic carcinoma, according to pooled OR for 5-year LFS. TLM may not require exceptional surgical skills. In supraglottic area tumors, exposure is prone to be substantially more attainable than in the glottic area and acquisition of safe margins is usually simpler.

In these included studies, patients with T3 laryngeal carcinomas had certain limitations by TLM. Patients without distant metastases or secondary carcinomas had not undergone any previous treatment. Patients with cervical lymph node metastasis underwent neck dissection and/or adjuvant (chemo) radiation therapy. Thus, pooled results of OS, DSS, and LFS indicated a favorable efficacy of TLM. Additionally, TLM could preserve laryngeal function and reduced complications for T3 laryngeal carcinomas. Regardless of treatment method, there was risk of recurrence. Results also indicated that patients by TLM were no exception and some patients underwent total laryngectomy after recurrence.

Based on the present meta-analysis, TLM is an effective option for T3 laryngeal carcinomas. However, this study had some limitations. For example, number of included studies and samples were small and there were differences and high heterogeneity between included studies. These factors may have degraded the reliability of results of this meta-analysis.

In the future, evidence from a large sample of randomized controlled studies is necessary. More prospective studies are needed to confirm the results of this study and for systematic comparison between TLM and other treatment methods. TLM can be used reasonably. according to its indications and contraindications, to better serve patients with T3 laryngeal carcinoma and improve quality of life.

Conclusion

TLM offers patients with T3 glottic or supraglottic carcinomas better oncologic outcomes. TLM may be a valid option for organ-preserving surgery. However, its efficacy should be confirmed by more prospective clinical trials.

Acknowledgements

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Disclosure of conflict of interest

None.

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