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REVIEW

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Systematic review and meta-analysis of transoral laser microsurgery in hypopharyngeal carcinoma

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Abstract

Background: Transoral laser microsurgery has been suggested as an alternative treatment modality for hypopharyngeal carcinoma. The purpose of this study is to systematically review the oncologic and functional outcomes of patients with hypopharyngeal carcinoma when treated with primary transoral laser microsurgery.

Methods: A comprehensive literature search was performed using PRISMA methodology on OVID MEDLINE and EMBASE. Meta-analysis was completed for oncological outcomes.

Results: Six studies reported quality of life outcomes five reported oncologic outcomes. A median of 95% (range 0.83-0.98) patients achieving gastrostomy independence, a median of 3% (range 0%-6%) were tracheostomy dependent, and a median of 97% (Range 0.89-1.0) were able to preserve their larynx. Pooled five-year overall survival was 54% (CI, 0.50-0.58, I^2 = 29%), pooled disease-specific survival was 72% (CI, 0.68-0.77, I^2 = 46%), and pooled local control rate was 78% (CI, 0.72-0.85, I^2 = 69%).

Conclusion: Systematic review supports improvements in functional outcomes and oncologic outcomes with transoral laser microsurgery.

KEYWORDS

cancer, carcinoma, laser microsurgery, outcome research, systematic review

1 | INTRODUCTION

Carcinoma of the hypopharynx represents 5% of all head and neck cancers and has the highest associated mortality of any subsite.[1] These cancers present at an advanced stage, have a rich lymphatic supply and have submucosal spread in a complex anatomical space making them challenging to treat.[2,3] Traditional treatment strategies prior to 1990 focused on primary surgery with total pharyngolaryngectomy which resulted in significant postoperative morbidity.[4] In the mid-1990s, the Department of Veteran Affairs Laryngeal Cancer Study Group phase III clinical trial compared concomitant chemoradiation and surgery followed by radiation for advanced laryngeal carcinoma.[5] This study concluded there was no significant difference in survival at 2 years.[5] As a result, treatment strategies changed to focus on chemoradiation as the primary treatment modality owing to its ability to preserve the native larynx.[6] These "organ preservation" treatment strategies resulted in a present, but not necessarily functional larynx.[7] Two years later the

ABBREVIATIONS: AJCC, American Joint Committee on Cancer; CRT, chemoradiotherapy; EORTC, European organization for research and treatment of cancer; MDADI, M.D. Anderson Dysphagia Inventory; NCCN, National comprehensive cancer network; PRISMA, preferred reporting items for systematic reviews and meta-analyses; RT, radiotherapy; TLM, transoral laser microsurgery; VHI-30, voice handicap index-30.

European Organization for Research and Treatment of Cancer (EORTC) trial explicitly focused on hypopharyngeal carcinoma.[8] The EORTC trial compared induction cisplatin 5-fluorouracil chemotherapy and radiation vs surgery with postoperative radiotherapy at 5 years and again found no differences in survival.[8]

Since then acute and late effects of chemoradiation on quality of life have become more apparent,[7,9] whereas the structural framework of the larynx remains intact, radiation focused on the pharyngeal constrictors results in significant dysphagia and aspiration risk. [7,10] Despite this, recent data from the Surveillance, Epidemiology, and End Results Program (SEER) database indicates radiotherapy is increasingly favored as the primary treatment modality in the United States.[6]

Transoral laser microsurgical technique offers a favorable alternative to primary chemoradiation. This minimally invasive technique was popularized by Steiner for the treatment of laryngeal carcinoma and subsequently translated to the hypopharynx.[11,12] The transoral approach allows for preservation of the cartilaginous laryngeal framework, the surrounding musculature, and the pharyngeal nerve plexus important for swallowing function.[11] Studies in the treatment of hypopharyngeal carcinoma with transoral laser microsurgery have been focused in specialized centers experienced in the method and show promising results with limited morbidity.[12,13] Thus, this study aims to systematically review the oncologic and functional outcomes of patients with hypopharyngeal carcinoma when treated with primary transoral laser microsurgery.

2 | MATERIALS AND METHODS

2.1 | Literature review

Systematic review was done in accordance with PRISMA guidelines. Study design for systematic review was developed with the primary objective to evaluate oncologic outcomes of transoral laser microsurgery for hypopharyngeal carcinoma. The principal author (C.L.) and systematic review librarian (J.L.) collaborated to develop a search strategy for EMBASE and MEDLINE databases (Figure S1). References of full-text articles were also screened and included. Duplicate abstracts were removed using Mendeley reference manager software. Title screening was completed by two authors (C.L. and N.V.) in Rayyan QCRI software using the PRISMA methodology.

2.2 | Selection criteria

Inclusion criteria were English language, use of transoral laser microsurgery as the primary treatment modality, adult population, pathological proven squamous cell carcinoma of the hypopharynx, reported oncologic outcomes, and greater than 20 patients. The exclusion criteria were studies in which oncologic outcomes were not specific for the hypopharynx and studies with a duplicate cohort from the same institution.

2.3 | Quality assessment

No standard technique is broadly adopted to assess study quality for case series. This study utilized the National Institute for Health and Clinical Excellence quality assessment form for case series used previously.[14]

2.4 | Outcome measure

Demographics, oncologic outcome, and functional outcome data were extracted from full-text articles for further analysis. Demographic data included the number of patients, T stage, best reported American Joint Committee on Cancer (AJCC) or National Comprehensive Cancer Network (NCCN) stage, adjuvant radiation, neck dissection, and best-reported follow-up. We extracted all reported outcomes measures for overall survival, disease-specific survival, recurrence/disease-free survival, and local control. Extracted functional data included tracheostomy rate, gastrostomy rate, and laryngeal preservation rate.

2.5 | SEER database

This study used SEER-18 Data set consisting of 18 cancer registries across United States between 2000 and 2016. Data were extracted using the SEER Stat version 8.3.4. Histologically diagnosed cases of hypopharyngeal carcinoma were identified by the codes (ICD-O-3 C13.0, C13.1, C13.2, C13.8, and C13.9). Cases of distant metastatic disease were excluded. AJCC seventh edition staging was used to determine T1 and T2 status tumors irrespective of N status.

2.6 | Statistics

Studies were included in the quantitative meta-analysis if they reported 5-year oncologic outcome data. The SE was calculated using the reported proportion of survival and total samples from each study.[15] The meta-analysis used the generic inverse variance method and the random effect model. Heterogeneity between studies was assessed using the I^2 statistic, and the *P*-value of .1 was considered significant for heterogeneity as suggested for meta-analysis.[16] We calculated the pooled proportion of survival for oncological outcomes at the 5-year time point. Publication bias was assessed using a visual interpretation of Funnel plots.[17] Subgroup analysis was not conducted because of the limited number of studies per predefined subgroups.[17] The systematic review program RevMan (5.3), Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014, was used for meta-analysis.[18] Database comparison was calculated with a one-way analysis of variance (ANOVA) statistical test.

3 | RESULTS

The search strategy identified 677 results and three articles obtained from a review of article references. Title screening identified 140 duplicate

results. A total of 540 original article abstracts were screened for inclusion and exclusion criteria. This resulted in 11 abstracts, which underwent full-text review. Five were removed due to duplicate reporting of the patient series or insufficient outcome data. Six articles satisfied the inclusion and exclusion criteria for qualitative analysis. One article reported 4-year outcomes which was only included in the qualitative synthesis; the remaining five articles were used in the quantitative meta-analysis (Figure 1).

3.1 | Quality assessment

Six studies were included in the qualitative analysis for the country of origin (Table 1). Studies originated in Portugal (1), Taiwan (1), Spain (1), and Germany (3). The National Centre for Excellence quality assessment tool for case series was used to evaluate article suitability for systematic review. Articles scored five or six out of eight corresponding with a fair or good rating, respectively. (Figure S2) None of the included studies were prospective or involved a multicenter approach.

3.2 | Demographics

In total there were 477 patients included from six studies. Publication dates ranged from 2003 to 2018. The shortest series was 4 years with the longest was 30 years. Five studies reported the primary tumor site subsite. The majority of tumors were centered in the piriform sinus subsite (82%) of the hypopharynx. Five studies described the NCCN or AJCC staging of the primary tumor. There were 73 cases (26%) of early stage I or II, and 278 cases (74%) of late-stage III or IV hypopharyngeal carcinoma. Five studies reported adjuvant treatment modalities including radiotherapy (RT) and concurrent chemoradiotherapy (CRT) postoperatively. Studies reported different decision strategies for adjuvant therapy depending on institutional practices. Adjuvant radiotherapy was used to treat 71% of patients (range 43% to 86%). In addition, patients underwent neck dissections in 84% of patients (range 70% to 100%). One study reported a mean follow-up shorter than 60 months; this was excluded from the meta-analysis. The remaining five studies reported mean or median follow up ranging from 61 to 78 months.

3.3 | Oncologic outcomes

Survival outcomes were reported using the Kaplan Meier method in each study included in the qualitative analysis. Weiss et al. reported the most extensive series of patients treated with a transoral laser including 211 patients with a 55% 5-year overall survival. Similarly, Breda found an overall survival of 50%, Hung found a 59% survival, and Rudert found 48% survival. Two studies reported a 3-year overall

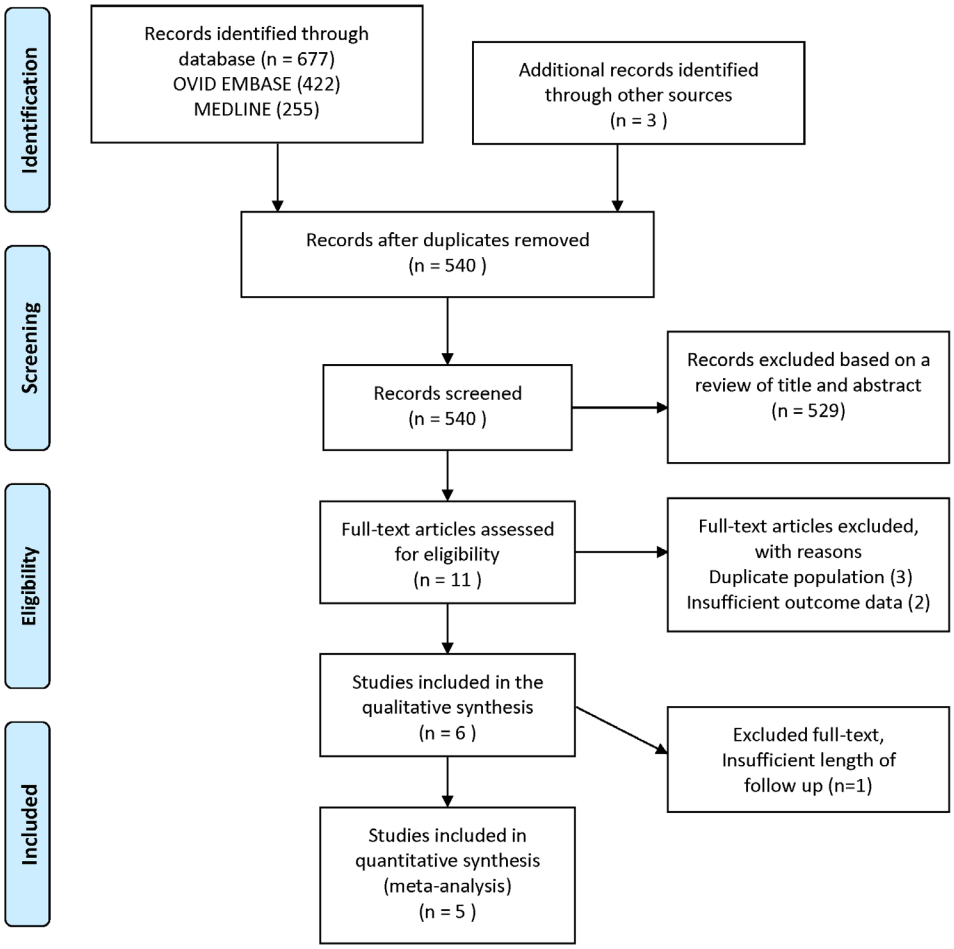

FIGURE 1 PRISMA flow diagram

TABLE 1 Patient demographics

Author	Year	Patients	T-Stage		Prognostic stage		Tumor subsite			Postoperative radiotherapy (%)	Neck dissection (%)	Follow-up in months (Median) [Mean]
			Early (T1 & T2) (%)	Advanced (T3 & T4) (%)	Early (I & II) (%)	Advanced (III & IV) (%)	Piriform (%)	Postcricoid (%)	Posterior hypopharynx (%)			
Breda	2017	37	78	22	32	68	95	2.7	2.7	NR	NR	(72)
Hung	2018	46	61	39	30	70	78	2	20	70	70	(61)
Vilaseca	2004	28	64	36	21	79	NR	NR	NR	43	100	(40)
Weiss	2017	211	38	62	16	84	75	5.2	8.5	70	88	[65]
Rudert	2003	29	93	6.9	31	69	83	6.9	10	86	89	[78]
Karatzanis	2010	119	100	0	NR	NR	71	9.2	12	83	78	[71]
Cumulative		470	64	36	26	74	82	6.3	11	71	84	

survival of 77% and 62%. One study reported 4-year overall survival of 43%. All six studies reported disease-specific survival. For 5-year disease-specific survival for transoral laser ranged from 58% to 77% at 5 years. Vilaseca et al reported a four-year disease-specific survival of 59%. Only two studies reported recurrence/disease-free survival. Weiss found a 556% disease-free survival and Rudert found an 82% disease-free survival. Five-year local control rates ranged from 72% to 85% among the four studies reporting this outcome. (Table 2).

3.4 | Functional outcomes

All six studies included in the qualitative synthesis reported functional outcomes. Gastrostomy rates ranged from 2.2% to 17% with a median of 95% achieving oral intake. There was a median tracheostomy dependence of 3% (range 0%-6%). Laryngeal preservation was reported in five studies with a median organ preservation rate of 97% (range 0.89-1.0). Of note, laryngeal preservation was higher than 96% in four of these studies. One study reported function outcomes of Voice Handicap Index-30 (VHI-30) and M.D. Anderson Dysphagia Inventory (MDADI) on a subgroup of 34 patients. Mean VHI-30 was 8.7 and mean global MDADI was 89.[3] Furthermore, Hung et al reported a significant improvement in function for those patients received single modality TLM compared with those treated with TLM and adjuvant radiotherapy for both VHI-30 (P = .01) and MDADI (P = .02, Table 3).

3.5 | Meta-analysis and database comparison

Five studies reported 5-year overall survival outcomes including a total of 330 patients. Pooled overall survival using the random effects model was 54% (95% CI, 50-58), associated with a low degree of heterogeneity (I^2 = 29%). Disease-specific survival included 449 patients from five studies and pooled survival was 72% (95% CI, 68-77) and was associated with a moderate degree of heterogeneity (I^2 = 46%). Finally, 5-year local control rates reported in four studies representing 396 patients. The pooled local control rate was 78% (95% CI, 72%-85%) associated with substantial heterogeneity (I^2 = 69%). Meta-analysis of recurrence/disease-free survival was not completed as only two studies reported this outcome (Figure 2, Table 4).

Finally, we compared pooled survival outcomes from this meta-analysis to large population-based cohort of patients from the SEER database. We extracted two groups of patients treated for hypopharyngeal carcinoma from the SEER database as comparators. The first group were patients with T1 or T2 stage disease, the second group included all stage groups without distant metastatic disease. Patients from both groups underwent standard treatment in their region. Patients treated with transoral laser microsurgery and included this meta-analysis has significantly better overall survival (P < .0001) and disease-specific survival (P < .0001) compared to the SEER patient groups (Figure 3).

TABLE 2 Oncological outcomes of hypopharyngeal carcinoma treated with transoral laser microsurgery

First Author	Overall survival (3-year) {4-year} [5-year]	Disease specific survival (3-year) {4-year} [5-year]	Recurrence/disease free survival [5-year]	Local control {4-year} [5-year]
Breda et al[37]	[50%]	[72%]	NA	[74%]
Hung et al[38]	(77%) [59%]	(83%) [77%]	NA	NA
Vilaseca et al[39]	{43.4%}	{59.4%}	NA	{87.1%}
Weiss et al[40]	[55%]	[74.1%]	[55.9%]	[75.7%]
Rudert et al[41]	(62%) [48%]	(70%) [58%]	[82%]	[72.4%]
Karatzanis et al[42]	NA	[72.6%]	NA	[85.4]

TABLE 3 Functional outcomes of hypopharyngeal carcinoma treated with transoral laser microsurgery

First author	Gastrostomy tube rate (%)	Tracheostomy rate (%)	Organ preservation rate (%)
Breda et al[37]	5.2	0	97.3
Hung et a[38]	2.2	6	89
Vilaseca et al[39]	10	3.5	100
Weiss et a[40]	4.3	3.8	99.5
Rudert et al[41]	17	0	96
Karatzanis et al[42]	2.5	2.5	NA
Median	4.75	3.00	97.30

4 | DISCUSSION

Clinical trials have failed to show a survival difference between primary surgery and primary radiation for the treatment of hypopharyngeal carcinoma.[8,19] Thus, there are multiple suggested modalities for this subsite of head and neck carcinoma[20] The minimally invasive technique of transoral laser microsurgery has been suggested over more traditional open surgical techniques to minimize morbidity.[21] Reviews on the subject of transoral laser for hypopharyngeal carcinoma are not systematic in nature and risk author bias.[12,22] The strengths of this study are that it is the first systematic review and meta-analysis of oncologic outcomes of transoral laser microsurgery for hypopharyngeal carcinoma.

Patients included in this systematic review presented in later stages of disease characteristic of hypopharyngeal carcinoma.[1] The presence of advanced stage disease in hypopharyngeal cancer is commonly related to the presence of regional nodal disease. These advanced staged patients may present with early T-stage disease. As well, five of six studies treated advanced T-stage disease. This conflicts with some articles, which discuss the concept of limiting transoral laser surgery to patients with early T-stage disease.[23] It is important to note the importance of vocal cord fixation in related to T-stage disease has undergone changes over the past few decades. Prior to 1997, T3 tumors were staged according to the presence of vocal cord fixation. Since 1997, staging manuals include vocal cord fixation or tumors larger than 4 cm as T3.[24] The tumors included in this review were staged according to the historical staging criteria at the time of treatment. Considering these changes, there may be an elemental of stage migration, which was not accounted for in our review.

Studies in this review report a high proportion of patients' subject to multi-modality treatment with adjunctive radiotherapy or chemoradiotherapy (Table 2). Interestingly, others have suggested an intensification protocol for advanced hypopharyngeal carcinoma due to its aggressive nature.[25] Inversely, nearly 30% (n = 123) of patients received only single modality transoral laser microsurgery, sparing the late effects and lifelong sequela of radiotherapy.[26]

Trends in survival of hypopharyngeal carcinoma have shown little to no improvement over the past few decades. [4,6] The pooled overall proportion of survival in this meta-analysis of primary transoral laser microsurgery was 54%. Studies did not have significant heterogeneity providing strength to this calculation. A literature review of population-based studies reveals 5-year overall survival between 25%-41% in patients free of distant metastasis.[4,6] Disease-specific survival mirrored the improvements in overall survival with a pooled proportion of survival of 72% at 5 years. In comparison, EORTC found significantly worse disease-specific survival of 25%.[27]

Patients included in this meta-analysis treated with TLM has improved survival compared to early T1 and T2 stage disease from the SEER database. The SEER database is a large national database in the United States, which provides information on cancer statistics. Prior studies of survival trends in hypopharyngeal cancer using this database were consistent with the survival results in this study.[6] One explanation for this improved survival is the high percentage of patients treated with multi-modality surgery and radiation.

Local control rates provide a measure for the efficacy of management at the primary site. Pooling studies in this review revealed a 78% local control at 5 years. In comparison, a recent multicenter trial found local control rates of 82% and 63% for traditional pharyngolaryngectomy and chemoradiotherapy, respectively.[28] Thus, there appears to be no inferiority for local control for selected patients treated with transoral laser microsurgery. However, this comparison would be associated with significant selection bias in the transoral laser surgery group.

Of particular interest were the functional outcomes for patients treated with transoral laser microsurgery as this has been the main drawback for open surgery. This systematic review revealed high rates of laryngeal preservation, with most studies reported rates above 96%.

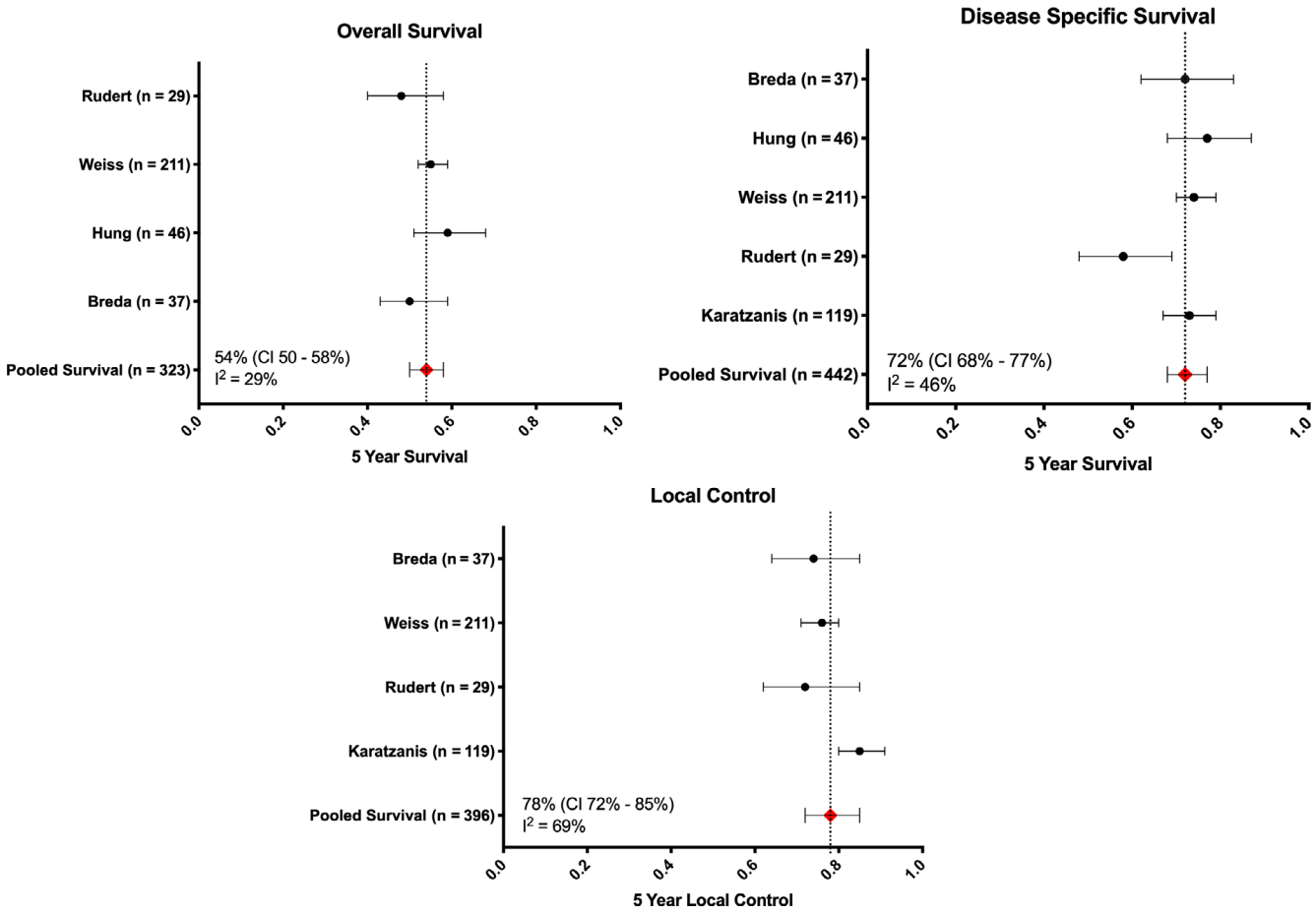

FIGURE 2 Forest plots of 5 year proportion of survival for hypopharyngeal carcinoma treated with transoral laser microsurgery

TABLE 4 Pooled proportion of survival for oncological outcomes for hypopharyngeal carcinoma treated with transoral laser microsurgery

	Overall survival	Disease specific survival	Local control
Breda et al[37]	0.5 [0.43, 0.59]	0.72 [0.62, 0.83]	0.74 [0.64, 0.85]
Hung et al[38]	0.59 [0.51, 0.68]	0.77 [0.68, 0.87]	
Weiss et al[40]	0.55 [0.52, 0.59]	0.74 [0.70, 0.79]	0.76 [0.71, 0.80]
Rudert et al[41]	0.48 [0.40, 0.58]	0.58 [0.48, 0.69]	0.72 [0.62, 0.85]
Karatzanis et al[42]		0.73 [0.67, 0.79]	0.85 [0.80, 0.91]
Heterogeneity	P = .24 I^2 = 29%	P = .12 I^2 = 46%	P = .02 I^2 = 69%
Pooled proportion of survival	0.54 [0.50, 0.58]	0.72 [0.68, 0.77]	0.78 [0.72, 0.85]

However, laryngeal preservation may not necessitate function. Thus, a hard measure of tracheostomy and gastrostomy tube dependence are essential to evaluate function. Tracheostomy rates in this review ranged from 0% to 6%. Small studies looking at tracheostomy in patients treated with chemoradiation ranged between 36% and 57%.[29,30]

Furthermore, previous work has shown that gastrostomy tube placement is associated with reduced quality of life.[31,32] In this review, studies ranged widely between 2.2% and 17% for gastrostomy placement with a median rate of 4.7%. In comparison, studies of patients treated with chemoradiotherapy found 36% to 70% of patients required initial gastrostomy tube placement.[33,34] A comparative study of open surgery to chemoradiotherapy found a 7.1% feeding tube dependence for open surgery and 13.1% for chemoradiotherapy.[35] One key limitation in interpreting these results is the duration of gastrostomy tube placement. Gastrostomy tubes may be placed temporarily during treatment or present permanently due to functional deficit. Thus, further comparative studies are needed to describe the duration of gastrostomy tube placements with TLM vs chemoradiotherapy.

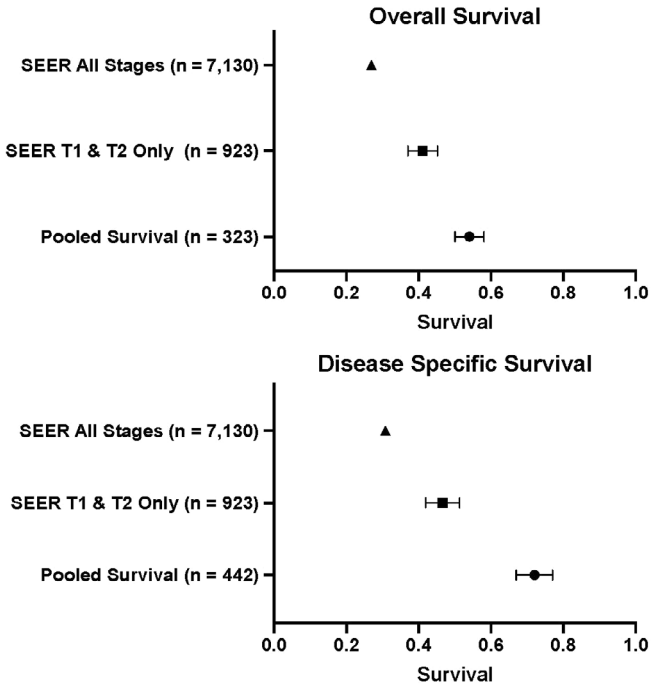

FIGURE 3 Five-year overall survival and disease-specific survival of hypopharyngeal carcinoma patients from seer database vs meta-analysis of transoral laser microsurgery

The limitations of this study are those related to a meta-analysis of case series. Hypopharyngeal carcinoma is rare with an incidence of 0.6 to 1 per 100 000 persons per year, making prospective controlled trials difficult.[6,36] Studies in this review were limited to a retrospective methodology. This analysis was restricted to English language articles for reasons of accessibility of articles. This review may be associated with publication bias for those institutions with good outcomes.

Additionally, transoral laser microsurgery technique is associated with selection bias. This population is limited to patients with good oral access and cervical spine mobility. As well, surgeon experience is a critical feature in determining the success of surgery.[37] Patients with advanced T stage with cartilage involvement or transglottic spread would be excluded. Certain authors showed a selection bias for patients with early T-stage disease. The outcomes of this study should be interpreted in the context of these limitations.

5 | CONCLUSION

This review identified transoral laser microsurgery as an alternative treatment modality for select patients with hypopharyngeal carcinoma in specialized centers. Meta-analysis reveals improved oncologic outcomes for patients treated with transoral laser. Functional outcomes support the concept of improvements in feeding independence and laryngeal preservation with transoral laser microsurgery over traditional treatment strategies.

CONFLICT OF INTEREST

The authors report no conflicts.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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