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Systematic Review

Elective Neck Dissection During Salvage Laryngectomy: A Systematic Review and Meta-analysis

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Objectives: The primary objective was to determine the rate of occult cervical nodal metastasis in patients undergoing elective neck dissection (END) during salvage laryngectomy. The secondary objective was to compare survival and postoperative complication rates between patients undergoing END versus observation.

Methods: A medical librarian performed a comprehensive search for END outcomes in laryngeal cancer patients undergoing salvage laryngectomy after primary chemoradiation therapy. Seventeen retrospective studies and 1 prospective study met inclusion criteria, with a total of 1,141 patients (799 END, 350 observed).

Results: The rate of nodal positivity was 11% among patients who underwent END during their salvage laryngectomy. Three studies and 155 patients were included in a 5-year overall survival (OS) analysis with no significant difference in OS (95% confidence interval [CI]: 0.82-2.22). After inclusion of six studies and 494 patients (249 END, 245 observed), the risk of fistula formation was not statistically different (95% CI: 0.61-2.56). Due to significant heterogeneity between studies and inadequate data, most patients could not be included in the meta-analysis of outcomes.

Conclusion: Salvage laryngectomy patients undergoing END have an occult nodal positivity rate of 11%. Meta-analysis showed no statistically significant differences in 5-year OS between patients undergoing END versus observation.

Key Words: Salvage laryngectomy, occult node, elective neck dissection, systematic review, meta-analysis.

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INTRODUCTION

Laryngeal cancer remains prevalent amongst head and neck cancers, with an estimated incidence in the United States of 12,410 new cases in 2019.[1] Prior to landmark organ preservation studies, the standard of care for advanced-stage larynx cancer was total laryngectomy.[2,3] This practice largely changed following the Veterans Affairs (VA) Cooperative Study in 1991, which demonstrated equivalent 2-year overall survival (OS) in advanced-stage larynx cancer patients randomized to primary chemoradiation therapy (CRT) versus surgery.[4] Despite 36% of the primary nonsurgical patients later requiring a salvage laryngectomy for local recurrence, the VA study established nonsurgical therapy as the standard of care for advanced disease in many centers.[2,3] Subsequently, the cohort of patients undergoing primary nonsurgical therapy for larynx cancer increased, with a relative increase in the number of patients undergoing salvage surgery.[3,5] Follow-up studies demonstrated worse survival for certain subsets of those patients who undergwent primary CRT, specifically those with advanced tumor (T) stage supraglottic cancer, yet this approach remains prevalent.[3] With an increasing number of patients facing salvage total laryngectomy, controversy exists regarding management of the clinically node-negative (cN0) neck.

A small number of largely retrospective studies have explored this question and report rates of occult nodal disease in recurrent laryngeal cancer as ranging from 0% to 27%.[6–23] The decision to perform an elective neck dissection (END) during salvage surgery remains unclear due to conflicting evidence of its impact on survival.[13,14,24,25] There are also reports of increased postoperative complication and fistula rates after salvage neck dissection.[14,18,20,26] With the existing evidence, there is a lack of consensus to definitively guide clinical decision making.

The primary objective of this systematic review and meta-analysis was to determine the rate of occult cervical nodal metastasis in patients undergoing END during salvage laryngectomy. The secondary objective was to compare

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survival and postoperative complication rates between patients undergoing END versus observation.

METHODS

This study was exempt from the Washington University Human Research Protection Office, as it used data from published literature. No review protocol was registered for this study.

Search Strategy and Study Selection

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed for this systematic review.[27] Utilizing the PICOS (Population, Intervention, Comparator, Outcome, Study design) framework, the population of interest was adults aged >18 years who previously underwent primary CRT therapy for laryngeal cancer and subsequently underwent salvage total laryngectomy; the intervention was END; the comparator was observation; the primary outcome was incidence of occult nodal positivity in patients undergoing neck dissection and the secondary outcomes were survival complications, and rate of postoperative fistula formation; and the study design was all study types except case reports.

A medical librarian created search strategies using a combination of keywords and controlled vocabulary to identify records of END outcomes in salvage laryngectomy patients after primary CRT. Searches were performed in Ovid MEDLINE from 1946, Embase from 1947, Scopus from 1823, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, and Clinicaltrials.gov from 1997, and were completed in July 2017. The identical search was performed again in May 2019 to update the results prior to analysis. A total of 62 articles were exported to an EndNote (University of North Carolina at Chapel Hill, Chapel Hill, NC) citation library. Thirty-three records were identified and removed from the project library using the automatic deduplication finder in EndNote, resulting in 29 unique records in the project library (Fig. 1). All published English-language abstracts were screened by two independent reviewers (J.H.G., P.P.), and 27 unique articles had available full text and were read in full. Studies were included if they reported outcomes of patients undergoing salvage laryngectomies for recurrent laryngeal cancer after primary CRT. Studies were excluded if they reported pathology other than squamous cell carcinoma, had fewer than five included patients, or did not perform standard selective neck dissections. Fifteen studies were excluded for the following reasons: four studies did not include salvage laryngectomy patients, three studies (two review articles, one guideline) did not contain any original data, two studies described elective node plucking rather than selective neck dissections, two studies only had abstracts available without full text, two studies had fewer than five included patients, one study's results could not be separated from nonsalvage laryngectomies, and one study only included patients with carcinoid tumor. An attempt was made to contact the author of one of the abstracts without full text, but there was no response. The other abstract was presented at a conference without a corresponding published article, and it did not contain enough information for inclusion. Fourteen remaining articles met inclusion criteria, and four additional articles were identified by reviewing the references. Fully reproducible search strategies for each database can be found in the Supporting Information, Appendix, in the online version of this article.

Data Extraction and Quality Assessment

Data related to all outcomes were extracted from the included studies (J.H.G.) and transferred to an electronic data collection form. Thirteen of 15 study authors were contacted to augment the meta-analysis, and nine authors responded with varying levels of additional data provided. Two authors (J.H.G., P.P.) assessed the quality of each study according to the Methodological Index for Nonrandomized Studies criteria listed in Table I.[28] All but one study (Wax and Touma[15]) were retrospective and therefore did not have prospective data collection. No included studies described a prospective calculation of study size.

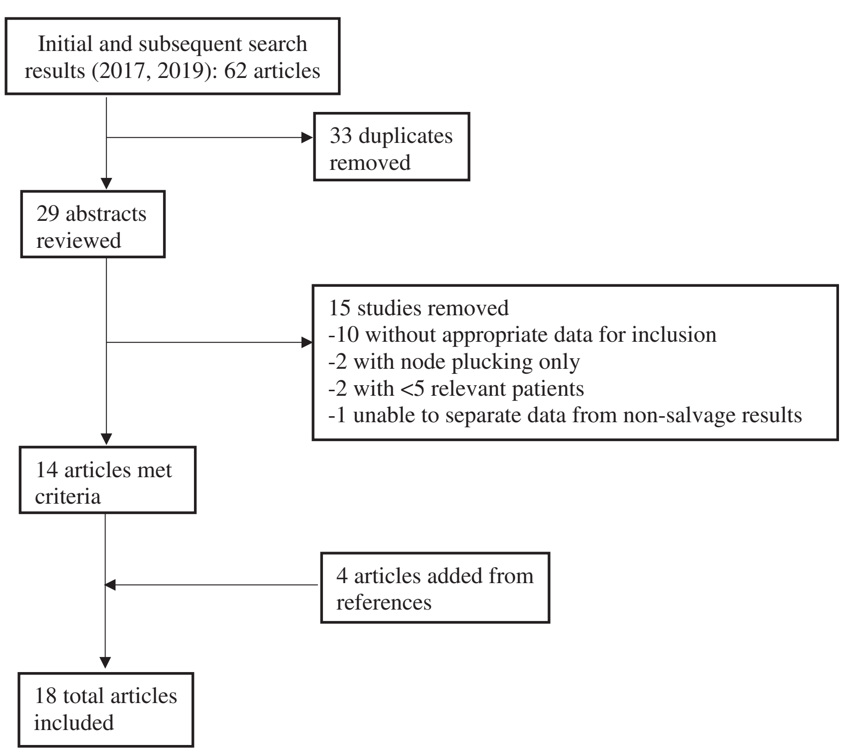

Fig. 1. Flow diagram of reviewed studies.

TABLE I.
Methodological Index for Nonrandomized Studies Criteria.

Author	A Clearly Stated Aim	Inclusion of Consecutive Patients	Prospective Collection of Data	Endpoints Appropriate to the Aim of the Study	Unbiased Assessment of the Study Endpoint	Follow-up Period Appropriate to the Aim of the Study	Loss to Follow-up <5%	Prospective Calculation of the Study Size	Total Score
Amit	2	2	0	2	2	2	2	0	12
Asimakopoulos	2	2	0	2	2	1	1	0	10
Basheeth	2	2	0	2	2	2	2	0	12
Bernard	2	2	0	2	2	2	2	0	12
Birkeland	2	2	0	2	2	2	0	0	10
Bohannon	2	2	0	1	2	1	1	0	9
Dagan	2	2	0	2	2	2	2	0	12
Deganello 2008	1	2	0	0	2	2	2	0	9
Deganello 2014	2	2	0	2	2	1	2	0	11
Farrag	2	2	0	1	2	2	2	0	11
Freiser	2	2	0	2	2	2	1	0	11
Hilly	2	2	0	2	2	0	2	0	10
Hussain	2	2	0	2	2	1	1	0	10
Koss	2	2	0	2	2	2	0	0	10
Pezier	1	2	0	1	2	2	0	0	8
Wax	2	2	2	2	2	2	2	0	14
Yao	2	2	0	2	2	2	2	0	12
Yirmibesoglu	2	2	0	2	2	2	1	0	11

0 = not reported; 1 = reported but inadequate; 2 = reported and adequate.

Statistical Analysis

Descriptive statistics were used for studies that were unable to be included in the meta-analysis due to heterogeneity in reported outcome measures. A random-effects meta-analysis was performed to quantify 2-year and 5-year OS, as well as fistula formation in patients undergoing END versus observation. A random-effects meta-analysis of proportions was performed to examine the rate of occult nodal positivity in patients undergoing END. Consistency between studies was measured with I^2.[29] All analyses were performed in Stata version 14.1 (StataCorp, College Station, TX) and Excel version 15.2 (Microsoft, Redmond, WA).

RESULTS

After the comprehensive search and application of appropriate exclusion and inclusion criteria, 18 studies were included for systematic review, with a total of 1,141 patients (799 END, 350 observed).[6–23] All but one study (Wax and Touma[15]) were retrospective. Details of each included study are displayed in Tables II and III. Reporting of general demographic data was too heterogeneous and was therefore not included. The initial tumor laryngeal subsites and time from initial treatment to recurrence are also not listed, as these data were generally not reported. All 18 articles describe patients who underwent END, and their rates of pathologic occult nodal disease are recorded. Only 12 studies compare outcomes between patients with END and observed necks. Discrepancies in denominators are due to missing data or unseparated data points. Some individual data (both demographics and outcomes) could not be separated between larynx and nonlarynx (i.e., oropharynx) tumor subsites or between END and observed. Those data that could not be separated were not included in meta-analysis. Blank spaces correspond with no reported data.

Systematic Review for Elective Neck Dissections

Most patients (67%) in this pooled cohort initially presented with T1/T2 laryngeal cancer, received definitive radiation therapy (71%), and recurred locally with advanced T3/T4 disease (64%). Based on absolute data, the rate of positive occult nodal disease ranged from 0% to 27%. The 5-year OS in electively dissected patients ranged from 21% to 67%, with an overall OS of 46%, and the 5-year disease-free survival (DFS) was 56%. Forty-one percent of these patients developed postoperative complications of any kind, and 23% of patients developed postoperative fistulas. Postoperative complications included wound infection, pulmonary embolus, hematoma, chyle leak, flap failure, and death.

Ten of the 18 included studies provided survival data for the 80 patients who had positive occult nodal disease found during END. Those patients had a 5-year OS range of 0% to 100%, with a total 5-year OS of 28%. DFS and disease-specific survival were generally not documented.

Systematic Review for Observed Necks

Most patients (77%) in this pooled cohort initially presented with T1/T2 laryngeal cancer, received definitive radiation therapy (79%), and recurred locally with early T1/T2 disease (53%). The 5-year OS in these patients ranged from 33% to 65%, with an overall OS of 56%, and the 5-year DFS was 60%. Twenty-eight percent of these patients developed postoperative complications of any kind, and 18% of patients

TABLE II.
Elective Neck Dissections.

Author	Sample Size	Initial Staging (T1/T2; T3/T4)	Initial Treatment (RT; CRT)	Recurrent Staging (T1/T2; T3/T4)	Recurrent Laryngeal Subsite (Supragl; Gl; Subgl; Transgl)	Salvage Neck Dissection (Unilateral; Bilateral)	Positive Nodal Disease (%)	5-Year OS	5-Year DFS	Postoperative Complication Rate (%)	Postoperative Fistula Rate (%)
Amit	42	24; 18	20; 22	10; 32	22; 26; 0; 0	33; 9	19%				
Asimakopoulos	45	25; 20	36; 9				11%				20%
Basheeth	38	24; 14	24; 14	9; 29	9; 15; 2; 8	20; 18	8%			61%	40%
Bernard	27	16; 11	21; 6	6; 21		21; 6	4%	62%	74%	37%	22%
Birkeland	203	117; 68	124; 79	102; 101	81; 120; 2; 0	0; 203	17%				
Bohannon	38	18; 11	27; 11	3; 35	4; 34; 0; 0	6; 32	8%			42%	32%
Dagan	28	17; 23	28; 0	19; 21	13; 13; 0; 0	6; 34	11%	45%		48%	25%
Deganello 2008	11	11; 0	11; 0	9; 2			27%	67%	67%	19%	6%
Deganello 2014	7	7; 0	7; 0	4; 3		5; 2	0%	57%	29%	72%	57%
Farrag	29	32; 2	29; 0	5; 29	8; 24; 2; 0	20; 14	3%				
Freiser	98	66; 13	80; 17	18; 81	14; 68; 0; 16	47; 51	10%	53%		42%	26%
Hilly	48	30; 17	20; 28	12; 36	26; 22; 0; 0	39; 9	13%		57%		
Hussain	17				1; 13; 1; 0	0; 19	6%	33%		37%	32%
Koss	51	28; 17	40; 27	11; 38	9; 11; 2; 29	0; 51	25%	21%	21%		
Pezier	28					24; 4	7%	37%	47%		>50%
Wax	34	28; 6	34; 0	12; 22	14; 20; 0; 0	30; 4	18%	25%	25%		
Yao	41	38; 3	41; 0	33; 8	10; 31; 0; 0	0; 41	12%	56%	56%	19%	12%
Yirmibesoglu	14	15; 5	13; 17	15; 15		13; 17	14%			50%	29%
Total	799	496; 238	555; 230	268; 473	198; 397; 9; 60	556; 222	13%	46%	56%	41%	23%

Discrepancies in denominators are due to missing data or unseparated data points. Blank spaces correspond with no reported data.
CRT = chemoradiation therapy; DFS = disease-free survival; Gl = glottic; OS = overall survival; RT = radiotherapy; Supragl = supraglottic; Subgl = subglottic; Transgl = transglottic.

TABLE III.
Observed Necks.

Author	Sample Size	Initial Staging (T1/T2; T3/T4)	Initial Treatment (RT; CRT)	Recurrent Staging (T1/T2; T3/T4)	Recurrent Laryngeal Subsite (Supragl; Gl; Subgl; Transgl)	5-Year OS	5-Year DFS	Postoperative Complication Rate (%)	Postoperative Fistula Rate (%)
Amit									
Asimakopoulos									
Basheeth	7	2; 5	4; 3	0; 7	2; 3; 1; 1			29%	29%
Bernard	59	40; 19	56; 3	26; 33		41%	59%	36%	24%
Birkeland									
Bohannon	33	16; 19	25; 8	3; 35	8; 25; 0; 0			21%	9%
Dagan	8	6; 11	16; 1	13; 4	2; 6; 0; 0	56%		29%	18%
Deganello 2008	15	15; 0	15; 0	13; 2		55%	45%	13%	7%
Deganello 2014	97	97; 0	97; 0	62; 35		65%	68%	27%	13%
Farrag	17		17; 0						
Freiser	27	24; 1	24; 3	11; 15	3; 22; 0; 2	53%		48%	33%
Hilly	39	21; 13	14; 25	18; 21	31; 8; 0; 0		57%		
Hussain									
Koss	15	11; 2	40; 27	9; 6	4; 4; 0; 7	33%	33%		
Pezier									
Wax									
Yao	22	14; 8	22; 0	19; 3	12; 10; 0; 0	36%	36%	32%	32%
Yirmibesoglu	11	5; 9	8; 6	7; 7				18%	9%
Total	350	251; 77	282; 73	182; 162	62; 78; 1; 10	56%	60%	28%	18%

Discrepancies in denominators are due to missing data or unseparated data points. Blank spaces correspond with no reported data.
CRT = chemoradiation therapy; DFS = disease-free survival; Gl = glottic; OS = overall survival; RT = radiotherapy; Supragl = supraglottic; Subgl = subglottic; Transgl = transglottic.

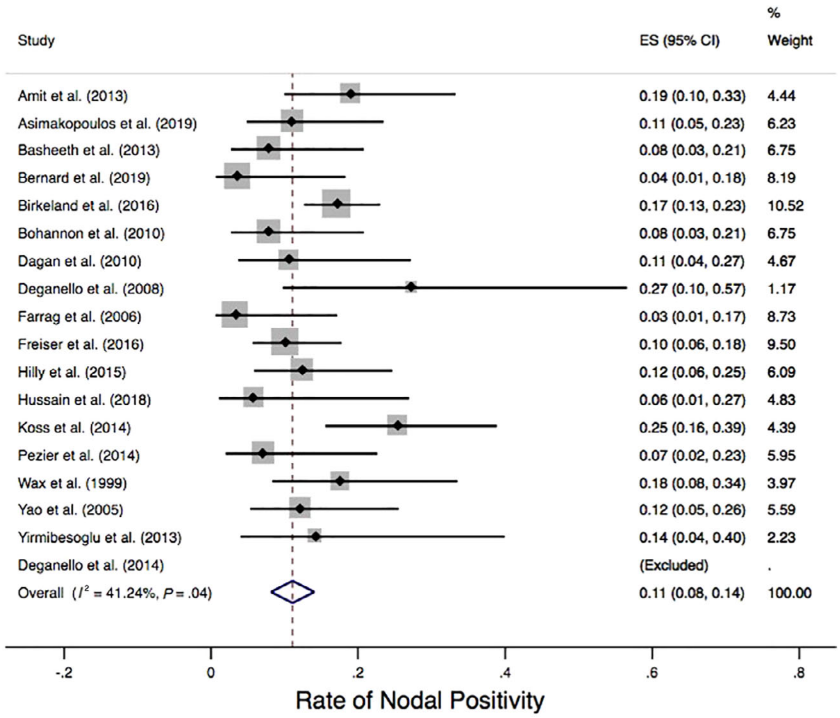

Fig. 2. The rate of occult nodal disease in elective neck dissection patients. CI = confidence interval. ES = effect size. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

developed postoperative fistulas. Postoperative complications included wound infection, pneumonia, hematoma, flap failure, myocardial infarction, carotid blow-out, and death.

Meta-analysis

The rate of occult nodal positivity during salvage laryngectomy was examined in all 18 included studies. The pooled rate was 11% (95% confidence interval [CI]: 8%-14%, I^2 = 41.2) among the 799 END patients (Fig. 2).

Despite contacting and receiving replies from most of the authors, multiple studies did not have the individual data points required to calculate OS and DFS for meta-analysis. As a result, only three studies (including 103 elective necks and 52 observed) were used for the meta-analysis for OS.[11,16,17] Meaningful DFS could not be calculated due to insufficient data. The 2-year OS outcomes are illustrated in a forest plot in Figure 3. Due to excessive heterogeneity (I^2 = 84.9%, P = .001), we could not make meaningful conclusions from this meta-analysis. The same three studies and 155 patients

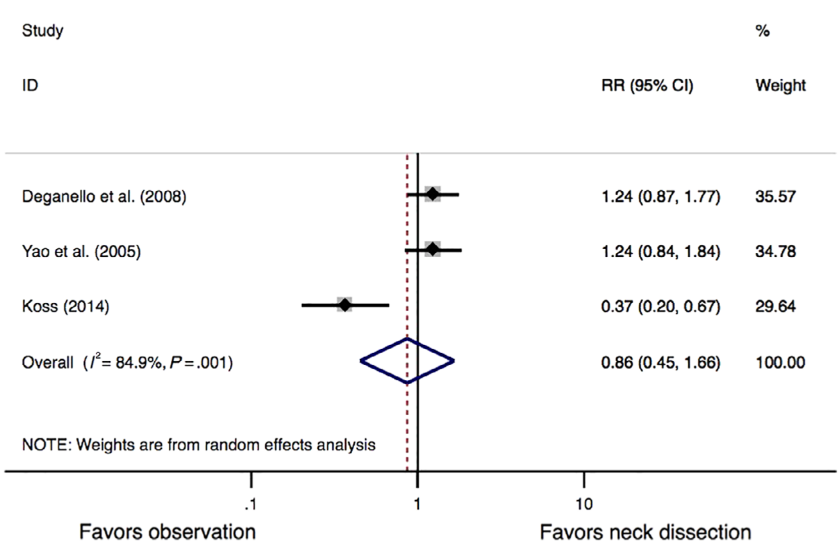

Fig. 3. Forest plot for overall survival at 2 years, comparison between patients with observed and electively dissected necks. CI = confidence interval; RR = relative risk. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

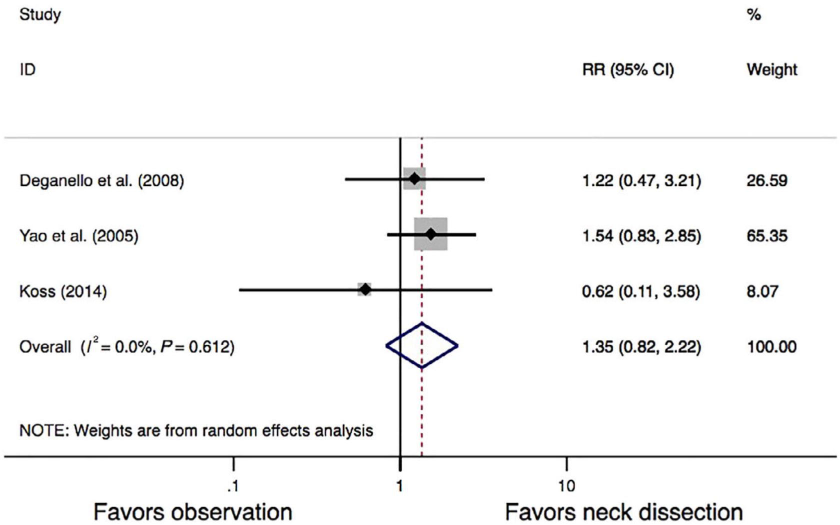

Fig. 4. Forest plot for overall survival at 5 years. Comparison between patients with observed and electively dissected necks. CI = confidence interval; RR = relative risk. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

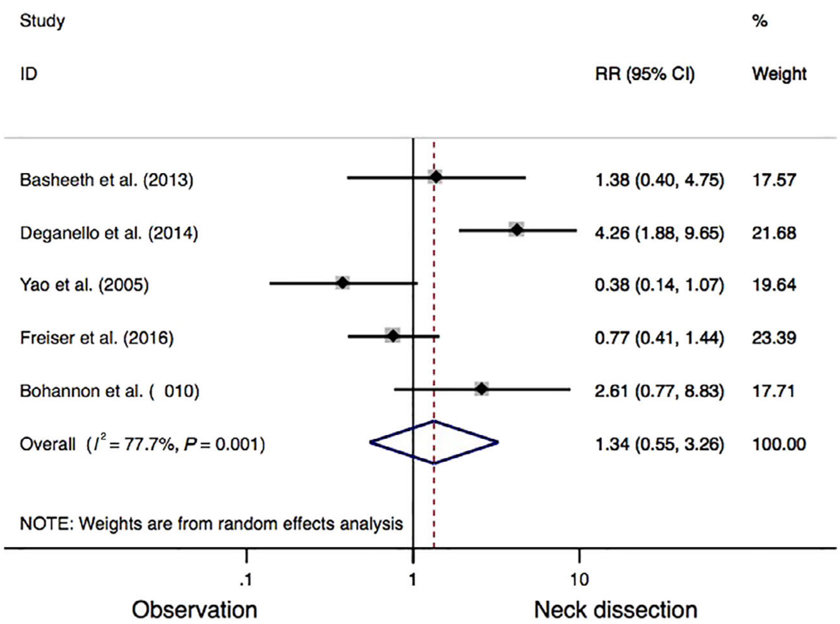

Fig. 5. Forest plot for postoperative fistula rates. Comparison between patients with observed and electively dissected necks. CI = confidence interval; RR = relative risk. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

were included in a 5-year OS analysis, with no evidence of heterogeneity (I^2 = 0%, P = .6) (Fig. 4). Meta-analysis showed no significant difference in overall survival between the two groups (95% CI: 0.82-2.22).

Five studies were included in the meta-analysis for postoperative fistula formation, with a combined total of 408 patients (222 END, 186 observed).[8,10,19–21] There was no statistically significant difference in the risk of fistula formation between the two groups (95% CI: 0.61-2.56) (Fig. 5). However, the statistical heterogeneity was high (I^2 = 72.6%, P = .003). Predictive factors of nodal positivity, survival differences, postoperative fistula, or complication rates could not be calculated due to the significant heterogeneity and small number of included studies.

DISCUSSION

This systematic review and meta-analysis demonstrate that patients with recurrent larynx cancer after treatment with primary nonsurgical treatment who undergo elective neck dissection during salvage laryngectomy have an 11% rate of occult cervical nodal disease. The standard based upon the 1994 Weiss et al.[30] decision-tree analysis is to perform an END for head and neck cancer if the risk of occult nodal disease in the primary setting is >20%. The application of this decision tree to the salvage setting is more unclear, however. Looking specifically at the included studies by Birkeland et al., Wax and Touma, Yao et al., and Koss et al., they report a ≥20% risk of occult nodal disease with recurrent supraglottic tumors and advanced tumor (T) stage (T3–T4) tumors and therefore recommend END for those subsets.[6,15–17] Based on the existing standard and the above data, it may be reasonable to observe the necks of a recurrent laryngeal cancer unless it is an advanced T stage or of supraglottic subset.

One important factor to consider is whether an END improves OS and/or DFS in these patients. Data from two of the above-listed studies (Yao et al. and Koss et al.[16,17]), combined with results from Deganello et al.,[11] were included in the meta-analysis of 155 patients, and there was no statistically significant difference in 5-year OS between patients with END versus observation (95% CI: 0.82-2.22, I^2 = 0%). A meta-analysis of the same three studies for 2-year OS demonstrates too much heterogeneity to make a meaningful conclusion (I^2 = 84.9%). DFS could not be calculated due to insufficient data. These results suggest that although presence of occult nodal disease may be higher in certain subsets of patients with recurrent laryngeal cancer, those patients may not have an OS advantage from undergoing END. Our initial goal with the meta-analysis was to identify a certain subset of patients who might have a survival benefit from an END. Unfortunately, due to inconsistent data reporting and heterogeneity between studies, a subset meta-analysis could not be performed.

However, we were able to collect the survival data for most of the 107 included patients who had an END with positive occult nodal disease. The combined results of 10 studies (80 total patients) demonstrated a 5-year OS range of 0% to 100%, with a total 5-year OS of 28%. DFS and disease-specific survival were generally not documented. In contrast, it is important to consider the OS rate for those patients with observed necks who develop a regional recurrence after salvage surgery. The available data were limited, heterogeneous, and inconsistently reported, but these patients did tend to die from their disease recurrence and could not be salvaged. Of the four included studies with these data, only one of 14 patients with a regional recurrence after an observed neck had long-term survival (5-year OS = 7%).[10,11,19,21] Other included studies showed equivalent rates of regional recurrence between END and observed necks, or even greater rates in END patients, without report of their survival.[8,9,13]

An additional factor to consider is whether the postoperative complication rate after END is justifiable for a potential small increase in OS or DFS. END has been shown to be associated with an increased risk of postoperative complications and/or pharyngocutaneous fistula formation.[8,10,19,26] In our systematic review, END patients had a 23% risk of postoperative fistula and 41% risk of postoperative complication, compared with 18% and 28% for observed patients, respectively. However, on meta-analysis of six studies and 494 patients, there was no significant difference in the risk of fistula formation (95% CI: 0.61-2.56), but the statistical heterogeneity was too high to make a meaningful conclusion (I^2 = 72.6%).[8,10,16,19–21] Without definite conclusions, the potential increase in morbidity with END is important to consider, especially in the setting of a lack of clear benefit to OS.

This study has several limitations that should be considered. Most of the included studies were retrospective, and they had notable heterogeneity between them, making it difficult to extract the required data and to perform the meta-analysis. As a result, the 2-year OS, DFS, and postoperative fistula rates were too heterogeneous to make meaningful conclusions. Additionally, risk factors, including T stage, recurrent laryngeal subsite, laterality of neck dissection, presence of primary neck irradiation, could not be investigated due to the significant heterogeneity and the small number of included studies. Another limitation was the inability to separate some of the individual data between larynx and nonlarynx tumor subsites or between END and observed. As a result, those studies could not be included in the meta-analysis. Additionally, this review includes studies over many years (1999–2019), during which there have been significant improvements in diagnostic techniques, specifically with positron emission tomography/computed tomography (PET/CT).[31] Prior to the improved diagnostic accuracy of PET/CT, some patients with presalvage cN+ necks may have been incorrectly categorized as cN0. Despite these limitations, to our knowledge, this is the first systematic review and meta-analysis investigating the outcomes and complications of END versus neck observation during salvage laryngectomies. Future prospective studies are needed to further clarify these results.

CONCLUSION

In this systematic review and meta-analysis, we found that cN0 salvage laryngectomy patients undergoing END had an occult nodal positivity rate of 11%. There were no statistically significant differences in 5-year OS between patients undergoing END versus observation.

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