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Elective neck dissection for salvage laryngectomy: A systematic review and meta-analysis

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ABSTRACT

Objective: Elective neck dissection (END) for salvage laryngectomy remains controversial due to variability in reported occult nodal metastasis rates and postoperative complications. We performed a meta-analysis to examine the role of END for treatment of the clinically N0 (cN0) neck in the salvage setting.

Methods: A PubMed search, without limit on years searched, was conducted for English language articles. Additional sources were found by reviewing bibliographies of pertinent articles. Studies had to include END data for salvage laryngectomy for locally recurrent squamous cell carcinoma of the larynx with clinically negative regional metastasis. For patients who underwent END, pathological node status had to be reported. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) recommendations were followed. Data were pooled using a random-effects model.

Results: Nineteen studies were included in the analysis. Within the END group, 31% were supraglottic, 61% were glottic, 6% were transglottic, and 1% were subglottic. The pooled rate of occult nodal metastasis was 14% (95% CI = 0.11–0.17) for all subsites. In subsite-specific analyses, occult nodal metastasis rates were 24% for supraglottic, 9% for glottic, and 17% for transglottic recurrences. Occult nodal metastasis was higher in recurrent T3/4 tumors (21%) compared to recurrent T1/2 tumors (9%) (relative risk (RR) = 2.17, 95% CI = 1.23–3.63, p = 0.003). The RR of postoperative complications with END compared to observation was 1.72 (95% CI = 0.96–3.10, p = 0.07).

Conclusions: The highest rates of occult nodal metastasis are associated with supraglottic recurrence and recurrent T3/T4 tumors. These data should be considered when deciding whether to perform END for salvage laryngectomy.

Introduction

Over the past twenty years, treatment paradigms for locally advanced squamous cell carcinoma of the larynx have undergone a significant evolution, in large part due to the VA Larynx and RTOG trials of the 1990s and early 2000s [1,2]. Because of these landmark studies, there was a shift from primary laryngectomy to organ preservation therapy for advanced laryngeal cancers. However, a significant subset of patients with persistent or recurrent disease after nonsurgical treatment will require a surgical approach, namely salvage laryngectomy.

In cases of locally recurrent/persistent squamous cell carcinoma of the larynx, there is continued debate over the role of elective neck dissection (END) for clinically negative nodal metastasis (cN0), defined as nodal disease that cannot be detected by clinical exam or radiographic studies. Many studies have sought to answer this important question over the past 2 decades with mixed results [3–21]. Some authors advocate for END, while others argue that END should only be pursued in select cases [5,6,9,11,17–19]. Still, there are others who do not support END, due to the morbidity of neck dissection-related complications, especially in previously irradiated patients [4,6,13,21].

There is a paucity of high level evidence on this topic, and the majority of the prior studies have been limited to retrospective studies with limited patient numbers. Thus, this topic deserves further evaluation given the potential therapeutic and/or prognostic implications

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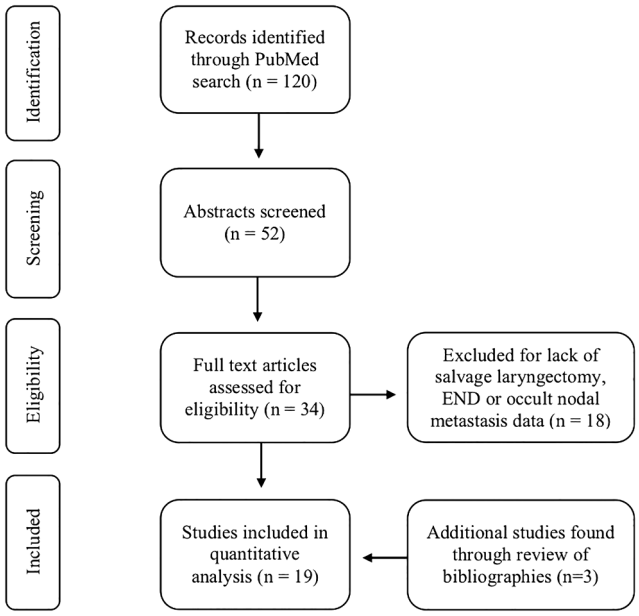

Fig. 1. Flowchart of study inclusion.

to performing END in the context of salvage laryngectomy. Here, we present a systematic review and meta-analysis of studies published on this topic to better understand the role of END in these patients.

Methods and materials

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.

Eligibility criteria

We included studies involving patients who underwent END with salvage laryngectomy for locally recurrent squamous cell carcinoma of the larynx with clinically negative regional staging (cN0). Unilateral and bilateral END were eligible for inclusion. Of the cN0 patients who underwent END, the rate of pathological node positivity (pN+) had to be reported. There was no restriction on type of primary treatment received or nodal status at the time of primary treatment. Studies had to be published in the English language. All study designs were included.

Database search

PubMed was used to search for articles using the following Boolean operators: ((neck dissection) OR (nodal dissection)) AND (salvage laryngectomy). There was no limit on years considered. References within each study were explored to identify other studies. The date last searched was October 25, 2018.

Data collection

Of the 120 articles that were found with the above stated search using English language only, 52 abstracts were reviewed (Fig. 1). If abstracts appeared relevant, the full text article was reviewed. Of the 34 articles assessed, 16 met all inclusion criteria and were included in the analysis. Three additional studies that were found through review of bibliographies met inclusion criteria and were included in the analysis. Variables assessed included number of patients in the eligible studies, occult nodal metastasis, subsite/T stage of recurrence, regional recurrence, disease free survival (DFS), overall survival (OS), and postoperative complications.

Statistical analysis

We performed a meta-analysis of proportions and relative risks (RR) using Stata 13 (StataCorp LP, College Station, Texas). Heterogeneity was assessed using Cochran's Q, Tau^2 and I^2. The random effects model was used to pool proportions and RRs from included studies.

Results

Our literature search revealed 120 potentially relevant articles. A total of fifty-nine manuscripts were reviewed, and 19 were included in the study (Table 1). Three of the 19 studies were found through review of bibliographies [7,17,21]. Aside from one study published in 1999, all other studies ranged from 2005 until 2018 [3–15,17–22]. One study was prospective in design, while all other studies were retrospective [18].

A total of 922 patients were managed with END and 276 patients were observed following salvage laryngectomy. Ninety-eight percent of patients were previously treated with primary radiation therapy with or without chemotherapy. The rate of occult nodal metastasis reported in the included studies ranged from 0% to 30%. The pooled rate of occult nodal metastasis was 14% (95% CI = 0.11–0.17) (Fig. 2).

Recurrence subsite data was available for 839 patients in 16 out of 19 studies, of which 31% were supraglottic, 61% were glottic, 6% were transglottic, and 1% were subglottic [3–7,9,11,15,17–19,22]. Meta-analysis revealed a pooled rate of occult nodal metastasis based on subsite recurrence of 24% for supraglottic (95% CI = 0.15–0.34), 9% for glottic (95% CI = 0.06–0.13), and 17% for transglottic (95% CI = 0.04–0.35) (Fig. 3). The rate of subglottic recurrence could not be calculated due to the limited number of studies. The supraglottic subsite had a significantly higher likelihood of occult nodal metastasis when compared to the glottic subsite (RR = 2.78, 95% CI = 1.76–4.08, $p < 0.001$).

Recurrent T stage data was available for 451 patients in 6 out of 19 studies [5,9,11,18,19,22]. Patients were stratified into rT1/2 (n = 179) and rT3/4 (n = 272). The rate of occult nodal metastasis was 9% for rT1/2 tumors vs 21% for rT3/4 tumors. The pooled RR of occult nodal metastasis of T3/4 compared to T1/2 was 2.17 (95% CI = 1.295–3.625) (Fig. 4). Thus, recurrent T3/4 tumors have almost double the risk of occult nodal metastasis compared to recurrent T1/2 ($p = 0.003$).

Among 9 studies reporting regional recurrence rates after END in salvage laryngectomy, the rate of regional recurrence ranged from 0% to 9% [4,6–10,12,17,18,20,21]. Regional recurrence rates in the observation group ranged from 0% to 15% [4,6–10,21]. No study found a statistically significant difference in regional recurrence between END and observation groups. No study reported a statistically significant survival difference in disease free survival (DFS) or overall survival (OS) between the two groups [6–8,10,19,22].

Regarding postoperative complications related to END, we collected data on fistula formation, wound infection, wound dehiscence, chyle leak, hematoma, revision procedure, flap failure, medical complications, carotid blowout, and total complications. Data was available for 370 patients in 5 out of 19 studies (Table 2) [4,6,8,21,22]. Of these patients, 195 patients underwent END and 175 patients were observed. Overall, there were 92 complications in 181 patients who underwent END (51%) vs 56 complications in 164 patients (34%) who were observed. There was an additional study that was not included in the

Table 1
Summary of studies.

	Author	Years of study	END (n)	Observation (n)	Follow up (months)	Subsites	Rate of occult nodal metastasis	Regional recurrence	Overall survival	Disease free survival
1	Amit et al.	1991–2011	42	0	–	Supraglottic, glottic	19%	–	–	–
2	Basheeth et al.	1996–2011	34	7	24	Supraglottic, glottic, transglottic, subglottic	6%	0% for both	–	–
3	Birkeland et al.	1997–2014	203	0	–	Supraglottic glottic, subglottic	17%	–	–	–
4	Bohannan et al.	2001–2007	38	33	18	Supraglottic, glottic	8%	7.9% END vs 15% observation (p = 0.5)	52% END vs 48% observation at 2 yrs (p = 0.48)	–
5	Dagan et al.*	1965–2006	26	8	51	Supraglottic, glottic	12%	0% for both	45% END vs 56% observation at 5 yrs (p = 0.21)**	–
6	Deganello et al.	1995–2005	7	97	45	Glottic	0%	0% END vs 3.1% observation (p = 1)	43% END vs 62% observation at end of study (p = 0.7)	
7	Farrag et al.	1988–2005	34	17	36	Supraglottic, glottic, subglottic	12%	0% for both	–	–
8	Freiser et al.	2000–2012	98	27	24	Supraglottic, glottic, transglottic	10%	–	53% END vs 53% observation at 5 yrs (p = 0.72)	56% END vs 59% observation at 2 yrs (p = 0.76)
9	Hilly et al.	1994–2011	48	39	40	Supraglottic, glottic	13%	8.3% END vs 7.7% observation	No rates reported (p = 0.12)	No rates reported (p = 0.08)
10	Koss et al.	1997–2011	53	16	16	Supraglottic, glottic, transglottic, subglottic	28%	–	No rates reported (p = 0.08)	–
11	Pennings et al.	1990–2000	21	0	60	Supraglottic	19%	5% END	–	–
12	Pennings et al.	1990–2000	77	0	58	Glottic	13%	9% END		
13	Pezier et al.	2003–2010	28	0	18	Unknown	7%	–	–	–
14	Riviere et al.	2008–2015	41	0	28	Unknown	7%	–	–	–
15	Rosko et al.	2002–2014	46	0	–	Supraglottic, glottic, subglottic	26%	–	–	–
16	Solares et al.*	1997–2003	37	0	23	Supraglottic, glottic	24%	0% END	60% END at 5 yrs**	–
17	Wax et al.***	1991–1997	34	0	48	Supraglottic, glottic	18%	0% END	–	–
18	Yao et al.	1970–1998	41	22	>54	Supraglottic, glottic	12%	–	58% END vs 40% observation at 5 yrs (glottic, p = 0.87), 50% END vs 33% observation at 5 yrs (supraglottic, p = 0.49)	–
19	Yirmibesoglu et al.*	1997–2010	14	11	33	Unknown	14%	0% END vs 0% obs	No rates reported (p = 0.40)**	–

* Study found through review of bibliographies.
** Other sites included in survival analysis (e.g., oral cavity, oropharynx, and/or hypopharynx).
*** Wax et al. was the only prospective study. All other studies were retrospective.

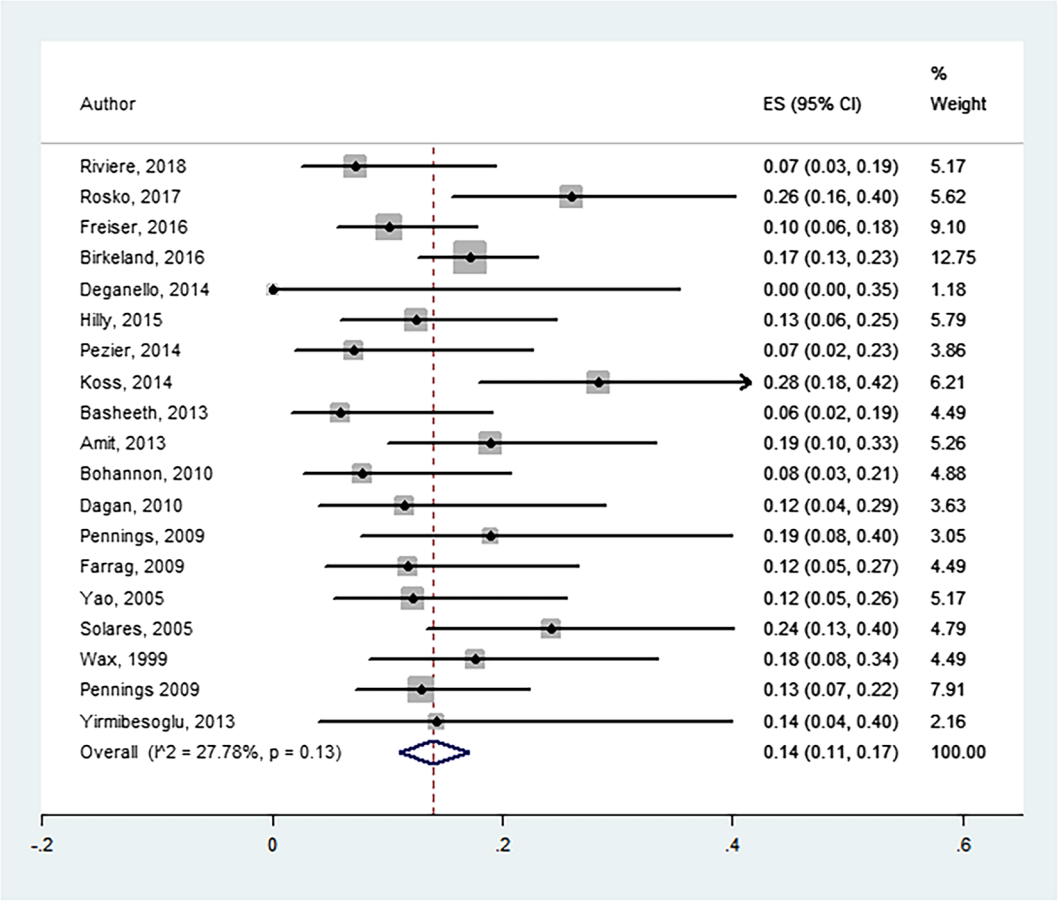

Fig. 2. Rate of overall occult nodal metastasis for total laryngectomy patients. The pooled rate of occult nodal metastasis across all studies was 0.14 or 14% (95% CI = 0.11–0.17, p < 0.01). Heterogeneity measures: Cochran's Q = 24.92, p = 0.13, I-squared = 27.78% and Tau-squared = 0.01.

analysis because it did not list specific complications and only stated that greater than 50% of their 28 END patients experienced postoperative complications [13]. The pooled relative risk of postoperative complications with END compared to observation was 1.72 (p = 0.07, 95% CI = 0.96–3.10) (Fig. 5).

Discussion

The role of END for cN0 in the context of salvage laryngectomy for squamous cell carcinoma of the larynx remains controversial. The results of our meta-analysis reveal an overall occult nodal metastasis rate of 14%, which falls below the historically quoted rate of greater than 20% reported by Weiss et al. [23]. However, subgroup analysis revealed a higher rate of occult nodal metastasis in patients with supraglottic and transglottic recurrences as well as recurrent T3 and T4 tumors.

Subsite analysis of occult nodal metastasis rates revealed higher rates in supraglottic (24%) and transglottic (17%) recurrences. Although studies have shown higher rates of occult nodal metastasis for primary supraglottic carcinomas, this analysis shows this to be true in the recurrent supraglottic setting too [24,25]. Several authors have recommended END for supraglottic recurrence based on higher rates of occult metastasis compared to glottic recurrence with most studies reporting rates greater than 20% and extending as high as 60% for the supraglottic subsite [5,11,18,19]. In the largest study of 203 patients who were treated with END, Birkeland et al. found a significantly higher pN+ with supraglottic recurrence compared to glottic recurrence (28% vs 10%, respectively) [5]. Koss et al. also found a significantly higher rate of occult nodal metastasis in supraglottic (60% vs 9% in glottic) recurrences and found the pN+ in transglottic recurrences (30%) to be elevated too [11]. The authors recommended END for both subsites [11].

Many of the studies that advocated for END in supraglottic recurrences also argued for END in the setting of T3/4 tumors [5,10,18,19]. Birkeland et al. found that T4 status was significantly associated with increased pN+ in both univariate (34% rate of occult nodal metastasis) and bivariate analyses when paired with the supraglottic subsite (50% rate of occult nodal metastasis) [5]. Interestingly, Hilly et al. found a significant difference in DFS and OS of patients with rT3/4 tumors when comparing END to observation [10]. DFS at 5 years was >60% for the END group and <20% for the observation group. Similar findings were found in overall survival [10]. This survival benefit was not seen in rT1/2 tumors. Among all studies, this was the only study that reported a survival benefit to END, although there was no benefit when the entire END cohort was compared to observation.

The lack of survival benefit reported by other studies should be interpreted with caution when deciding whether to perform an END [6–8,10,19,21,22]. In addition to all studies being retrospective, there was significant bias in selecting those patients who underwent END vs observation. Freiser et al. reported a significant difference in recurrent

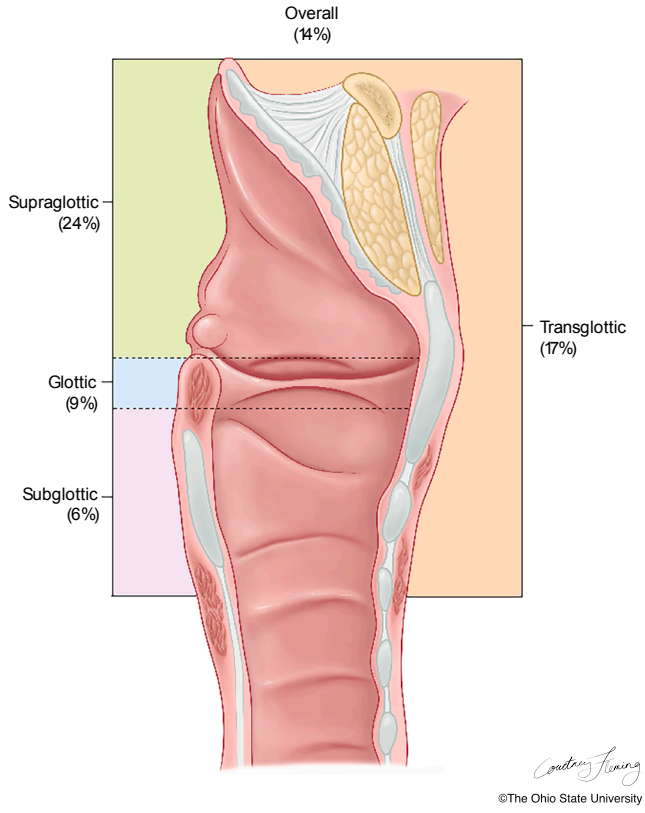

Fig. 3. Occult nodal metastasis by subsite recurrence. The pooled rate of occult nodal metastasis for supraglottic recurrence was 24% (95% CI = 0.15–0.34), $p < 0.01$. Heterogeneity: Cochran's Q = 18.32, p = 0.05, I-squared = 45.40% and Tau-squared = 0.05. The pooled rate of occult nodal metastasis for glottic recurrence was 9% (95% CI = 0.06–0.13), $p < 0.01$. Heterogeneity: Cochran's Q = 4.98, p = 0.93, I-squared = 0% and Tau-squared = 0. The pooled rate of occult nodal metastasis for transglottic recurrence was 17% (95% CI = 0.04–0.35), $p < 0.01$. Heterogeneity: Cochran's Q = 3.72, p = 0.16, I-squared = 46.19% and Tau-squared = 0.05. *The pooled rate of occult nodal metastasis for subglottic recurrence was 6%, which did not reach formal statistical significance.

T stage between the two groups (p = 0.009) with >40% of the observation group made up of rT1/2 tumors, while <20% of the END group consisted of rT1/2 tumors [22]. Despite having the largest number of patients in their survival analysis amongst all studies that reported on survival, they did not find a benefit in DFS or OS, however, the disproportionately high number of rT3/4 tumors in the END group likely confounds these findings [22]. The remaining studies consisted of much smaller numbers of patients and were likely underpowered to detect a survival benefit [6–8,10,19,21]. Therefore, whether or not END provides a survival benefit likely remains unclear due to limitations of the current data.

Among the studies reviewed, the rate of occult nodal metastasis varied greatly from 0% to 30% [3–22]. This heterogeneity may be explained by the evolution of organ preservation therapy over the past few decades. Despite nearly all included studies being published in 2005 and onward, most of these studies started their retrospective review in the 1990s and continued into the 2000s. Ninety-eight percent of patients in this study were treated primarily with radiotherapy with or without chemotherapy, but the studies did not comment on the type of chemoradiotherapy delivered. There have been significant advances in radiotherapy modalities including hyperfractionation and intensity modulated radiotherapy (IMRT) in an effort to improve local control while decreasing surrounding tissue toxicity [26]. Additionally, contributions from the VA and RTOG 91-11 trials have changed the role of chemotherapy in the treatment of advanced primary laryngeal cancer [1,2]. The rise of PET-CT imaging to detect subclinical nodal metastasis in locally recurrent laryngeal cancer, although controversial, may also explain the range of occult nodal metastasis rates [11,15,19,27]. Another factor that is likely playing a role in the wide range is the number of studies with small study populations (N < 30–40 patients) that were treated with END [4,6–9,12,13,17,18]. While a few studies reported occult nodal metastasis rates <10%, Dagan et al. had the fewest number of patients treated with END (N = 7) amongst all studies and reported no cases of pN+ in this group [7].

Perhaps most importantly, there is significant variation in the distribution of subsites represented in these studies [6,11,22,28]. For example, Bohannan et al. reported one of the lowest occult nodal metastasis rates of 8% (3 out of 38 patients), yet 89% (34 out of 38 patients) of recurrences were at the glottis [6]. Similarly, Feiser et al. reported an overall occult nodal metastasis rate of 10%, but 9 out of 10 recurrences came from the glottis, which had the highest representation (68% of the study cohort) [22]. In contrast, Koss et al. reported the highest rate of occult nodal metastasis at 28%, but a relatively low number of glottic recurrences were represented (21%) and the majority of recurrences came from transglottic and supraglottic subsites [11].

The justification for performing END has often been based on the occult nodal metastasis rate of greater than 20%. This cut off is based on the 1994 decision analysis model presented by Weiss et al. [23]. Their mathematical model was designed to find the optimal threshold for primary treatment of the cN0 neck for all head and neck cancers by examining three current management strategies of the neck: END, radiation, and observation. Their results suggested that END or irradiation should be performed when the rate of occult nodal metastasis was 20% or greater [23]. In 2013, Hilly et al. developed a decision analysis model to specifically determine the need for END in the cN0 neck of patients with laryngeal cancer who had failed organ preservation therapy [29]. Their decision model was based on two management strategies of the neck: END and observation. In their model, the mortality rate of END vs observation groups was similar but there was a much lower rate of complications in the observation group. Additionally, their results revealed that neck dissection should only be performed if the probability of cure was greater than 82%. Because this cut off is higher than historical rates of cure ranging from 50 to 65% after salvage laryngectomy, they used reported rates of cure to suggest that END be performed only if the rate of regional recurrence is greater than 20% [6,18,28,29]. This is an identical rate to that reported by Weiss et al. if the assumption that the rate of occult nodal metastasis is comparable to regional recurrence. Ultimately, Hilly et al. did not recommended END because of regional recurrence rates under 8% reported in the literature [29].

Although no study has shown a survival benefit in the entire END cohort vs observation in the setting of salvage laryngectomy, there is prognostic value in determining pathologic nodal status. Feiser et al. showed dramatic differences in DFS and OS between pN+ and negative nodal pathology (pN0). DFS at 2 years was doubled in patients with pN0 status (60%) compared to pN+ status (30%) [22]. OS at 2 years was also significantly increased in patients with pN0 status (75%) compared to pN+ status (50%) [22].

When considering whether to perform END in the setting of salvage laryngectomy, morbidity of the procedure is strongly considered in the decision making process [4,6,11,21,22,30]. Comparing the overall rate of wound complications between END and observation groups, our analysis did not show a statistically significant increase in the risk of

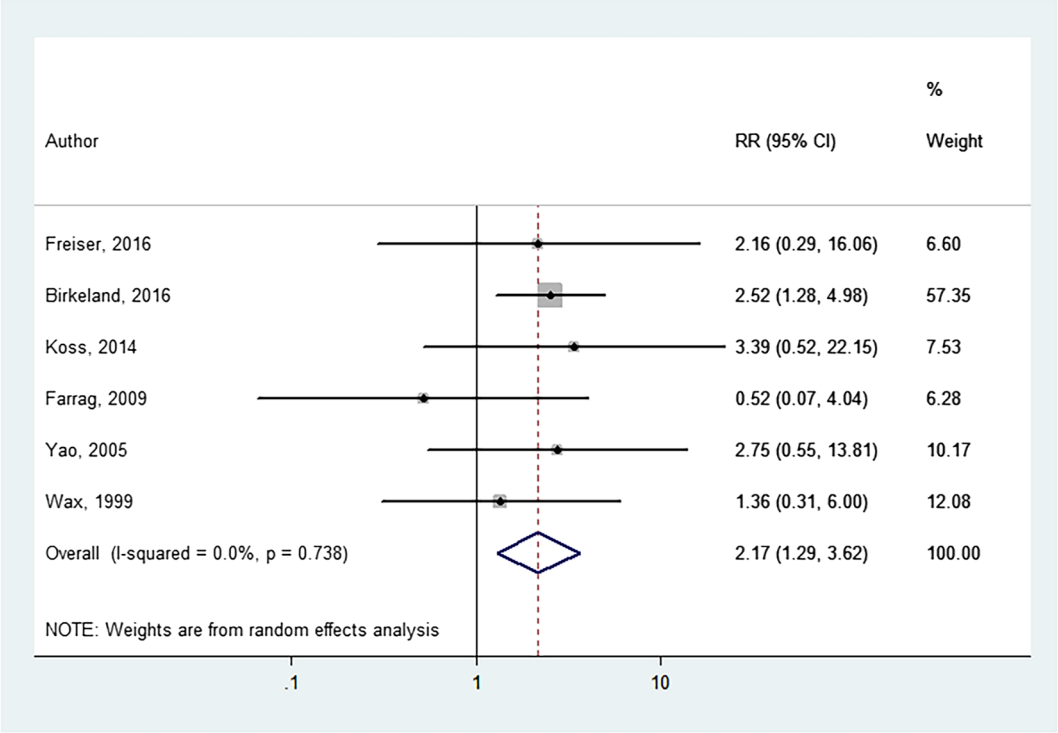

Fig. 4. Relative risk of occult nodal metastasis between rT3/4 vs rT1/2. Pooled relative risk of occult nodal metastasis in T3/T4 compared to T1/T2 was 2.166 (95% CI = 1.295–3.625, p = 0.003). Heterogeneity: Cochran's Q = 2.76, p = 0.738, I-squared = 0%% and Tau-squared = 0.

Table 2
Comparison of wound complications in END vs observation. Data was collected from 5 studies: Basheeth et al., Bohannon et al., Deganello et al., Freiser et al., Yirmibesoglu et al. **Heterogeneity measures: Cochran's Q = 10.86, p = 0.028, I-squared = 63.2% and Tau-squared = 0.2510.

	END (N = 195)	Observation (N = 175)	Relative risk
Total complications	97 (50%)	57 (33%)	1.72 (p = 0.07)**
Fistula formation	57 (29%)	28 (16%)	
Revision procedure	24 (13%)	12 (7%)	
Wound dehiscence	19 (10%)	4 (2%)	
Wound infection	16 (8%)	5 (3%)	
Hematoma	12 (6%)	5 (3%)	
Flap failure	4 (2%)	1 (1%)	
Carotid blowout	3 (2%)	1 (1%)	
Chyle leak	2 (1%)	0 (0%)	
Medical complications	14 (7%)	11 (6%)	

complications in the END group (p = 0.07). Among the five studies reporting data, results were mixed on whether unilateral or bilateral neck dissection increases the risk of complications [4,6,8,22]. Feiser et al. did not find that END increased the risk of postoperative complications (p = 0.56), including in the case of bilateral neck dissections [22]. While Basheeth et. al. found that unilateral neck dissection had a similar rate of complications (30%) compared to observation (29%), there was a statistically significant increase in rate of complications with bilateral neck dissection (67%) [4]. Bohannon et al. reported a much higher rate of complications, particularly in fistula formation, in their END group (p = 0.04) [6]. However, they utilized free flap reconstruction (18 out of 38 patients) far more than the other two studies (7 out of 136 patients), which preferred pectoralis major reconstruction or primary closure. Neck dissection has been associated with increased fistula formation in the setting of free flap reconstruction [6,31]. Although our meta-analysis did not show an increased risk of complications between the two groups, there was a higher percentage of complications in the END group compared to observation (50% vs 33%). If a greater number of free flaps were used in the setting of END for salvage laryngectomy, it is possible that neck dissection would increase the risk of postoperative complications.

There are some limitations to this study. First, our analysis was based primarily on retrospective studies with relatively small numbers of patients given the lack of prospective and randomized controlled trials in the literature to date. Our results are only as reliable as the data collected and reported by those studies. Second, it is possible that our review of the literature through a single database (PubMed) missed additional relevant studies. However, our review of the literature yielded 19 studies, which exceeded the number reported by other authors including a recent systematic review and meta-analysis [16]. Regarding unilateral vs bilateral neck dissection, we were unable to report on rates of occult nodal metastasis specific to unilateral vs bilateral neck dissections due to a lack of specificity in most studies [3,4,12,14,21,22]. Some studies report no occult nodal metastasis in the contralateral neck while other studies did not comment on differences in laterality [3,18]. Future studies should include this data in order to determine if unilateral END is as efficacious as bilateral END, while decreasing the risk of complications, as reported by Basheeth et al. [4]. These limitations could be addressed with a well-designed prospective and/or randomized controlled trial comparing END to observation of the neck in cN0 salvage laryngectomy.

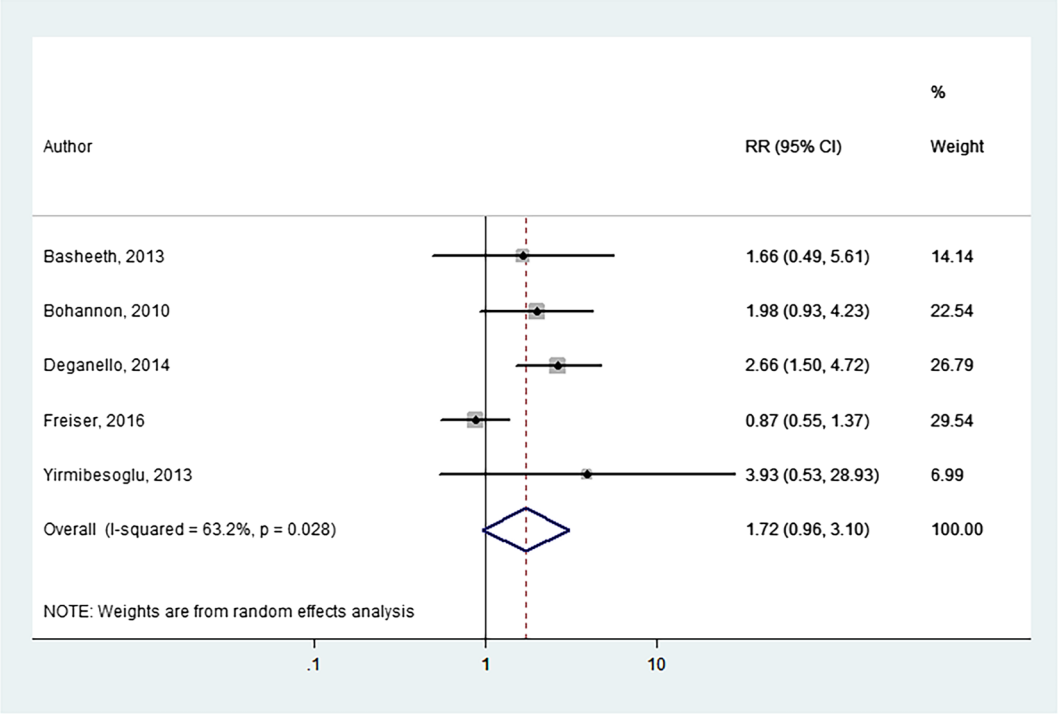

Fig. 5. Relative risk of postoperative complications between END and observation. The pooled relative risk of having complications in END compared to observation was 1.72 (95% CI = 0.96–3.10) with p = 0.07. Therefore, the risk of total complications was the same in both groups. Heterogeneity measures: Cochran's Q = 10.86, p = 0.028, I-squared = 63.2% and Tau-squared = 0.2510.

Conclusion

Outcomes following END in cN0 salvage laryngectomy patients are highly heterogeneous in the literature. Prior studies are compromised by heterogeneity in the analyzed patient cohort due to variable proportions of subsite cohorts and long periods of time over which changes in primary organ preservation therapy have occurred. Our meta-analysis reveals an overall occult nodal metastasis rate of 14%, with higher rates of occult nodes in the supraglottic subsite (24%) and recurrent T3/4 tumors (21%). These data should be considered when deciding whether to perform END with salvage laryngectomy.

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Declaration of Competing Interest

None declared.

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