



Elective Paratracheal Lymph Node Dissection in Salvage Laryngectomy

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ABSTRACT

Background. Indications for and efficacy of paratracheal nodal dissection (PTND) in patients undergoing laryngectomy (salvage) for persistent or recurrent laryngeal squamous cell carcinoma are not well-defined.

Methods. A retrospective cohort study was performed for patients undergoing salvage laryngectomy with clinically and radiographically negative neck disease between 1998 and 2015 ($n = 210$). Univariate and multivariate Cox regression analyses were performed.

Results. PTND was performed on 77/210 patients (36%). The PTND cohort had a greater proportion of advanced T classification (rT3/rT4) tumors (78%) than subjects without PTND (55%; $p = 0.001$). There was a 14% rate of occult nodal metastases in the paratracheal basin; of these, 55% did not have pathologic lateral neck disease. Multivariate analysis controlling for tumor site, tumor stage, and pathologic lateral neck disease demonstrated that PTND was associated with improved overall survival [OS] ($p = 0.03$; hazard ratio [HR] 0.60, 95% confidence interval [CI] 0.38–0.96), disease-free survival [DFS] ($p = 0.03$; HR 0.55, 95% CI 0.31–0.96), and distant DFS survival ($p = 0.01$; HR 0.29, 95% CI 0.11–0.77). The rate of hypocalcemia did not differ between subjects who

underwent bilateral PTND, unilateral PTND, or no PTND ($p = 0.19$ at discharge, $p = 0.17$ at last follow-up).

Conclusions. PTND at the time of salvage laryngectomy was more common in patients with rT3/rT4 tumors and was associated with improved OS and DFS, with no effect on hypocalcemia. In patients undergoing PTND, the finding of occult paratracheal metastases was often independent of lateral neck metastases.

Laryngeal cancer is associated with significant morbidity and mortality.¹ With the establishment of larynx-preserving treatment approaches,^{2–5} morbidity from laryngeal squamous cell carcinoma (LSCC) treatment has decreased over the last two decades. Unfortunately, a significant number of patients treated with larynx-preserving radiation with or without chemotherapy experience persistent or recurrent disease and require secondary (salvage) total laryngectomy. Locoregional recurrence for T4 and stage IV tumors was estimated at 56% and 44%, respectively, in the landmark Veterans Affairs Laryngeal Cancer study.²

Current management for persistent or recurrent disease after larynx-preserving treatment is salvage surgery.^{6–8} However, there are few data informing when to perform an elective neck dissection for an N0 neck in the setting of persistent or recurrent LSCC, and there are even less data regarding the elective treatment of the paratracheal nodal basin.^{9–15} Paratracheal nodal dissection (PTND), or otherwise called central neck dissection, is not without morbidity. Temporary and permanent hypocalcemia is the

most common risk, which occurs in approximately 25–45% and 5–20% of patients after central neck dissection, respectively.^{16–19}

Indications with regard to PTND have varied at our institution, which presented an opportunity to examine whether this procedure impacts patient outcomes. Therefore, a study was undertaken to determine the rate of paratracheal metastases and any survival advantage associated with elective PTND in patients undergoing salvage laryngectomy.

METHODS

A single-institution retrospective cohort study was performed. Clinicopathologic data were gathered for patients who underwent salvage laryngectomy with curative intent between 1998 and 2015 for recurrent or persistent LSCC after failed radiation with or without chemotherapy. Epidemiologic data included patient demographics, initial cancer characteristics, initial cancer treatment, and recurrent cancer clinical characteristics. Postoperative ionized calcium values (at 1 week and 30 days) and calcium supplementation data (preoperatively, at discharge, and at last clinical encounter) were also collected. Subjects were considered to have new hypocalcemia at the time of discharge if they were not taking any calcium supplementation preoperatively, were discharged with calcium supplementation, and had an ionized calcium value < 1.12 mmol/L during their hospitalization. Patients were staged according to the 7th edition of the American Joint Committee on Cancer staging system.²⁰ Death was verified via the electronic medical record and the social security death index.

The presence or absence of clinically positive nodes at the time of tumor recurrence (cN+ and cN0, respectively) was determined by clinical examination and by preoperative imaging, and only patients with no evidence of clinical nodal disease (cN0) at the time of recurrence were included. Elective paratracheal node dissection was performed as previously described and at the surgeon's discretion.²¹

Primary outcome measures included overall survival (OS; time from salvage surgery to death from any cause), disease-specific survival (DSS; time from salvage surgery to death from recurrent/persistent LSCC), disease-free survival (DFS; time from salvage surgery to LSCC recurrence), locoregional DFS (time from salvage surgery to locoregional recurrence), and distant DFS (time from salvage surgery to distant recurrence). Survival months were tabulated until the date of last follow-up and at 5 years after salvage surgery using the Kaplan–Meier method (median follow-up time 72 months).

Descriptive statistics were obtained for the patient cohort. Two-sided *t*-tests, Wilcoxon rank-sum test, and Fisher's exact tests were applied where indicated. Cox regression analysis was performed for OS, DSS, DFS, locoregional DFS, and distant DFS. Wald multivariate Cox regression analysis was performed to control for other tumor stage, tumor site, and lateral neck disease as these have been shown as predictors of survival in salvage laryngectomy.²² Statistical analyses were conducted using SPSS version 25 (IBM Corporation, Armonk, NY, USA) using two-sided statistical tests ($p < 0.05$). This study was approved by the University of Michigan Institutional Review Board for Human Experimentation (HUM00081554).

RESULTS

Clinical Cohort

Overall, 210 subjects did not have evidence of clinical nodal disease (cN0) at the time of recurrence. Of these subjects, only 12 patients (6%) did not have a neck dissection, and 17 patients (8%) underwent a unilateral neck dissection, 181 patients (86%) underwent a bilateral lateral neck dissection, and 77 (37%) underwent PTND. The majority of PTNDs were bilateral ($n = 59$, 77%). All patients who underwent PTND also underwent a lateral neck dissection.

There was no significant difference in sex, tobacco use, initial tumor subsite or stage, or primary treatment (radiation with or without chemotherapy) for patients who underwent a PTND versus those who did not in the cN0 cohort (Table 1). There was a greater proportion of higher recurrent T-classification tumors (rT3/rT4) in the PTND cohort (78%) than in subjects without PTND (55%; $p = 0.001$). Both supraglottic and glottic cancers were similar in their likelihood to be treated with bilateral PTND ($p = 0.69$).

Paratracheal Disease

Of the 77 subjects who underwent PTND, 11 subjects (5 with supraglottic recurrences, 5 with glottic recurrences, and 1 with a subglottic recurrence) had pathologic evidence of metastatic cancer in the paratracheal nodal basin, none of which was detected by clinical examination or preoperative imaging (Table 2). Paratracheal node disease was associated with pathologic disease in the lateral neck ($p = 0.005$). Six of the patients with positive paratracheal nodes (55%) did not have any positive nodes identified in other lymph node levels of the neck.

TABLE 1 Summary statistics for salvage laryngectomy subjects without clinical nodal positivity on recurrence [$n = 210$]

	Paratracheal nodal basin not dissected [$n = 133$]	Paratracheal basin dissected [$n = 77$]	p value ^a
Mean age at salvage, years	62.1 ± 10.2	62.1 ± 9.4	0.96
Sex			
Male [$n = 176$]	109 (82)	67 (87)	0.44
Female [$n = 34$]	24 (18)	10 (13)	
Tobacco			
Current [$n = 76$]	51 (38)	25 (33)	0.21
Former [$n = 130$]	78 (59)	52 (68)	
Never [$n = 4$]	4 (3)	0 (0)	
Subsite			
Supraglottis [$n = 87$]	56 (42)	31 (40)	0.69
Glottis [$n = 120$]	76 (57)	44 (57)	
Subglottis [$n = 3$]	1 (1)	2 (3)	
Median time to local recurrence, months	14	11	0.53
Primary treatment			
ChemoRT [$n = 89$]	57 (43)	32 (42)	0.89
RT [$n = 121$]	76 (57)	45 (59)	
Initial T stage			
T1 [$n = 47$]	29 (22)	18 (23)	0.93
T2 [$n = 66$]	41 (31)	25 (33)	
T3 [$n = 58$]	39 (29)	19 (25)	
T4 [$n = 22$]	14 (11)	8 (10)	
Tx [$n = 17$]	10 (8)	7 (9)	
Initial nodal status			
N0 [$n = 168$]	108 (81)	60 (78)	0.83
N+ [$n = 26$]	16 (12)	10 (13)	
Nx [$n = 16$]	9 (7)	7 (9)	
Recurrent pT stage			
I [$n = 7$]	5 (4)	2 (3)	0.001
II [$n = 70$]	55 (41)	15 (20)	
III [$n = 56$]	36 (27)	20 (26)	
IV [$n = 77$]	37 (28)	40 (52)	

Demographic and treatment variables were compared based on whether the paratracheal nodal basin was dissected

Data are expressed as n (%) unless otherwise specified

RT radiotherapy

^aBold values indicate statistical significance ($p < 0.05$)

Postoperative Calcium Levels

The rate of new onset hypocalcemia at discharge was not statistically different between subjects who underwent bilateral PTND ($n = 9/52$, 17%; missing = 7), unilateral PTND ($n = 1/16$, 6%; missing = 2), or no PTND ($n = 10/124$, 8%; missing = 9) [$p = 0.19$]. Similarly, a long-term need for calcium supplementation did not statistically differ for subjects who underwent bilateral PTND ($n = 5/43$, 12%; missing = 16), unilateral PTND ($n = 1/10$, 10%; missing = 8), or no PTND ($n = 4/91$, 4%; missing = 42) [$p = 0.17$].

Multivariate Analysis of Survival

Previous work has identified tumor stage, tumor site, and pathologically positive (pN+) lateral neck disease as predictors for survival in patients undergoing salvage laryngectomy.²² We therefore performed multivariate analysis to confirm the survival advantage of paratracheal node dissection independent of these variables. Controlling for tumor stage, tumor site, and pathologically positive lateral neck disease, PTND in cN0 subjects was associated with improved OS ($p = 0.03$; HR 0.60, 95% CI 0.38–0.96),

TABLE 2 Characteristics for tumors [$n = 11$] with associated metastases to the paratracheal nodal basin

Tumor subsite	Initial tumor laterality	Recurrent tumor laterality	Recurrent tumor overall stage	Recurrent tumor T stage	Laterality and number of paratracheal metastases (positive/removed)	Levels of other nodal metastases
Supraglottis	L	L	IV	4	L: 1/6 R: 1/7	L: none R: none
Supraglottis	L	L	IV	4	L: 1/8 R: 0/17	L: none R: none
Supraglottis	L	L	IV	4	L: 1/1 R: ND	L: none R: ND
Glottis	R	R	IV	4	L: 0/3 R: 1/2	L: none R: none
Glottis	L	L	IV	3	L: 0/1 R: 1/7	L: none R: none
Glottis	R	R	III	3	L: ND R: 1/6	L: ND R: none
Supraglottis	R	R	IV	4	L: ND R: 2/8	L: none R: III
Supraglottis	L	R	IV	4	L: 4/8 R: 5/9	L: II, III R: II, III, IV
Glottis	L	L	IV	4	L: 1/1 R: ND	L: IV R: none
Glottis	L	L	IV	4	L: 1/14 R: 3/17	L: IV R: IV
Subglottis	Unknown	L	IV	4	L: ND R: 1/2	L: III R: none

L left, R right, ND not dissected

DFS ($p = 0.03$; HR 0.55, 95% CI 0.31–0.96), and distant DFS ($p = 0.01$; HR 0.29, 95% CI 0.11–0.77) (Fig. 1).

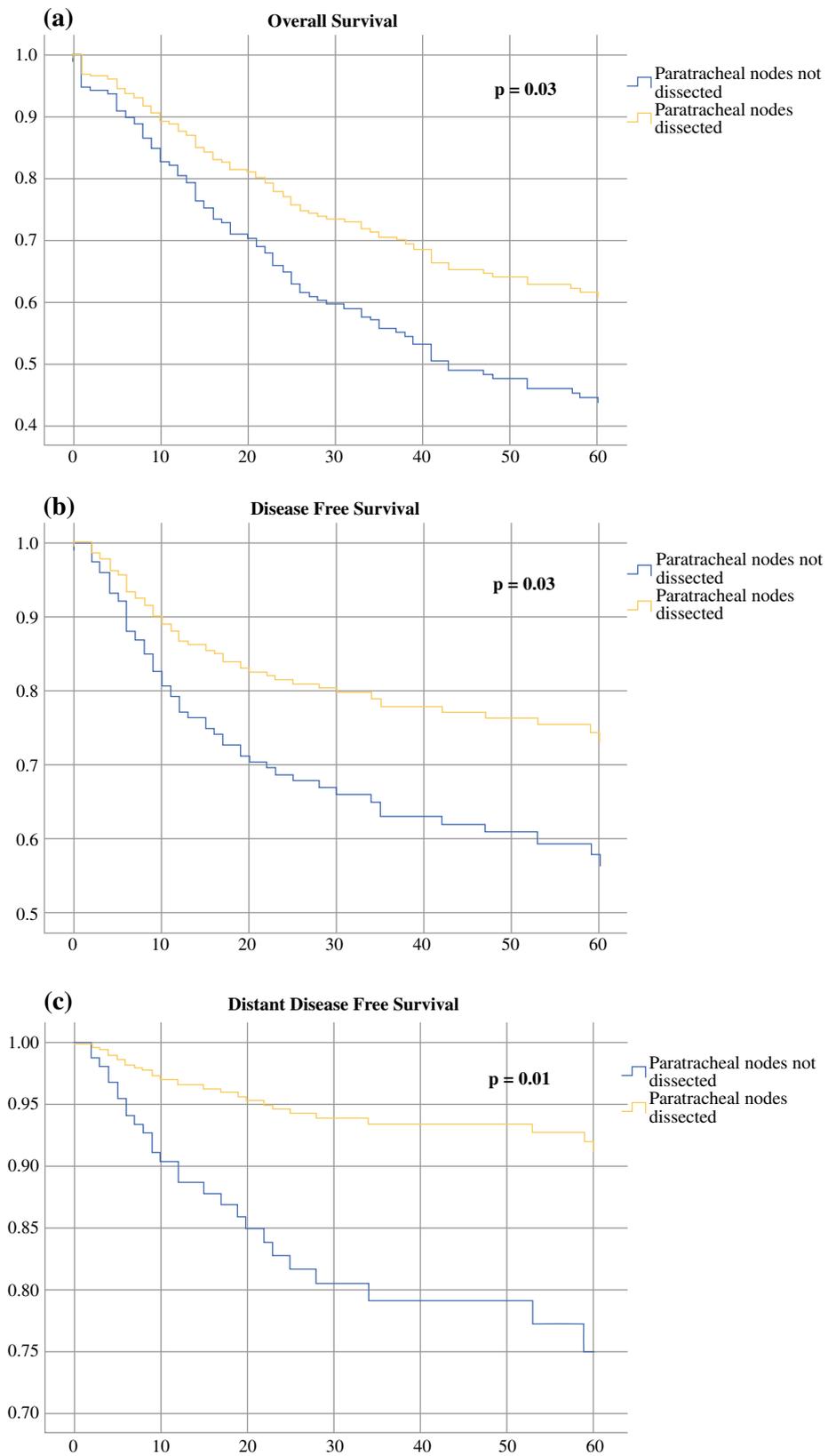
DISCUSSION

Salvage surgery remains the preferred treatment for persistent or recurrent LSCC after radiation or chemoradiation. For patients with advanced disease who are candidates for organ-preserving treatment approaches, surgery for recurrence usually entails total laryngectomy. Practices differ on whether the cN0 neck at the time of recurrence should be prophylactically treated.^{9–15} When elective surgery for the cN0 neck is pursued, typical lymph node-level dissections include levels II–IV, and are often bilateral.^{23,24} Selective neck dissection of the lateral neck is commonly employed at our institution for the cN0 neck. We have previously shown a histologically positive occult nodal rate of 17% in our salvage laryngectomy cohort, with higher rates associated with supraglottic subsite and more advanced T classification.²⁵

There is less evidence to inform management of the paratracheal nodal basin in recurrent laryngeal cancer. In a review of literature related to central compartment dissection in laryngeal cancer, Medina et al. report a 5–67% prevalence of metastases in the central neck, with notable differences based on subsites of the central compartment (prelaryngeal, pretracheal, and paratracheal nodes) and laryngeal cancer subsites (supraglottic, glottic, and subglottic).²⁶ Some surgeons choose to treat the paratracheal nodal basin based on studies suggesting that metastases to these nodes can lead to peristomal recurrences.^{27–29} Metastases to this basin have also been associated with decreased survival in previous, nonhomogenous cohorts.^{29,30}

In this analysis, occult nodal disease in the paratracheal basin was observed in 11 of 77 patients (14%), which approaches the threshold of lymph node metastasis typically considered as an indicator for selective neck dissection.²¹ We have previously shown that predictors of survival in salvage laryngectomy include tumor stage and lateral neck disease.²² While controlling for these factors and tumor site, the current analysis demonstrates that

FIG. 1 Multivariate Cox regression analysis comparing outcomes for patients undergoing versus not undergoing paratracheal node dissection and controlling for tumor stage, tumor site, and lateral neck disease. Kaplan–Meier panels: **a** overall survival; **b** disease-free survival; and **c** distant disease-free survival



PTND is associated with improved overall survival and distant DFS for subjects with clinically negative nodal status presenting for salvage laryngectomy. This is the first time this type of survival advantage for paratracheal disease has been shown and represents an important finding for patients undergoing salvage laryngeal surgery.

Importantly, six patients in our cohort with paratracheal metastases did not have metastases to any other nodal basins. Timon et al.²⁸ have previously shown paratracheal metastases without cervical metastases, although of the five patients they reported, only one had laryngeal cancer. In our cohort, two patients with paratracheal metastases independent of lateral neck disease only had a unilateral PTND. Three additional patients had bilateral PTND, with pathologic evidence of unilateral paratracheal disease independent of lateral neck metastases. Interestingly, one patient exhibited paratracheal disease in the contralateral side of the recurrent tumor. The final patient had nodal disease in both paratracheal basins, but not lateral neck disease on either side. These patterns do not conform to accepted lymphatic drainage patterns,²⁶ which supports the possibility that initial radiotherapy may alter expected routes of spread for recurrent tumors.

Arguments against elective neck dissection typically center on the morbidity of the procedure.^{9,10,31–33} Operating on irradiated tissues invariably leads to an increased risk of complications.³⁴ Neck dissections can also lead to increased operating time for patients with multiple comorbidities, delayed wound healing, including tracheostome breakdown and stenosis, and fistula formation.^{9,10,31} For central neck dissection in particular, hypocalcemia has been considered a significant risk in the thyroid cancer literature,^{17,19} although this has been disputed.³⁵ One study did not identify an increased relative risk of hypocalcemia if a central neck dissection was performed concurrently with laryngectomy.¹⁸ Of note, hypocalcemia is a common perioperative complication of laryngectomy patients regardless of neck dissection. One study found hypocalcemia in approximately 40% of laryngectomy patients, many of whom did not receive central neck dissections or full thyroidectomies.¹⁶ The authors in this study commented on the long-term effects of cervical radiation, preoperative malnutrition, delayed or not tolerated gastric feeding, and blood transfusions as possible etiologic factors. In our cohort, there was not a statistically significant difference in postoperative hypocalcemia among subjects with or without PTND.

To our knowledge, this study represents the largest cohort of patients undergoing salvage laryngectomy for which elective PTND has been reported and analyzed. Although some inherent bias in treatment selection is possible in such a retrospective observational study, the findings suggest a potential benefit of elective PTND,

especially for patients with T3/T4 recurrences. It is possible that variation in pretreatment radiation fields or techniques in a retrospective, single-institution study could also influence the distribution of occult nodal metastases. Additionally, this study was not designed to identify small effect sizes in the rates of hypocalcemia or devascularization of the stoma after PTND. There was no additional pathologic review of nodes beyond standard pathologic protocols. Despite these limitations, we believe our data are still compelling for strongly considering PTND when performing a salvage laryngectomy, especially for more patients with advanced local disease. More robust prospective data are needed to validate the advantages of this approach.

CONCLUSION

Elective PTND in patients undergoing salvage laryngectomy was associated with improved OS and DFS. Occult paratracheal metastases were often found in patients without clinical evidence of lateral neck metastases. Thus, surgeons should carefully consider these observations in decision making for performing elective node dissections in conjunction with salvage total laryngectomy.

AUTHOR CONTRIBUTIONS JLF, ACB, AJR, and MES contributed to the conceptualization, data curation, formal analysis, and original drafting of this manuscript. All authors made contributions to the acquisition and interpretation of data for the work, as well as to critical revision of the manuscript and final approval of the version to be submitted.

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