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Salvage laryngectomy following organ-preservation therapy – An evidence-based review☆

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ABSTRACT

Salvage total laryngectomy is often indicated in patients with recurrent or persistent laryngeal cancer after radiation or chemoradiation treatment. This article reviews and discusses key considerations regarding salvage laryngectomy. Within this article, a review of the salvage laryngectomy incidence in the major organ preservation trials, survival rates, predictors of outcomes, complication rates, and the roles of elective neck dissection and free tissue transfer for reconstruction in patients undergoing salvage laryngectomy is provided.

Introduction

Non-surgical treatment strategies have permitted the ability to treat laryngeal cancer while preserving the larynx. When disease persists or recurs after organ preservation therapy, salvage surgery—often in the form of total laryngectomy—is indicated. A review and summary of key findings throughout the literature is provided, including the incidence of salvage laryngectomy in the major organ preservation trials, survival outcomes, complication rates, and predictors of survival. An appraisal of the evidence for elective neck dissection and free tissue transfer in the salvage setting is also included.

Salvage laryngectomy in VA larynx and RTOG 91-11

Prior to the early 1990s, the standard treatment of advanced laryngeal cancer was total laryngectomy with concurrent neck dissection [1]. Due to significant functional and quality of life concerns associated with total laryngectomy (specifically, the loss of one's natural voice and resultant permanent tracheostoma) non-surgical organ preservation trials were developed, beginning with the Veterans Administration (VA) trial in 1991 followed by the Radiation Therapy Oncology Group (RTOG) 91-11 trial in 2003 [1,2]. These landmark trials have had a tremendous impact on the management paradigm of advanced laryngeal cancer, permitting select patients to undergo laryngeal-preserving cancer treatment without impacting survival.

The VA laryngeal cancer trial randomized patients with previously untreated, American Joint Committee on Cancer (AJCC) Stage III/IV laryngeal cancers to either induction chemotherapy followed by radiation therapy (RT) or total laryngectomy (TL) followed by RT [2]. Patients in the induction chemotherapy group received a total of three cycles of cisplatin and 5-fluorouracil and went on to receive definitive RT if there was a clinical tumor response following the second cycle of chemotherapy. If there was (1) recurrence, (2) persistent disease after RT, or (3) absent clinical response after two cycles of induction chemotherapy, patients underwent laryngectomy. This trial showed equivalent survival in the induction chemotherapy and primary surgery arms. Importantly, this clinical trial was predicated on a meticulous follow up schedule with early salvage surgery for treatment failures or persistent disease. Similarly, if there was no response to induction chemotherapy, patients went on to salvage laryngectomy rather than RT. Of the 166 patients in the induction chemotherapy arm, 36% underwent laryngectomy while 29% of patients had a laryngectomy either prior to the initiation of RT or within three months of completing RT. Notably, in the case of T4 cancers, 56% of patients in the chemotherapy arm required a laryngectomy. This landmark trial demonstrated equal survival between the induction chemotherapy and surgical arms with a

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64% laryngeal preservation rate; however, one must keep in mind the highly-controlled environment of this trial and the significance of prompt surgical salvage in the 36% of patients in the chemotherapy arm that either recurred or had no response to non-surgical treatment.

The RTOG 91-11 trial investigated the role of chemotherapy in organ preservation protocols [1]. This trial randomized patients with AJCC stage III/IV laryngeal cancer into three treatment groups: induction chemotherapy (cisplatin/5-fluorouracil) followed by RT, concurrent chemoradiation (CRT), and RT alone. Notably, RTOG 91-11 did not include a surgical arm, excluded high volume T4 larynx cancers, and excluded tumors with cartilaginous invasion or greater than one centimeter extension into the tongue base, resulting in 90% of patients with T2 or T3 tumors. RTOG 91-11 demonstrated superior locoregional control and laryngeal preservation rates in the concurrent CRT arm. Overall, 25% of patients required total laryngectomy; however, only 16% of patients in the CRT arm required a laryngectomy as compared to 29.5% and 34% in the induction and RT-alone arms, respectively [3]. Overall survival (OS) at 24-months in patients requiring salvage laryngectomy was 69% in the induction arm, 71% in the CRT arm, and 76% in the RT-alone arm; no differences were seen between initial treatment groups. Importantly, patients that underwent salvage TL had significantly poorer survival than their counterparts who did not require salvage surgery ($p < .001$, HR 1.9). A ten-year follow up analysis confirmed that patients who subsequently required a total laryngectomy for salvage experienced significantly worse survival when compared to patients that did not require salvage surgery when treated with either induction chemotherapy followed by RT or concurrent CRT (induction chemotherapy, $p = .03$; CRT, $p = .01$) [4].

In the VA larynx trial, timely surgical salvage in 36% of the chemotherapy arm expectedly played some role in achieving equal survival rates between the chemotherapy and primary surgical arms. This finding has led some observers to declare no harm in first attempting a non-surgical approach, reserving salvage surgery in the event of treatment failure without an impact on survival [5]. However, findings from the ten-year follow up of RTOG 91-11 directly rebukes this conclusion, as it is clear that in patients initially treated with a chemotherapy-based organ preservation protocol, the necessity for salvage laryngectomy portends poorer survival that cannot be overcome with salvage surgery alone [4].

Survival rates in salvage laryngectomy

Locoregional recurrence rates for laryngeal cancer treated primarily with organ-preserving techniques remains high and ranges from 30 to 66% throughout the literature [6–14]. Although variability in treatment algorithms exists, salvage laryngectomy tends to result in favorable oncologic and functional outcomes compared to other subsites. A meta-analysis by Goodwin and colleagues compared experience with salvage surgery for various head and neck subsites including the larynx, oral cavity, and pharynx. This analysis demonstrated that the larynx was more amenable to salvage surgery than either the oral cavity or pharynx with five-year OS rates of 48% in the larynx compared to 43%, and 26% in the oral cavity and pharynx subsites, respectively, for stage I and II disease [15]. Similarly, two-year disease free survival (DFS) was 76% in the larynx as compared to 36% in the oral cavity and 25% in the pharynx subsites. When analyzing stage III/IV laryngeal disease, the five-year OS rate decreased to 37% after salvage surgery. A similar trend was observed for two-year DFS with a rate of 51% for stage III/IV laryngeal cancer.

Similar findings were reported by Matoscevic et al. with an overall successful salvage rate of 49% for patients with laryngeal recurrence (mean survival time, 129.7 months) compared to 35% for oral cavity, 33% for oropharyngeal, and 17% for hypopharyngeal subsites [16]. The authors additionally found that lower initial T and N stages were associated with improved oncologic outcomes: early T1-2 tumors versus T3-4 tumors experienced improved survival times compared to T3-4 tumors (130 versus 112.1 months, respectively) and patients with laryngeal recurrence presenting with a positive node had a reduced survival (105.2 months versus 137 months in N0 patients). Together, these series suggest that patients with recurrent laryngeal cancer following organ-preservation treatments—specifically those with primarily staged early laryngeal tumors—are amenable to successful surgical salvage [15,16].

The largest single-institution analysis from Birkeland et al. reported on a balanced cohort of 244 patients undergoing salvage laryngectomy for recurrent and/or persistent laryngeal SCC following either RT (139 patients, 57%) or CRT (105 patients, 43%) [13]. Among this cohort, 6% had T1 recurrent disease while 40%, 27% and 28% had T2, T3 and T4 recurrence, respectively. 56% of patients had glottic recurrence, while 44% recurred within the supraglottic region. Altogether, the five-year OS was 49% with a DFS of 58% and DSS of 68% at five years.

A 20-year experience of 218 patients who underwent salvage total laryngectomy for persistent or recurrent disease after RT or concurrent CRT demonstrated comparable findings with five-year OS and disease control rates of 57% and 65%, respectively [14]. Of the 218 patients with recurrent laryngeal SCC, the majority (160, 73%) were initially treated with RT alone while 66 (27%) underwent CRT. Patients were stratified into two separate groups: salvage total laryngectomy for early recurrence (less than 2 years from previous treatment; $n = 150$) and late recurrence (greater than 2 years from end of previous treatment; $n = 68$). Within this review, patients with a disease-free interval less than two years after initial treatment were more likely to develop a recurrence ($p = .001$) and die of disease ($p = .032$) after salvage laryngectomy. Notably, the disease-free interval following the completion of RT was also found to impact disease control ($p < .001$) with a five-year disease control rate of 92% for a disease-free interval greater than five years compared to 60% for patients with a disease-free interval of less than two years. This series also reflects favorable contemporary salvage rates despite prior organ-preserving regimens and showed that a shorter time to recurrence (e.g. less than two years after primary treatment) appears to be associated with poorer outcomes following salvage laryngectomy [13,14].

Although surgical salvage rates are favorable, a proportion of patients will go on to develop locoregional recurrences despite salvage surgery. Others have reported a higher rate of locally recurrent disease in as many as 29% of patients after salvage laryngectomy [17]. Similar findings were observed by Matoscevic et al. with 26 of 61 (43%) patients experiencing a second recurrence after salvage laryngectomy with 10 patients developing yet a third recurrence. Of the 61 patients undergoing salvage surgery, 16 (26%) developed distant metastasis with the lung being the most common site. In all, survival in patients that recur after salvage laryngectomy remains poor, with the majority succumbing to their disease within the first year of recurrence [18].

Impact of pre-salvage radiation and chemotherapy on survival

A review of two separate series by van der Putten and colleagues highlights differences between pre-salvage treatment regimens and the impact of concurrent chemotherapy on survival outcomes following salvage laryngectomy. In one study, 120 patients who underwent total laryngectomy for recurrent or residual laryngeal SCC following RT or CRT were analyzed [17]. The vast majority (114 of 120, 95%) of patients within this cohort had RT as the single treatment modality, whereas only 6 (5%) patients received concurrent CRT. This population was skewed towards early stage disease for the initial tumor and was comprised of 20% T1 tumors, 48% T2, 19% T3 and 13% T4; 104 of 114 (87%) patients had N0 disease. In all, a five-year disease specific survival (DSS) of 58% was noted with a total five-year disease free control rate of 57% (local, 70%; regional, 79%; distant, 86%). In contrast, a 2015 retrospective study by the same author demonstrated significantly reduced five-year survival rates among a separate cohort of patients receiving initial CRT for laryngeal or hypopharyngeal SCC [7]. Of 60

patients with locoregional disease following curative chemoradiation, 22 (33%) underwent salvage surgery for local, regional or locoregional disease. In comparison to patients undergoing curative RT in the earlier series, a worse five-year prognosis was experienced for those undergoing CRT with overall survival of 27% versus 50%. Likewise, the five-year DSS rate was 35% among the CRT group and 58% for the previous RT only group with a local disease free survival rate of 35% versus 57%, respectively. Differences in survival between those treated with RT and CRT are likely reflected by more advanced disease in the CRT cohort and direct comparisons between these groups may be affected by selection bias.

Goodwin et al. also observed that patients who received chemotherapy prior to salvage surgery experienced a marked decrease in five-year DFS following salvage surgery [15]. The authors observed that those who received chemotherapy had a median survival of 8.8 months compared to 26.9 months in patients without a history of previous chemotherapy ($p = .0007$) even after adjusting for covariates. The same association was reflected in the analysis of two-year DFS with 5.0 months compared to 24.5 months, respectively ($p = .001$). In all, five-year locoregional surgical control rates following RT and CRT are favorable with overall five-year survival rates ranging from 30 to 60% with some citing rates as high as 86% [3,6,8,13,14,17,19–32]. These results are displayed in Table 1; of note, studies including hypopharyngeal and regional recurrence in addition to partial salvage laryngectomy procedures are excluded given the highly heterogeneous nature of these groups.

Predictors of survival

Given the multitude of treatment options, it is critical to identify factors that predict which patients will benefit from surgical salvage and/or need for adjuvant treatment. Predictors of survival within the salvage setting are varied, with some studies failing to discern any prognostic variables. Birkeland et al. further performed a multivariate analysis to identify prognostic variables in the salvage setting and the strongest predictors of five-year OS were severe comorbidity (hazard ratio [HR] 3.76) as determined by the Adult Comorbidity Evaluation-27 index and positive recurrent nodal status (HR 2.91). The authors suggest attention to modifiable risk factors including hypertension, depression, diabetes, obesity and alcohol abuse should be strongly considered and addressed prior to salvage surgery.

One prospective analysis from Tan et al. reviewed 38 patients to provide a stratification scheme that predicts post-salvage survival [9]. Multicovariate analysis confirmed that stage IV disease (HR 4.1) and

Table 1
Overview of laryngeal-specific salvage outcomes and fistula rates following organ-preservation treatment regimens.

Author	Year	N	Pre-salvage treatment regimen	Fistula, overall N (%)	OS	DFS	DSS	LRC	Comments
Davidson [20]	1994	58	RT CRT	28 (48%)	30% (5-year)				
Stoeckli [6]	2000	36	RT	5 (14%)			63% (5-year)		
Leon [8]	2001	25	IC + RT	5 (16%)	57% (5-year)				
Weber [3]	2003	129	IC + RT, 48 (28%) CRT, 27 (16%) RT, 54 (31%)	12 (25%) 8 (30%) 8 (15%)	69% (2-year) 71% (2-year) 76% (2-year)	56% (2-year) 72% (2-year) 69% (2-year)		74% (2-year) 74% (2-year) 90% (2-year)	
Ganly [22]	2005	70	RT, 32 (46%) CRT, 38 (54%)	5 (16%) 12 (32%)					
Righini [23]	2005	60	RT	23%					
Fung [21]	2007	14	RT, 2 (14%) CRT, 12 (86%)	4 (14%)					
Withrow [24]	2007	37	RT, 25 CRT, 12	13 (35%)					
Furuta [25]	2008	51	RT, 17 (33%) CRT, 34 (67%)	3 (18%) 8 (24%)					Excluding surgical arm
Gil [26]	2009	80	RT, 51 (75%) CRT, 11 (25%)	19 (24%)					
Patel [27]	2009	17	RT, 6 (35%) CRT, 11 (65%)	4 (24%)					
van der Putten [17]	2011	120	RT, 114 (95%) CRT, 6 (5%)	36 (30%)	50% (5-year)		58% (5-year)	70%, local (5-year) 70%, regional (79%)	
Li [28]	2013	100	RT, 76 CRT, 24		55–70% (5-year)		52–78% (5-year)	70% (5-year)	Stratified by early and advanced-stage
Patel [29]	2013	359	RT, 129 (71%) CRT, 136 (76%)	94 (27%)					
Powell [30]	2014	45	RT, 41 CRT, 4	10 (22%)					
Sayles [31]	2014	1721	IC + RT RT CRT	443 (26%)					Systematic review and meta-analysis
Hasan [32]	2016	3292	RT, 1,826 (56%) CRT, 850 (26%) Unspecified, 613 (19%)	859 (29%)					Systematic review and meta-analysis
Sandulache [14]	2016	218	RT, 160 (73%) CRT, 66 (27%)	18 (8%)	57% (5-year)			65% (5-year)	
Birkeland [13]	2017	244	RT, 139 (57%) CRT, 105 (43%)	84 (34%)	49% (5-year)	59% (5-year)	68% (5-year)		

OS: overall survival, DFS: disease free survival, DSS: disease specific survival, LRC: locoregional control, RT: radiotherapy, CRT: chemoradiation, IC: induction chemotherapy.

the presence of concomitant locoregional failures (HR 3.8) were independent predictors of survival after salvage surgery. The authors further demonstrated that two-year OS rates for the presence of either both, one or none of these predictive factors were 0%, 49% and 83%, respectively ($p = .0005$).

More recent work analyzed a large, consecutive series of 147 patients who underwent salvage surgery after RT with or without chemotherapy between 1995 and 2016, again finding that increased tumor stage in addition to sarcomatoid/spindle cell pathology and the presence of lymphovascular invasion were independently associated with poorer DFS [19]. Pathologic nodal staging and comorbidity status did not have a significant impact on outcomes in contrast to previous reports. In a retrospective study of 924 primary tumors, recurrence was observed in 236 (26%) cases with the majority (23%) occurring within the larynx [33]. Recurrent N1 disease and primary management with surgery alone were independent predictors of successful salvage following the treatment of isolated neck recurrences. Similar to prognostic predictors for primary laryngeal SCC, an appraisal of successful surgical salvage for various head and neck subsites performed by Matoscevic et al. observed that primary tumor location, lower initial T and N staging, female gender, and extent of salvage treatment (e.g. multimodality regimens) were predictive of favorable outcomes [16]. Earlier studies have reported similar predictors which include age, TNM staging, primary and recurrent disease burden, differentiation grade, as well as time to treatment failure as independent prognostic factors in the salvage setting; however, subsequent analyses have failed to identify significance with respect to these variables [7,15,17,34–39].

The impact of cigarette smoking and alcohol use as independent prognostic factors has also been well-described [40–43]. One study showed that continuing to smoke throughout the duration of RT results in lower rates of response and survival with a documented relative risk of 2.5 favoring patients who abstain from cigarette use [40]. Compliance with RT is another important source of prognostication [44–46]: treatment breaks and premature discontinuation of either RT or concurrent CRT results in suboptimal survival with one large study of Medicare beneficiaries demonstrating that patients with laryngeal tumors who experienced an interruption in radiotherapy had a 68% increased risk of death compared to those patients without interruption [45]. Regardless of smoking status and alcohol intake, these findings highlight a lack of uniformity in defining clear predictors of successful salvage. In general, it appears that timely diagnosis, a clear definition of tumor extent, and the presence of locoregional involvement is key in developing effective salvage strategies.

Speech and swallowing outcomes following salvage laryngectomy

A prospective Phase II clinical trial which included stage III or IV laryngeal disease was conducted by Fung et al. to determine differences in voice and swallowing function between those undergoing successful laryngeal preservation treatment versus those requiring salvage laryngectomy [47]. Utilizing the validated Voice-Related Quality of Life Measure (V-RQOL) and List Performance Status Scale for Head and Neck Cancer Patients (PSS-HN), the authors demonstrated that patients with an intact larynx experienced significantly higher ($p = .02$) V-RQOL scores compared to those who underwent salvage laryngectomy with mean scores of 80.3 and 65.4, respectively. Speech understandability was better in patients who maintained their larynx ($p = .0001$). Lower T-stage, successful laryngeal preservation, and longer duration since treatment were identified as predictors of higher total V-RQOL scores. Although it did not reach statistical significance, 88.9% of patients with an intact larynx were able to obtain nutrition consisting of oral intake alone without supplementation compared to only 64.3% of salvage laryngectomy patients ($p = .09$) [47].

Van der Putten and colleagues also published functional outcomes among 120 patients undergoing salvage total laryngectomy [17]. Within one year following salvage laryngectomy, 87% were able to produce alaryngeal speech by means of a tracheoesophageal voice prosthesis while the remainder communicated via esophageal speech (9%), electrolarynx (1%) and writing/sign language (3%). Attaining adequate tracheoesophageal speech by means of a voice prosthesis is associated with high success rates (approximately 90%) following both primary and salvage laryngectomy; however, voice prosthesis-related complications in the salvage setting appear to be more common following primary placement as reported by Starmer et al. [14,21,47–50]. With regards to swallowing outcomes, van der Putten et al. additionally showed that 84% of patients were able to tolerate a “normal” or “soft” diet (68% and 16%, respectively) with only 9% of patients relying on a nasogastric or gastrostomy tube at one year post-salvage laryngectomy [17]. Comparable results were found in a retrospective study of functional outcomes among 82 patients undergoing organ preservation therapy with curative RT or CRT, only 5 (6.1%) patients were dependent on their gastrostomy tube for intake following radiation at last follow up (mean duration 43 months; range, 18–61 months) [51]. This is in contrast to a retrospective review of 218 salvage total laryngectomy patients by Sandulache and colleagues who reported a 20% rate of continued gastrostomy tube utilization at last follow up with use more common among those who underwent free flap reconstruction at the time of salvage (19 of 42 patients, 45%) versus those who did not (26 of 176 patients, 15%; $p < .05$) [14].

While varying degrees of swallowing dysfunction are experienced among salvage laryngectomy patients, pharyngeal stenosis or stricture may occur as a late complication of treatment; this was found to occur in 80 of 560 patients (14.3%) as reported in one systematic review and meta-analysis by Hasan et al. and is generally increased in the setting of flap reconstruction [21,32,52,53]. Fung et al. conducted a retrospective review of a prospective cohort of 14 patients who underwent salvage total laryngectomy with free tissue reinforcement and compared them to a historical cohort (surgical patients in arm 2 of RTOG 91-11) who did not undergo flap reconstruction and found a higher rate of pharyngeal stricture requiring dilation in the flap group (6 of 14 patients, 42%) compared to those in the non-flap/RTOG 91-11 group (7 of 27 patients, 25.9%). Furthermore, the authors demonstrated a 100% rate of tracheoesophageal speech with complete oral intake achieved in 13 of 14 (93%) patients and favorable V-RQOL and PSS-HN scores following free flap reinforcement.

Complications in salvage surgery

Overall complication rates in the literature range from 5 to 78% with the most common complication being pharyngocutaneous fistula formation occurring in as many as 73% of cases in the salvage setting (Table 1). Complications are most commonly defined as major or minor, with major complications requiring operative intervention including the need for locoregional or free flap reconstruction for pharyngocutaneous defects, revision of microvascular anastomoses, hematoma evacuation, carotid blowout and death.

A systematic review and meta-analysis including 50 studies and encompassing 3292 patients reported an overall complication rate of 67.5%, with pharyngocutaneous fistula being the most common complication (28.9%) [32]. The most common complications included wound infection (14.1%, range 1.4–33.3%), pharyngeal stenosis/stricture (14.3%, range 2.3–43.9%), bleeding including hematoma and hemorrhage (5.9%, range 1.2–36.4%) and dysphagia (18.6, range 2.9–30.2%).

Salvage total laryngectomy following RT is associated with higher complication rates when compared to upfront surgery [6,12,22,54–56]. The addition of chemotherapy to treatment algorithms increases the frequency and severity of complications including the development of pharyngocutaneous fistula [7,22,55,57]. A retrospective review of 183 patients compared postoperative complications between primary and salvage total laryngectomy (excluding patients with laryngopharyngectomy for primary oropharyngeal or hypopharyngeal malignancy)

following RT and CRT was performed by Ganly et al. [22]. For those undergoing salvage total laryngectomy, the initial therapy included RT in 32 (46%) and CRT in 38 (54%) patients. While univariate analysis failed to show a significant difference in the frequency of complications between the primary and salvage laryngectomy following RT groups, there was a statistically significant increase in local (e.g. fistula, wound infection, dehiscence, flap necrosis, carotid rupture, chyle leak) complications (45% vs. 25%, $p = .02$) and pharyngocutaneous fistula (32% vs. 12%, $p = .012$) for those undergoing surgical salvage after CRT. After multivariate analysis, the authors highlighted that initial treatment with CRT was the only significant predictor of local complications with patients being nearly three times more likely to develop a local wound complication compared to primary total laryngectomy or salvage laryngectomy following RT. CRT was also the only independent predictor of pharyngocutaneous fistula development after total laryngectomy with patients in the salvage group being twice as likely to develop a fistula. Van der Putten et al. reported similar findings with an increased rate of total complications in those receiving CRT versus RT alone with rates of 73% and 56%, respectively [7,17].

The majority of recurrent laryngeal cancers are diagnosed within the first 24 months following RT or CRT; a median interval between time of initial treatment and detection of recurrent cancer as low as nine months has been reported [7,11,14,17,35,58,59]. The impact of time to recurrence on complications is not well defined. Multiple studies have cited an increased incidence of complications with a shorter interval duration between RT/CRT and salvage surgery [24,60,61] while others failed to observe any association between time between nonsurgical treatment and salvage surgery with complication rates [3,7,62].

Elective neck dissection in salvage laryngectomy

Few would argue the need to perform a neck dissection in the presence of clinical or radiologic node positivity; however, in the N0 neck, elective neck dissection remains controversial in the salvage setting. In addition to clinical examination, imaging options for surveillance after treatment are varied and include computed tomography (CT), magnetic resonance imaging (MRI), fluorodeoxyglucose positron emission tomography (FDG-PET), or combination of these techniques. Numerous studies have compared the utility of these modalities in the detection of persistent or recurrent disease, with one systematic review and meta-analysis highlighting the improved accuracy of PET compared to CT or MRI alone [63]. Other series have documented similar findings with improved specificity of PET in detecting neck metastases [64–69]. Yao et al. demonstrated that FDG-PET imaging was associated with a negative predictive value of 100% with rates of 100% sensitivity and 94% specificity in patients 12 weeks following definitive RT with or without chemotherapy for stage N2a disease or greater [64]. Rosko et al. published contrasting results after reviewing 46 clinically and radiographically N0 patients with recurrent laryngeal cancer who underwent PET-CT imaging prior to salvage laryngectomy [70]. The authors calculated a sensitivity of 16.7%, specificity of 97.1%, and negative predictive value of 76.7% and concluded that PET-CT examination was an imperfect predictor of nodal disease in cases of recurrent laryngeal cancer. Although PET-enhanced imaging is increasingly utilized to improve staging accuracy in recurrent cases [71], radiographic results should be carefully interpreted when informing the need for elective neck dissection in the N0 setting.

The published rate of occult metastasis ranges from 0 to 30% throughout the literature [37,65,72–79]. The largest published series in the literature is by Birkeland et al. who analyzed occult nodal positivity rates in 203 clinically N0 (cN0) patients undergoing salvage laryngectomy for local recurrence after non-surgical treatment, in which 35 patients (17%) had pathologically positive occult nodal metastasis [79]. Predictors of occult nodal metastasis were increasing T stage and supraglottic tumor subsite. In this series, 34% of T4 tumors had occult nodal disease, while nodal metastasis rates for T1-T3 tumors were 9%, 10%, and 16%, respectively. With regard to tumor subsite, 28% of supraglottic tumors had occult nodal disease as compared to 10% of glottic tumors. When stratified by T stage and subsite, the highest risk was identified in T4 supraglottic tumors, where 50% metastasized to regional nodes, despite being cN0 prior to salvage surgery. Even early supraglottic tumors showed a high rate of nodal metastasis, with 21% of T1/T2 supraglottic tumors found to harbor occult nodal metastasis. On the other hand, the rate of nodal positivity in T1/T2 glottic tumors was less than 5%. Importantly, when glottic tumors developed occult nodal metastases, the most common locations were the ipsilateral and contralateral paratracheal nodal basins, emphasizing the importance of dissecting the paratracheal nodal basins for advanced stage recurrent glottic tumors.

Amit et al. presented similar findings in a cohort of 42 cN0 patients undergoing salvage laryngectomy and neck dissection after failed CRT [80]. In this cohort, 19% (8 of 42) were found to have occult nodal metastasis after neck dissection with predictors of occult metastasis being advanced T stage (22% for T3/T4 vs. 14% in T1/T2) and supraglottic subsite (25% occult metastasis rate vs. 15% in glottic subsite). Wax et al. published an occult nodal positivity rate of 18% (6 of 34) in patients undergoing salvage laryngectomy and neck dissection, with 28% of supraglottic tumors and 10% of glottic tumors having occult metastasis, thus concluding that all supraglottic tumors and advanced glottic tumors warrant elective dissection of the neck [75]. Further evidence for neck dissection for advanced recurrent laryngeal cancers is provided by Yuen and colleagues who elected for observation of the neck in 126 patients with T3/T4 N0 recurrent laryngeal cancers initially receiving non-surgical treatment [81]. Following adequate control of the primary site without neck dissection, 18% of patients ultimately continued on to experience disease recurrence in the neck.

In contrast to these findings, Bohannon et al. reported on 38 patients undergoing salvage laryngectomy with concurrent neck dissection and only noted a 4% nodal metastasis rate [82]. Furthermore, they compared the neck dissection group to an observation group and found that those within the neck dissection group experienced significantly higher complication rates with nearly twice the complication rate without any survival advantage. Other studies have also shown higher complication rates with neck dissection compared to observation [83]. Bohannon et al. also performed a survival analysis comparing patients undergoing neck dissection against those within the observation group and ultimately showed that there was no survival advantage in patients undergoing neck dissection. This finding is not surprising given that the authors had a relatively low rate of occult nodal positivity (4%) compared to others in the literature. This may be partially explained by the high proportion of glottic cancers in the neck dissection group (90% glottic tumors vs. 11% supraglottic tumors).

In summary, the overall rate of occult nodal positivity in the literature approximates 17% [79] and is dependent on tumor stage and supraglottic tumor subsite [84]. The authors' practice is to proceed with elective neck dissection in all patients with all supraglottic tumors and all T3/T4 glottic tumors, including the paratracheal nodal basin in glottic and subglottic tumors. Since the authors also support the use of vascularized tissue in the salvage setting for hypopharyngeal reconstruction, the neck dissection serves a dual purpose and also permits recipient vessel preparation. While the literature contains a wide range for the incidence of nodal metastasis, the rate of positivity likely depends on the proportion of supraglottic tumors included in the series – the higher the proportion of supraglottic tumors, the higher the rate of overall occult metastasis.

Vascularized flaps in salvage laryngectomy

The role for vascularized tissue in upfront and salvage laryngectomy has been the subject of substantial recent interest. In particular, the objective impact of vascularized tissue in the form of pedicled or free

flaps on complications such as wound healing, pharyngocutaneous fistula, length of stay (LOS), and time to oral intake remains poorly defined; however, a role for vascularized flaps in salvage laryngectomy is now the standard of care. Chemoradiation failure clearly has negative effects on wound healing and fistula rates. Long-term outcomes in the RTOG 91-11 cohort, for example, suggest that the risk of pharyngocutaneous fistula after laryngectomy is 30% with CRT compared to historically reported rates as low 4% in upfront surgery [3].

In the context of upfront laryngectomy, vascularized tissue is primarily utilized in cases where the closure of the residual remaining mucosa would yield an inadequate lumen size or suture line on tension. This framework offers a fairly straightforward decision tree in these select patients. In the salvage setting, there was initially controversy over the need for vascularized tissue [26]; however, multiple studies have now demonstrated the importance of vascularized tissue in these patients, ideally harvested from tissue outside the previously radiated field. Thus, in our view, vascularized tissue is indicated in the salvage setting [21,29,31,85,86].

Historically, the pectoralis major myocutaneous flap (PMMF) has served as a reliable reconstructive option in upper aerodigestive tract defects, in part due to its bulk and versatility. The context of salvage laryngectomy is no exception, with the well-vascularized muscle of the PMMF assisting in the prevention and treatment of pharyngocutaneous fistula. Other pedicled flap options including supraclavicular and temporoparietal fascial flaps [87,88] have been described, but PMMF has been by far the most utilized and studied. Single institutional studies report 18–22% absolute risk reduction rates in fistula after salvage laryngectomy with PMMF onlay [85,86], while a meta-analysis of 33 studies suggested a reduction in fistula rates from 28% without flap coverage to 10% with onlay flap-reinforced closure [31]. More recently, a multi-institutional retrospective review of total laryngectomy patients who received RT with or without chemotherapy was completed, with an analysis of 359 patients from eight institutions over a seven-year period. This group reported an overall fistula rate of 27%, with primary closure resulting in a 34% rate of fistula compared to 15% for onlay PMMF [29]. Thus, there is historically strong data for PMFF in preventing major fistula (requiring hospitalization or revision surgery) with reduced overall time to fistula closure.

Although these prior studies of PMMF outcomes suggest that vascularized tissue may be utilized effectively in salvage laryngectomy patients, we prefer the use of free tissue transfer as it avoids shoulder and arm donor site morbidity associated with PMFF [21], while providing similar outcomes, greater versatility, and improved cosmesis [89]. Fung and colleagues reported that free flaps applied in an onlay fashion resulted in a similar overall fistula rates as with primary closure, but lower fistula duration due to smaller fistulas, no exposed major vessels, and management with outpatient care rather than hospitalization or return to the operating room [21]. This same group also studied the effects of free tissue on salvage hypopharyngeal defects, reporting improvements in fistula size and time to closure [90], further supporting the utility of free flaps in the post-chemoradiated patient. Although these initial studies were limited to small case series, one multicenter retrospective study has extended these conclusions. In 37 salvage laryngectomy patients, 17 underwent free flap reconstruction versus 20 who had primary closure [24]. The fistula rate in the free flap group was 18% compared to 50% with primary closure. In addition, free flap use resulted in lower stricture rates (18% vs. 25%), feeding tube dependence (23% vs. 45%), and LOS with fistula (7 days vs. 19 days). More recently, a multi-institutional study of the salvage laryngectomy cohort revealed a significant reduction in fistula with interposed free flaps (25% vs. 34% for primary closure), with multivariate analyses confirming a significantly lower fistula rate and duration of fistula (14.0 weeks with primary closure vs. 9.0 weeks for PMMF vs. 6.5 weeks for free flaps) [29]. The decision to incorporate vascularized free tissue transfer in the salvage setting differs between institutions; however, given these findings, we consider free tissue interposition or onlay after salvage total laryngectomy to be the best hypopharyngeal reconstructive option in patients undergoing salvage laryngectomy.

Conclusion

Laryngeal cancer that recurs after non-surgical treatment requires salvage surgery, most often in the form of salvage laryngectomy. Five-year OS after salvage laryngectomy is approximately 50% [13,15]. Prognostic factors in the salvage surgery setting include: advanced recurrent AJCC stage, severe medical comorbidities and recurrent nodal disease. Surgical complications are greater in the salvage setting compared to primary surgery with the most common complication being pharyngocutaneous fistula development. Furthermore, complications are more pronounced after CRT when compared to RT alone. The occult nodal metastasis rate is 17% in the salvage laryngectomy setting; many authors agree with elective neck dissection in the setting of T3-T4 disease and in tumors recurring in the supraglottic subsites. Free tissue transfer for hypopharyngeal reconstruction reduces major complications, risk of return to the operative room, and the severity of pharyngocutaneous fistulas.

Conflicts of interest

None declared.

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