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ORIGINAL RESEARCH

The effectiveness of salvage surgery after the failure of primary concomitant chemoradiation in head and neck cancer

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OBJECTIVE: To determine survival outcomes and locoregional control rates in patients with locoregional head and neck squamous cell cancer (HNSCC) who failed primary concomitant chemoradiation (CRT) intended for cure and underwent attempted surgical salvage.

STUDY DESIGN AND SETTING: Design was a nonrandomized retrospective cohort study. Of 204 patients with HNSCC who received primary concomitant chemoradiation intended for cure between 1995 and 2004, 38 recurred and underwent attempted salvage surgery at a tertiary care academic center.

RESULTS: Among the 38 patients undergoing surgical salvage, 12- and 24-month overall survival rates were 60 percent and 27 percent. Locoregional control at 24 months was 42 percent. Lower survival was seen with initial N3 disease ($P = 0.0115$). Overall surgical morbidity was 24 percent.

CONCLUSION/SIGNIFICANCE: The results of salvage surgery after failed chemoradiation for HNSCC are poor. Those with N3 disease fare least well. Patients should be well informed about the realistic chances of cure and potential morbidity of surgery.

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Organ-preserving therapy in head and neck squamous cell cancer (HNSCC) has been increasingly used over the past 10 years, and remains an active focus of research. The first attempts utilized neoadjuvant or induction che-

motherapy given prior to surgery and/or prior to radiation therapy (RT).¹ These investigations showed that while organ preservation was increased, survival remained unaffected.¹⁻³

More recently, concomitant chemoradiation (CRT) has become increasingly popular for advanced resectable cancers in an attempt at organ preservation. Chemotherapy is given concomitantly with RT with the goal of avoiding the need for surgery. CRT yields greater organ preservation than neoadjuvant chemotherapy followed by RT.⁴ However, there appears to be no survival advantage when compared with other forms of therapy.⁴⁻⁷ Previous studies have reported complication rates associated with surgical salvage following attempted organ-preserving treatment for HNSCC at 39 percent to 61 percent.⁸⁻¹⁰

When primary organ preservation therapy with concomitant chemoradiation is utilized, the role of surgery is not standardized. Some surgeons plan posttreatment neck dissections for patients with advanced nodal disease, if the primary is controlled. Others offer neck dissection only for persistent clinical or radiographic abnormalities that are felt to be suspicious. If primary or neck disease is clearly not controlled by the initial chemoradiation, then surgery is offered as salvage for surgically resectable disease.

There is limited survival analysis data of locoregionally

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advanced HNSCC patients who fail concomitant CRT intended for cure and subsequently undergo salvage surgery. Many studies have focused on surgical salvage outcomes following failure of all types of organ-preserving therapy, including surgical salvage following failure of single-modality RT or chemotherapy, and neoadjuvant chemotherapy followed by RT.¹¹⁻¹⁶ Limiting cohort inclusion criteria to those who only received CRT intended for cure is important because those who fail concomitant CRT may have alternate, and perhaps more aggressive, disease characteristics than those who fail radiation alone or neoadjuvant chemotherapy followed by RT.

Our primary objective was to determine the 2-year survival and locoregional control rates of patients with HNSCC undergoing unplanned salvage surgery following primary concomitant chemoradiotherapy that was intended for cure. Our secondary objectives were to identify patient or disease characteristics associated with decreased survival in this population and to determine surgical morbidity rates.

PATIENTS AND METHODS

Approval was obtained from the University of North Carolina School of Medicine Institutional Review Board. Patients who received primary concomitant CRT for cure between 1995 and 2004 were identified through searching the UNC Head and Neck Cancer Clinical Database and retrospective chart reviews. Records were examined to obtain: demographics, TNM subsites, initial stage, primary site, resectability at presentation, site of recurrence, time to recurrence, time to relapse after salvage surgery, pathology reports, and surgical morbidity. Patients were excluded if surgery after chemoradiation was planned as part of the initial treatment. Patients undergoing salvage surgery for purported recurrence that were found to have negative pathology, and therefore no true recurrence, were excluded. Dates of initial recurrences following CRT were defined according to the date that cancer-positive pathology was procured. Relapse following attempted salvage surgery was determined by either the date of pathology procurement or the date of radiologic studies revealing metastatic disease.

STATA version 8.0 was used to perform Kaplan-Meier survival analyses and to calculate median survival times. Log-rank tests were performed with STATA to assess the equalities of survivor functions and to obtain associated *P* values.

RESULTS

A total of 204 patients received primary concomitant CRT for cure between 1995 and 2004. Fifty-five patients (27%) had persistent disease or recurrences following primary CRT. Thirty-eight of these 55 patients had biopsy-proven locoregional disease and underwent attempted salvage surgery. The pathology from salvage surgery showed viable

carcinoma in all of the 38 patients. The remaining 17 patients recurred but did not receive salvage surgery, either because the disease was deemed unresectable or the patient refused. These 17 patients were therefore excluded from the analysis; 10 of these 17 patients had distant metastases.

Histologically proven persistent or recurrent SCC following CRT in these 38 patients occurred at the following sites: local in 21 patients (55%), regional in 12 (32%), and locoregional in 5 (13%). The median disease-free period after CRT in these 38 patients was 4 months. Thirty-nine percent of the patients ($n = 15/38$) had persistent disease, defined as biopsy-proven SCC within 3 months of completing CRT. The remaining 61% ($n = 23/38$) had recurrent disease following CRT, defined as biopsy-proven SCC occurring at a time greater than 3 months following primary CRT (range, 4-37 months).

Following the failure of CRT, salvage surgery was performed at the primary site with a neck dissection ($n = 18$), at the primary site alone ($n = 9$), or as a neck dissection alone ($n = 11$).

The mean and median follow-up times after salvage surgery were 17 and 11 months, respectively (range, 2-68 months). Of the 38 patients undergoing salvage surgery, 12 did not recur (32%). Twenty-six (68%) recurred following attempted salvage surgery; distant metastases without locoregional involvement occurred in 5 patients ($5/38 = 13\%$), distant metastases with locoregional involvement occurred in 5 patients ($5/38 = 13\%$), and the remaining patients recurred without distant disease ($13/38 = 34\%$) (see [Table 1](#)). Sites of recurrences following attempted salvage surgery were unavailable on 3 patients ($3/38 = 8\%$).

Disease-specific 12- and 24-month survival rates were 65.8% (95% CI, 46.5-79.6%), and 27.5% (95% CI, 11.0-47.1%), respectively ([Figure 1](#)). Overall 12- and 24-month survival rates were 60.0% (95% CI, 40.1-75.8%) and 26.7% (95% CI, 10.6-45.9%), respectively.

The disease-free median survival from the time of surgery was 9 months (95% CI, 5-19%) and the median overall survival was 16.6 months (95% CI, 10.8-22.0%). Locoregional control rates following salvage surgery at 12 and 24 months were 49.7% (95% CI, 32.0-65.2%) and 41.5% (95% CI, 21.3%-60.5%), respectively.

Those who initially presented with N3 disease had lower overall survival when compared to those without N3 disease ($P = 0.0115$) (see [Fig 2](#)). Only one out of five patients with initial N3 disease undergoing salvage surgery after failed chemoradiation lived beyond 7 months. One patient with N3 status had a neck dissection elsewhere following CRT before presenting to our institution requiring salvage surgery. Neck dissections were performed for four patients and a local resection without a neck dissection for one patient in the group initially presenting with N3 disease. Sites of recurrences for those with N3 disease were: lung metastases alone ($n = 2$), regional ($n = 1$), and lung and dermal metastases with a new primary ($n = 1$). One patient with N3

Table 1
Site of recurrence following salvage surgery correlated with extent of salvage surgery

	Local disease (n = 7)	Regional disease (n = 2)	Locoregional disease (n = 4)	Lung mets only (n = 2)	Lung + local (n = 2)	Lung + regional (n = 3)	Lung + ribs (n = 2)	Lung + spleen (n = 1)	Unknown (n = 3)
Local salvage surgery (n)	1	1	1		1			1	2
Salvage neck dissection (n)	2		1	2		1	1		
Local salvage surgery & neck dissection (n)	4	1	2		1	2	1		1

disease died as a result of hepatocellular carcinoma, and was censored accordingly from the survival analysis.

Those with positive margins or extranodal extension showed a slight trend towards poorer survival ($P = 0.1571$) compared to those with no extranodal disease or negative margins (see Table 2). T4 and stage IV status yielded no statistically significant survival difference after salvage surgery in our cohort. Additionally, site, gender, race, and age had no statistically significant effects on survival.

The surgical morbidity rate was 24 percent ($n = 9/38$). Surgical morbidities included: postoperative dysphagia ($n = 4$), wound breakdown requiring an operation ($n = 2$), respiratory failure ($n = 2$), mucocutaneous fistula ($n = 1$),

delirium ($n = 1$), esophageal variceal bleed requiring surgery ($n = 1$), and postoperative sepsis ($n = 1$). One of the patients who experienced wound breakdown received additional treatment following salvage surgery; the remaining 8 patients with surgical morbidities received no treatment after surgery. There were no statistically significant correlations between the occurrence of surgical morbidity and age, site, or stage.

DISCUSSION

The 27 percent 2-year survival rate in our study is lower than the survival outcomes in similar reports. A substantial

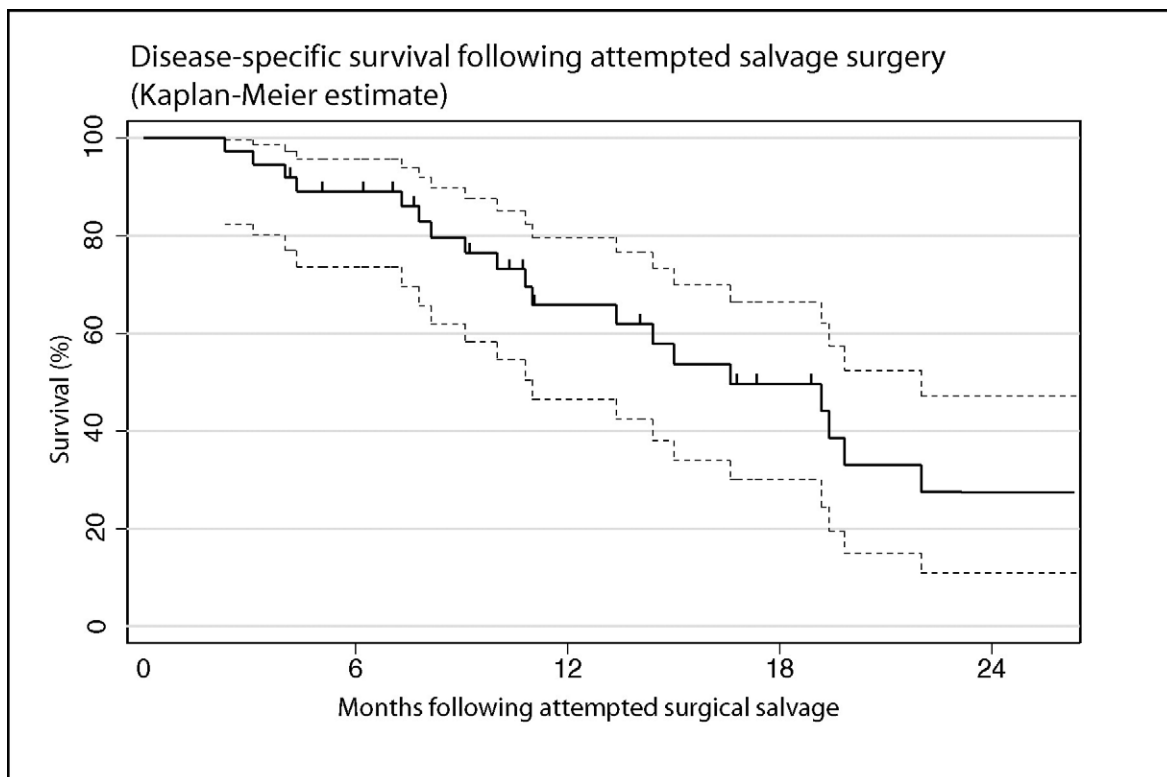


Figure 1 Disease-specific survival following attempted salvage surgery (Kaplan-Meier estimate). Solid line indicates survival from the time of salvage surgery. Dashed line indicates 95% confidence intervals. Vertical hash marks indicate censored.

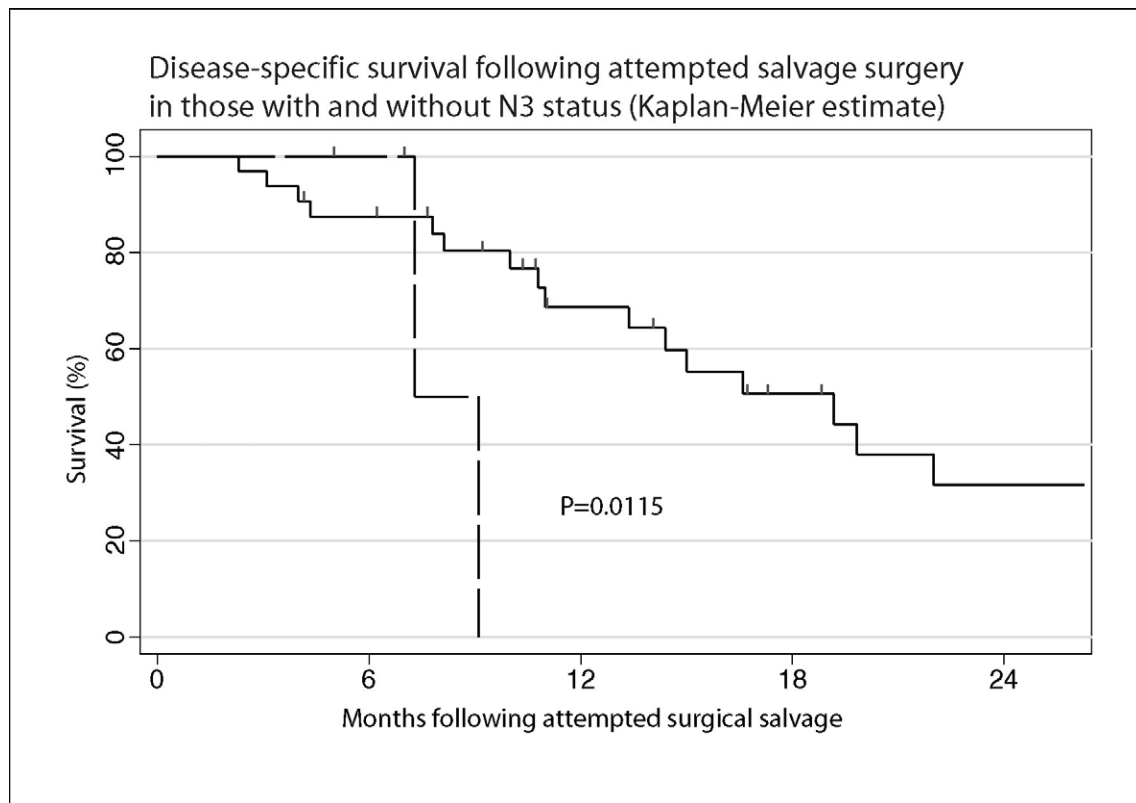


Figure 2 Disease-specific survival following attempted salvage surgery in subjects with and without N3 status (Kaplan-Meier estimate). Solid line indicates non-N3 status. Dashed line indicates N3 status. Vertical hash marks indicate censored.

difference between our cohort and cohorts in previous studies is our focused inclusion of those who received only concomitant CRT and subsequently had biopsy-proven recurrence and an initially unplanned salvage surgery. Additionally, the patients in our study had predominantly advanced SCC, with all but three patients having stage III or IV disease at initial presentation. A retrospective cohort study with survival rates similar to ours identified patients with T3 or T4 HNSCC who underwent salvage surgery after failing any attempted organ preserving treatment. The 2- and 5-year survival for 46 patients following salvage surgery was 31 percent and 15 percent, respectively; only 5 of 28 patients had long-term survival.¹⁴

The largest meta-analysis to date of salvage surgery efficacy reviewed 32 studies involving HNSCC patients who had received any attempted organ-preserving treatment prior to undergoing surgery.⁸ Overall median survival was 21.5 months, and the overall weighted average of 3-year survival rates was 37 percent. In this meta-analysis, if only the patients with stage III and IV disease are considered, 2-year disease-free survival was 33 percent and 22 percent, respectively.

One of the few studies that limited the cohort inclusion criteria to only those who received concomitant CRT intended for cure reviewed 31 patients with N3 head and neck cancer; 5 out of 19 who underwent salvage surgery had positive pathology.¹⁶ The 3-year overall survival for the entire group was 41 percent; survival analysis was not

performed specifically on the five who failed CRT and underwent salvage surgery, but would likely be lower than the 41 percent survival rate of the entire cohort. In another report, 12 of 54 HNSCC patients treated with definitive RT with or without chemotherapy failed to achieve local control; 4 of the 10 who underwent salvage surgery had documented recurrences.¹¹ The 2-year overall survival in the 12 who failed initial treatment was 47 percent.

The RTOG 91-11 trial randomized 547 patients with laryngeal carcinoma to 1 of 3 groups: neoadjuvant chemotherapy followed by RT, concomitant CRT, or RT alone.⁴ The three arms from the 91-11 trial were subsequently used to investigate the efficacy of salvage laryngectomy following attempted organ-preserving therapy. Following attempted salvage surgery, 24 percent ($n = 6/25$) in the CRT arm recurred and 2-year overall survival in this group was 71 percent.¹² Survival rates following salvage laryngectomy were similar in all three arms following the surgery.

The RTOG 91-11 study was focused exclusively on laryngeal cancer and excluded those who were unresectable or had large-volume stage T4 disease.⁴ Out of the 27 patients in the 91-11 concomitant CRT arm who recurred and had salvage laryngectomy, only two had T4 disease and none had N3. Lastly, patients required a Karnofsky performance score of 60 and above in the 91-11 study. It is probable that the inclusion of those with more advanced disease and poorer functional performance in our study gave a realistically poorer portrayal of survival.

Table 2
Differences in disease-specific survival following surgical salvage by demographics and disease characteristics

	N*	P value (Log-rank test)
Race	Blacks, n = 12 Whites, n = 25 Other, n = 1	0.2316
Age >60 at diagnosis, y	10	0.9507
Age 60 or less, y	28	
Gender	Males, n = 32 Females, n = 6	0.2351
T4 status	12	0.3891
Non-T4 status	25	
N3 status	5	0.0133
Non-N3 status	32	
Stage IV	26	0.4652
Non-stage IV	11	
Positive margins and/or extracapsular spread	15	0.1571
No positive margins and/or extracapsular spread	23	
Oral cavity	8	0.9927
Not oral cavity	30	
Oropharynx	16	0.8012
Not oropharynx	22	
Hypopharynx	2	0.9407
Not hypopharynx	36	
Larynx	12	0.8136
Not larynx	26	

*Staging-related N values do not total 38 because one patient's staging information was inaccessible.

At our institution, locoregionally advanced laryngeal primaries had no statistically significant survival difference when compared with nonlaryngeal primaries. This is inconsistent with the better survival outcomes usually observed in laryngeal compared with nonlaryngeal cancers. A retrospective cohort study investigated salvage surgery in 31 patients who had inadequate responses to neoadjuvant chemotherapy alone or neoadjuvant chemotherapy followed by RT between 1983 and 1991.¹³ Local control was achieved more in laryngeal (86%) than nonlaryngeal primaries (53%). Disease-specific survival was better in laryngeal than nonlaryngeal primaries (56% vs 24%; $P = 0.02$). Of note, patients with laryngeal cancer in this study are distinguished from those in our cohort by having received neoadjuvant therapy. Perhaps laryngeal primaries that fail concomitantly administered CRT are more aggressive cancers than those that fail neoadjuvant therapy, yielding a poorer outcome in our study when compared with other studies.

Sites of recurrences were unavailable for 3 of 26 patients with known recurrences following surgery. This missing data could affect locoregional failure rates. Ultimately, of the 35 patients undergoing salvage surgery for whom the site of recurrence was known, 17 of 35 (51%) achieved locoregional control (Table 1).

Our mean and median follow-up periods of 17 and 11 months seem short; however, long-term follow-up is difficult to achieve in a population with median survival of 16.6 months. Prospective data with longer follow-up are needed for this specific population.

Previous studies have reported complication rates associated with surgical salvage following all forms of organ-preserving treatment for HNSCC at 46 percent to 61 percent.⁸⁻¹⁰ In these previous studies, major complications occurred more often with surgery at the primary site when compared with neck dissections; mucocutaneous fistulas and wound breakdown were the most common morbidities. Our surgical morbidity rate of 24 percent included serious complications that required further treatments. In our cohort, there was no statistically significant correlation between the site of salvage surgery and the occurrence of surgical morbidity.

CONCLUSION

Our study is distinguished from the aforementioned retrospective cohort studies by our focused clinical question addressing surgical salvage efficacy in only those who had a biopsy-proven failure of primary concomitant CRT, and by our inclusion of patients with advanced, bulky disease carrying a poor prognosis. This data provides realistically poor survival estimates for initially resectable locoregionally advanced HNSCC patients who have undergone attempted surgical salvage following CRT intended for cure. Disease-specific 2-year survival in this group of patients was 27.5%, while 2-year locoregional control was 41.5%. Patients who initially presented with N3 disease had the

worst outcomes following salvage surgery. Twenty-four percent of patients suffered serious surgical morbidity. Although surgical salvage in this group of patients offers the only chance of cure, that chance is minimal. It does offer a chance at locoregional control, though most of these patients will ultimately die of distant disease. Patients and physicians should have realistic expectations regarding expected outcomes and patients should be well informed prior to embarking on such treatment. Larger prospective studies with long-term follow-up are needed to further investigate survival in this population.

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