Salvage Resection for Isolated Local and/or Regional Failure of Head/Neck Cancer Following Definitive Concurrent Chemoradiotherapy

Case Series and Review of the Literature.

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ABSTRACT - Background: Primary management of advanced head/neck cancers involves concurrent chemoradiotherapy. Subsequently, regional and local failures are managed with resection but there have been few reports that describe the morbidity and disease control outcomes of surgical salvage in this setting. Methods: Retrospective analysis describes complications, survival, and patterns of failure after salvage resection of isolated local and/or regional failures of head/neck cancer following definitive concurrent chemoradiotherapy. Results: Sixteen patients were identified for inclusion: laryngectomy in 11 patients, oral cavity/oropharynx resection in 2 patients, and neck dissection alone in 4 patients. Ten patients required graft tissue reconstruction (6 pedicle and 4 free flap). Median post-operative hospitalization was 7 days (range 3-19), and 4 patients required hospital re-admission. At a median survivor follow-up of 15.8 months (range 4.3-34.9), 10 patients were alive (6 without evidence of disease). Seven patients experienced disease recurrence at a median 6.7 months (range 0-12.6) following salvage resection (2 with isolated distant failures). Estimated 2-year local/regional control, freedom from failure, and overall survival were 58%, 39%, and 58%, respectively. Conclusions: Surgical salvage after primary definitive concurrent chemoradiotherapy is feasible with toxicity and outcomes similar to prior radiotherapy alone or sequential chemotherapy and radiation. Local and regional recurrence remains the predominant pattern of failure.

Keywords: Head and neck neoplasms, Combined modality therapy, Salvage therapy, Organ preservation therapy

INTRODUCTION
Locoregionally advanced head and neck cancers are optimally treated with definitive concurrent chemoradiotherapy or surgical resection followed by radiotherapy with or without chemotherapy. Despite aggressive local treatment, approximately 20-36% of patients will experience locoregional recurrence within 3-5 years, representing 50-67% of all recurrences (1-3). In patients who experience disease recurrence within a previously irradiated field, aggressive salvage surgical resection is the preferred intervention (4). Previously reported series of surgical salvage have generally included patients treated with suboptimal primary therapy (1).
therapy (radiotherapy alone or sequential chemother- apy and radiotherapy), while subsequent randomized trials (5-8) and a meta-analysis (9) have demonstrated superior locoregional control and survival for concurrent chemoradiotherapy over radiotherapy alone or sequential chemoradiotherapy (10, 11), albeit associated with increased risk of adverse effects (5). Few studies have evaluated the compli- cations and outcomes of surgical salvage of locore- gional failures following modern platinum-based concurrent chemoradiotherapy (10-13).

The present study is a retrospective analy- sis of complications, disease control, patterns of failure, and survival in a cohort of patients treated with salvage surgical resection at the Medical Uni- versity of South Carolina (MUSC).

METHODS

Ethical Considerations

Following Institutional Review Board ap- proval at MUSC, a research spreadsheet was cre- ated with study-specific patient, treatment, and out- come data fields. Non-protected health information remained within the primary sources (departmental chart, quality assurance database(s), and/or elec- tronic medical record system).

Selection Criteria

Eligible cases were identified by review of the radiation oncology departmental quality assurance database and a treatment management software. The database contained all patients at MUSC that were initiated on definitive chemoradiotherapy; eligible cases were identified within the database by searching for head and neck cancer patients. Surgical salvage was defined as curative-intent resection for residual disease or recurrent primary tumor, nodal disease, or second primary tumor within an irradiated field following platinum-based concurrent chemoradiotherapy. Primary definitive chemoradiotherapy and surgical resection and re- construction were not necessarily performed at MUSC in all cases. Exclusion criteria for this study included primary chemoradiotherapy at an outside institution, evidence of distant metastatic disease at the time of radiotherapy and/or post-salvage follow-up of less than 3 months (unless evidence of disease progression/recurrence and/or death). All patients included in descriptive outcomes analysis were required to have had pathologic proof of squa- mosus cell carcinoma recurrence.

Patient Work-Up and Management

All patients were initially evaluated at the MUSC Hollings Cancer Center multidisciplinary head and neck oncology clinic, with evaluations by surgical, medical, and radiation oncology phy- sicians as well as speech therapy and dental on- cology/maxillofacial-prosthodontic specialists as indicated. Following complete metastatic workup, which consisted of chest computed tomography (CT) and/or magnetic resonance imaging (MRI) (PET or PET/CT), patients were offered surgical salvage based on feasibility surgical resection and/or pa- tients’ medical operability. When microvascular “free flap” reconstruction was required, periheral vascular studies were performed in order to identify viable graft tissue harvest sites. Surgical intervention was left to the discre- tion of the treating head/neck surgeon and recon- struction specialist. All patients underwent at least selective neck dissection at the time of salvage resection and more aggressive intervention if indicated (where there was neck recurrence (particularly with radiographic and/or clinical evidence of extranodal extension). When reconstruction was indicated, rotational flaps were constructed from pectoralis major and free flaps were harvested from anterior thigh, radial forearm, or fibula sites. Following completion of treatment, patients were assessed at a minimum of every 3 months for 2 years, then every 6 months for 3 years, and annu- ally thereafter. Surveillance fibroptic endoscopy was performed routinely during follow-up appoin- tments. A neck CT or MRI was generally performed 2-3 months following salvage resection, then again 6 months later and/or as indicated based upon clini- cal suspicion. During the follow-up period, meta- static surveillance with chest X-ray and/or chest CT was generally performed once within 6 months of salvage, then required in situations of clinical sus- picion or at time of locoregional recurrence.

Endpoints and Definitions

The principal outcome measure of this study was overall survival which was measured from date of salvage resection to last follow-up or death. Secondary outcome measures included locoregional control, freedom from second recurrence (earliest sign of clinical, radia- tional, or pathologic disease) and last follow-up or if there was no evidence of disease recurrence. A patient was considered to have died of treatment- associated toxicity if there was clear association between toxicity and death or if the patient died during or within 30 days of hospitalization attributed to treatment-emission toxicity (CT) and/or positional emission tomography (PET). Treatment-associated mortality was considered an event for freedom from failure. If a patient died of unclear cause, but was known to have had recur- rent disease prior to death, he/she was considered to have died of disease. Patterns of failure were recorded by initial site(s) of disease recurrence.

Salvage Cohort

| Age (Median) | # | % |
|-------------|---|---|
| 59 yrs (40-80) | 8 | 50 |

| Gender | # | % |
|-------|---|---|
| Male | 12 | 75 |
| Female | 10 | 62 |

| Initial Disease Site | # | % |
|---------------------|---|---|
| Oropharynx | 5 | 31 |
| Larynx | 10 | 62 |
| Hypopharynx | 1 | 6 |

| Interval Since Definitive Chemoradiation | Median (Range) | # | % |
|------------------------------------------|--------------|---|---|
| 7.6 months (1-12.6) | 700 cGy | 7 | 41 |

| Prior RT Characteristics | Median Dose (Range) | # | % |
|--------------------------|---------------------|---|---|
| 7000 cGy | 4800-7000 | 7 | 41 |

| Relation to Prior RT Field | Median Dose | # | % |
|---------------------------|------------|---|---|
| In-Field | 7000 cGy | 14 | 88 |
| Field Margin | 2 | 12 |

| Recurrent Tumor Site | Median Dose | # | % |
|----------------------|------------|---|---|
| Primary | 10 | 62 |
| Second Primary | 1 | 6 |
| Irradiated Neck | 5 | 31 |

| Chest Staging at Recurrence | Median Dose | # | % |
|-----------------------------|------------|---|---|
| None | 1 | 6 |
| Chest Radiography | 5 | 31 |
| Chest CT & PET | 10 | 62 |

Table 1: Patient, tumor, and staging characteristics

| Excludes one patient without evidence of residual carcinoma at salvage resection. Chemoradiation (T) with or without concurrent chemoradiation. | 9 patients survived >5 years without recurrence. |}

Literature Review Search Criteria

An Ovid Medline search was performed using the search terms “head and neck cancer,” “local neoplasm recurrence,” “recurrence,” and “resection.” Articles were searched for post- surgery, post-chemoradiation, and post-radiotherapy experiences. A secondary search was performed by reviewing references from articles identified from the search.

Statistical Analysis

The Kaplan-Meier method was used to cal- culate estimated locoregional control, freedom from failure, and overall survival for the entire cohort. Proportionality was tested for each covariate of in- terest. Those that failed were either not included or were reported by the data source to the propor- tionality assumption. Cox regression was used to esti- mate the hazard ratio (HR) comparing risk of time- to-event outcomes by covariates. Disease control estimation, survival estimation, and univariate analy- ses were performed using R version 2.6.1 (The R Core Development Team; http://www.r-project.org).
salvage resection. Extranodal extension within the neck was documented in 5 cases. Salvage surgical intervention involved total laryngectomy in 8 patients, total laryngopharyngectomy in 1 patient, supracricoid laryngectomy in 2 patients, oral cavity/oropharyngeal composite resection in 2 patients, and neck dissection alone in 4 patients. All patients’ necks were surgically addressed at salvage, involving unilateral selective dissection in 5 patients, unilateral modified radical neck dissection in 2 patients, unilateral radical neck dissection in 1 patient, bilateral selective neck dissections in 6 patients, and bilateral modified radical neck dissections in 3 patients. 10 patients required flap reconstruction (6 pedicle and 4 free). The median post-operative hospitalization was 7 days (range 3-19), with significant complications of hematoma (4), wound breakdown (3), and fistula (1). 4 patients required a median duration 13 days (range 4-30) hospital admission following initial discharge Reasons for re-hospitalization included pharyngocutaneous fistula, wound breakdown, neck abscess, and bleeding at the gastrostomy site (associated with supratherapeutic anticoagulation). One patient received immediate post-salvage chemotherapy and one concurrent chemoradiotherapy for adverse pathologic features (surgical margin and extranodal neck disease, respectively). 2 out of 10 patients who underwent graft tissue reconstruction at the time of salvage developed complications requiring intervention. One patient developed necrosis along the distal margin of a rotational pectoralis flap, requiring takedown and reconstruction using a second pedicle flap. No further complications were observed. Another patient experienced delayed wound dehiscence of a free flap reconstruction, with pharyngocutaneous fistula formation approximately 2 months post-salvage/reconstruction. The flap was removed and the defect was reconstructed with a rotational pectoralis flap, resulting in no further complication.

Two patients died of treatment-associated complications. One patient underwent salvage bilateral modified radical neck dissections for failure within an irradiated neck (4 months after completion of chemoradiotherapy for T4aN2cM0 hypopharyngeal cancer originating at the pyriform sinus). Recurrent disease in the neck was significant for extension into the soft tissues of the neck as well as perineural and lymphovascular space invasion. The post-operative course was complicated by a neck hematoma requiring evacuation and an cutaneous fistula, with a salivary leak. The patient was ultimately discharged 10 days after salvage resection but died 3 days later of unspecified cause. Another patient required surgical salvage for residua/progressive primary tumor 10 weeks following concurrent chemoradiotherapy (initial cT3N0 oro-pharyngeal cancer). Following salvage palatoplasty with inferior maxilllectomy and partial glossectomy with anterolateral thigh free flap reconstruction and bilateral selective neck dissections, the patient experienced bleeding from the oronasal and neck incisions. These complications resolved following discontinuation of heparin, after which the patient was discharged (8 days post-salvage). The patient died later that day of an unspecified cause. At a median survivor follow-up of 15.8 months (range 4.3-34.9) post-salvage, 10 patients were alive (6 without evidence of disease) and 6 patients had died (3 of disease, 2 of intervention, and 1 of unknown cause). Seven patients experienced disease recurrence at a median 6.7 months post-salvage (range 0-12.0), involving 1 completely resected primary site, 1 incompletely resected primary site, 2 dissected necks, 1 resected extracapsular and dissected neck, and 2 isolated distant failures. Secondary surgical interventions included chemotherapy in 2 patients, concurrent chemoradiotherapy and re-irradiation in 1 patient, re-resection in 1 patient, and supportive care for 3 patients. The estimated median overall freedom from failure for the study group was 10.8 months, while the median overall survival had not yet been reached (and was thus inestimable). The estimated 1- and 2-year locoregional control were both 58.0% (95% confidence interval: 35.4%-95.2%), as demonstrated in Figure 1. The estimated 1- and 2-year overall freedom from failure were 46.9% (27.0%-81.4%) and 39.1% (20.2%-75.4%), respectively (Figure 2). The estimated 1- and 2-year overall survivals were 78.7% (59.7%-100%) and 58.3% (35.1%-97.0%), respectively (Figure 3).

Univariate analyses of patient-, tumor-, and treatment-related factors associations with locoregional control, freedom from failure, and overall survival are demonstrated in Table 3. Despite the limitation of small sample size, the pathologic nodal stage and presence of extracapsular carcinoma within the soft tissue of the neck were associated with significantly decreased rates of locoregional control and freedom from disease failure. The association of these factors with overall survival was not demonstrated at a statistically significant level; however, there was a trend toward worse survival for patients with metastatic carcinoma within neck soft tissue. Toxicities, local control, and survival outcomes from the present study are pooled with other published series of surgical salvage following concurrent chemoradiotherapy in Table 4.

DISCUSSION

The role of surgical resection in locoregionally advanced head/neck cancer has evolved over time. Modern platinum-based concurrent chemoradiotherapy yields equivalent disease control, and is the preferred primary therapy when functional organ preservation is feasible (14). Despite ag-

| Factor | Locoregional Control | Freedom From Failure | Overall Survival |
|--------|----------------------|----------------------|-----------------|
|        | HR p                 | HR p                 | HR p            |
| Gender | 1.420 0.75           | 1.350 0.87           | 1.520 0.71      |
| Race   | 0.865 0.87           | 0.396 0.25           | 0.280 0.26      |
| Age    | 0.910 0.13           | 0.954 0.23           | 1.010 0.88      |
| Active Tobacco Use | 1.790 0.56 | 0.601 0.53 | 0.360 0.36 |
| Time to Recurrence | 1.090 0.098 | 1.030 0.38 | 0.894 0.22 |
| rCT-Stage | 1.000 0.99 | 0.883 0.45 | 0.852 0.47 |
| rCN-Stage | 1.480 0.056 | 1.360 0.058 | 1.120 0.62 |
| rAJCC Stage | 1.660 0.27 | 1.570 0.2 | 1.080 0.87 |
| rPT-Stage | 0.953 0.81 | 1.050 0.71 | 0.847 0.45 |
| rPN-Stage | 1.940 0.024 | 1.700 0.012 | 1.370 0.19 |
| rAJCC Stage | 2.830 0.086 | 2.200 0.083 | 1.420 0.57 |
| Margin at Salvage | 4.670 0.094 | 3.260 0.097 | 1.750 0.54 |
| Lymphovascular | 1.860 0.54 | 1.850 0.46 | 0.972 0.98 |
| Perineural Invasion | 2.280 0.51 | 2.460 0.31 | 1.380 0.73 |
| Metastatic Carcinoma in Neck Soft Tissue | 12.000 0.034 | 8.300 0.013 | 4.960 0.088 |

Table 3: Univariate Analysis of Factors Associated with Study Endpoints.
In patients who experience disease recurrence within a previously irradiated field, aggressive salvage surgical resection is the preferred intervention, yielding 55% local control and 32-39% survival at 5 years (4,15). These have primarily included patients treated with radiotherapy alone or sequential radiotherapy and chemotherapy, which have demonstrated inferior disease control when compared with concurrent chemoradiotherapy (5-10).

Few reports have focused on the complications, disease control, and survival outcomes for concurrent chemoradiotherapy patients. The RTOG 91-11 study provides the best comparative data for salvage resection in the setting of radiotherapy versus concurrent chemoradiotherapy (5). Of 517 patients initially randomized, 129 required total laryngectomy (95% for recurrent/residual cancer) (10). While pharyngocutaneous fistula formation was less common in the radiotherapy alone arm (15%) compared to the concurrent chemoradiotherapy arm (30%), this did not reach statistical significance (p=0.05). Similarly, the overall incidence of major and minor complications was not significantly different between treatment groups (52-59%). These consisted mainly of fistulae formation, infection, wound dehiscence, dysphagia, and/or inability to take fluids, which are consistent with complications reported by other published series (10-12). Within the RTOG concurrent chemoradiotherapy group, the rate of fistula was somewhat higher than that described in single-institution series (30% versus 5-8%) (10-12). This may be associated with inherent differences between the therapies (disease site, reconstruction techniques) and inconsistent scoring of self-limited or “minor” fistulae in the retrospective analyses relative to the RTOG 91-11 analysis. If only “major” fistulae are considered for the RTOG study, the rate (11%) is more consistent with the retrospective series. Within our own series, 2 of the 3 fistulae were self-limited salivary gland leaks which resolved with conservative measures. Thus, the overall risk of significant fistula formation after surgical salvage for concurrent chemoradiotherapy failures is approximately 5-10%. Graft tissue reconstruction may have a beneficial impact on reducing these major complications. A single-institution analysis of salvage laryngectomy following radiotherapy or chemoradiotherapy demonstrated a reduced risk of fistula for free flap reconstruction compared with primary closure (18% versus 50%, p=0.08) (16). Similarly, the risk of stricture and feeding tube dependence was reduced with free flap reconstruction. It should be noted that this analysis was restricted to patients whose disease was generally limited to the larynx, excluding patients for whom partial pharyngectomy or total laryngopharyngectomy would have been required. Within the present study population, complications were similar regardless of graft tissue reconstruction (4 of 11 reconstructed patients versus 2 of 6 primary closure patients).

The present study demonstrated an estimated 2-year overall survival of 58%, which is comparable to other single-institution series of post-chemosalvage patients following radiotherapy or chemoradiotherapy demonstrated a reduced risk of fistula formation after surgical salvage for concurrent chemoradiotherapy (5-10%).

Table 4: Published Series of Toxicities and Outcomes for Salvage Resection of Concurrent Chemoradiotherapy Recurrences in Head/Neck Cancer.

Twelve of fourteen underwent surgical salvage for residual or progressive disease noted at post-chemosalvage assessment, local control and survival results reflect outcome recurrences rather than 2-year estimates. All survival data based upon 10 patients with pathologic disease at salvage, excludes one patient with squamous cell carcinoma at post-chemoradiotherapy biopsy but no evidence of disease following salvage laryngectomy.

![Figure 2: Freedom from disease failure for salvage resection population.](Image 936x93 to 1161x303)

![Figure 3: Overall survival for salvage resection population.](Image 688x93 to 914x303)
high-risk features of involved surgical margins and/or extranodal neck disease (11). Alternatively, these patients may simply have more advanced disease and would have a worse prognosis regardless of post-salvage intervention. Within the present study, two patients underwent immediate post-salvage therapy for high-risk pathologic features. One patient received immediate chemotherapy for involved surgical margins and another underwent concurrent chemotherapy and re-irradiation for extranodal carcinoma within their previously irradiated neck. Neither patient experienced significant post-salvage complications; however, both experienced local disease failure within 6 months.

Despite aggressive surgical salvage, the majority of disease recurrences involve the primary tumor site. Of 7 patients from the present series who experienced disease recurrence, 5 recurrences involved the tumor bed. This is consistent with other published data (11); however, the pattern of failure appears to shift toward more distant metastasis for advanced node-positive recurrences (11,13) and those treated with radiotherapy alone (10,20). The timing of post-salvage disease failure was also consistent with previously published series (median 9 months) (11,18); all but one patient within the present series failed within one year (isolated distant failure at 12.6 months). As suggested by Goodwin’s comprehensive review (4), the rapidity of post-salvage recurrence may be attributable to advanced stage at initial recurrence presentation. Specifically, the analysis demonstrated an inverse relationship between recurrent disease stage and post-salvage median disease-free survival (>22.1,
[81x240]14.4, and 5.5 months for stages I, II, III, and IV disease, respectively). Within the present series, all patients who experienced post-salvage disease failure had recurrent pathologic stage III (n=2) or IV (5) disease.

Salvage resection of local and/or regional head/neck cancer failures following platinum-based concurrent chemoradiotherapy is feasible and can provide the opportunity for disease control and survival. Post-operative complication rates, timing and patterns of disease failure, locoregional control, freedom from disease failure, and overall survival rates are similar to those described in series of surgically salvaged patients treated with prior radiotherapy alone or sequential chemotherapy and radiation.

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