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ORIGINAL ARTICLE

TOXICITY AND SURVIVAL OUTCOMES OF HYPERFRACTIONATED SPLIT-COURSE REIRRADIATION AND DAILY CONCURRENT CHEMOTHERAPY IN LOCOREGIONALLY RECURRENT, PREVIOUSLY IRRADIATED HEAD AND NECK CANCERS

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Abstract: *Background*. Reirradiation of locoregionally recurrent, previously irradiated head/neck cancer may be considered in situations of unresectability, medical inoperability, or adverse pathologic features found at salvage resection.

Methods. Retrospective cohort analysis of toxicity and survival outcomes in locoregionally recurrent, previously irradiated patients with head/neck cancer treated with hyperfractionated split-course radiotherapy and concurrent chemotherapy.

Results. Between March 1998 and September 2006, 39 patients initiated reirradiation at median of 2.3 years (range, 0.5–19) following prior radiotherapy. At median survivor follow-up of 24.5 months (range, 3–63.9), 10 patients are alive without evidence of disease. Median survival is 19.0 months, with estimated 1-, 2-, and 3-year overall survivals of 60.1%, 45.1%, and 22.7%, respectively. Locoregional failure was the predominant site of postreirradiation recurrence. Male sex, total radiotherapy dose, cycles of chemotherapy completed, and clinical response were associated with improved overall survival.

Conclusions. Reirradiation can offer long-term survival for patients with recurrent, previously irradiated head/neck cancers. © 2009 Wiley Periodicals, Inc. **31**: 493–502, 2009

Keywords: head and neck neoplasms; reirradiation; chemoradiotherapy; salvage therapy; squamous cell carcinoma

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Locoregionally advanced head and neck cancers are optimally treated with definitive concurrent

chemoradiotherapy or surgical resection followed by radiotherapy (RT) with or without chemotherapy.[1] Despite aggressive local treatment, approximately 20% to 36% of patients will experience locoregional recurrence within 3 to 4 years, representing 50% to 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.[4–6] Unfortunately, a significant number of patients are unable to undergo salvage resection, due to medical comorbidities, tumor invasion of unresectable structures (eg, carotid artery, prevertebral fascia), or patient decision.[4] Reirradiation of the head and neck after previous definitive or postoperative RT had once been considered contraindicated due to concerns for severe toxicities (such as fistula, carotid rupture, osteoradionecrosis, soft tissue necrosis, and/or radiation neuropathy); however, by employing a split-course RT regimen, altering the RT fractionation, and/or reducing field size to target only gross disease, several single institution reports demonstrated feasibility of the technique.[7–13] These findings were subsequently validated in 2 phase II Radiation Therapy Oncology Group (RTOG) studies, with 16% to 25% 2-year survival and 3% to 8% treatment-associated mortality.[14,15] We here describe the toxicity and outcomes of curative-intent salvage reirradiation and concurrent chemotherapy in a cohort of patients treated at the Medical University of South Carolina (MUSC).

MATERIALS AND METHODS

Following Institutional Review Board (IRB) approval at both MUSC and the Ralph H. Johnson Veterans' Affairs Medical Center (Charleston, SC), a research database was created with study-specific patient, treatment, and outcome data fields. Eligible cases were identified by review of departmental quality assurance database and office management software. After selection for head and neck–specific cases, a review of patient records was performed in order to eliminate palliative and nonhead/neck cancer cases. Inclusion criteria for the present study included: salvage reirradiation for head/neck squamous cell carcinoma recurrence or in-field/marginal second primary after prior definitive or adjuvant head/neck RT (exceeding 45 Gy), absence of distant metastatic disease, minimum postreirradiation follow-up of 3 months (unless evidence of disease progression/recurrence), and reirradiation administered twice-daily (hyperfractionated), every other week (split-course) with concurrent chemotherapy. Chemotherapy was administered on days of RT, typically between treatment fractions. The entire course of salvage therapy was conducted at MUSC.

All patients were initially evaluated at the MUSC Hollings Cancer Center multidisciplinary head and neck oncology clinic, with evaluations by surgical, medical, and radiation oncologists, as well as speech therapy and dental oncology/maxillofacial-prosthodontic specialists when indicated. Following complete metastatic workup, generally consisting of chest CT and/or positron emission tomography (PET or PET/CT), patients were offered surgical or nonsurgical therapy as appropriate. Patients were generally offered salvage concurrent chemoradiotherapy only when they were functionally independent at baseline, requiring only intermittent assistance with activities of daily living (equivalent to Karnofsky Performance Status score of $\geq$60%).

When patients were considered to have unresectable disease, were medically inoperable, elected nonsurgical curative salvage therapy, or demonstrated adverse pathologic features (involved margin, nodal extracapsular extension) at salvage resection, reirradiation was considered. Eligibility for reirradiation included minimum interval of 6 months since completion of previous head/neck irradiation and previous RT course spinal cord dose $\leq$45 Gy (in accordance with RTOG eligibility criteria).[14,15] Sites of recurrence were recorded with relation to previous irradiation fields: "in-field, primary," "in-field, neck," or "field margin." Radiation therapy treatment planning consisted of a head and neck CT with the patient lying supine, using a patient-specific thermoplast mask with bite block immobilization. Contrast was used whenever feasible and safe in order to optimize target delineation. Thin (2.5–3 mm) axial images were imported into the treatment planning software system, and a radiation therapy plan was designed for each patient. Early in the experience, patients were planned with 3-dimensional reconstruction and dosimetric verification. More recently, patients have been planned with intensity-modulated radiotherapy (IMRT), using an inverse-planning algorithm,

and treated with step-and-shoot multisegmented photon beamlets. Only the clinically and/or radiographically apparent site of recurrence (gross tumor volume [GTV]) was targeted; no elective lymph node regions or areas of subclinical disease were included in the treatment volume. Thus, the clinical target volume was equal to the GTV. A small expansion of 3 to 5 mm in all dimensions was made in order to account for daily setup variation. Block (or collimator) edges were extended beyond the PTV sufficient to ensure coverage of the PTV by the 95% isodose line. Dosimetric objectives included cumulative maximal spinal cord dose $<$ 50 Gy, maximal brainstem dose $<$ 54 Gy, and coverage of the PTV by the 95% isodose line (at minimum). The beam arrangement varied specific to the recurrence location, and bolus was used as necessary to ensure adequate dosimetric coverage of superficial targets (e.g., dermal involvement).

RT was delivered twice daily, 5 days per week (typically Monday through Friday), in a 1 week on/1 week off split course. The total dose prescribed to the site of recurrence was 60 Gy at 1.5 Gy per fraction twice daily, for a total of 40 treatment fractions. A minimum of 6 hours between treatment fractions was required; chemotherapy was typically administered during this interval. Two chemotherapy regimens were employed during the time period encompassed by this retrospective series: (1) 5-fluorouracil (5-FU, 300 mg/m^2 per day) and hydroxyurea (1500 mg/m^2 per day), used from 1997 through 2000; and (2) cisplatin (15 mg/m^2 per day) and paclitaxel (20 mg/m^2 per day), used thereafter.

Radiation-associated acute toxicity data was recorded in prospective fashion during weekly on-treatment patient assessments. Acute adverse effects were scored according to the RTOG Acute Toxicity Scoring system (http://www.rtog.org/members/toxicity/acute.html). RT was generally delayed or held only when the patient experienced radiation-associated grade 4 toxicity, hospitalization for nonhematologic treatment-associated toxicity, or other potentially life-threatening condition. Chemotherapy-associated adverse effects were determined retrospectively by review of patient records and routinely drawn hematologic profiles, and were scored according to National Cancer Institute-Common Toxicity Criteria grading system (NCI-CTC; http://ctep.cancer.gov/forms/CTCAEv3.pdf). Chemotherapy was generally delayed when patients experienced fevers associated with absolute neutrophil count $<$1000/mL, thrombocytopenia $<$25,000/mL, or severe nausea refractory to antiemetics and/or with dehydration requiring intravenous rehydration. Chemotherapy was reinitiated following reversal of these symptoms.

Following completion of treatment, patients were followed at a minimum of every 3 months for 2 years, then every 6 months for 3 years, and annually thereafter. Surveillance fiberoptic endoscopy was performed routinely during follow-up appointments. A neck CT, PET/CT, or MRI was generally performed 2 to 3 months following completion of RT, then every 6 months until 2 to 3 years after completion of therapy, and annually thereafter. During the follow-up period, metastatic surveillance with chest X-ray and/or chest CT was generally performed only in situations of clinical suspicion or at time of recurrence.

The principal outcome measure of this study was overall survival, measured from date of reirradiation start to last follow-up or death. Secondary outcome measures included freedom from failure, pattern of failure, treatment-associated toxicity, and identification of prognostic factors for overall survival. Patient status at last follow-up was recorded as "alive, no evidence of disease," "alive with disease," "died of or with disease," "died of treatment-associated toxicity," "died of other cause," or "died of unknown cause." Freedom from failure was measured from date of reirradiation initiation to date of recurrence (earliest sign of clinical, radiographic, or pathologic disease) or last follow-up 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 attributable to treatment toxicity (without other evident cause). Treatment-associated mortality was considered an event for freedom from failure. If a patient died of unclear cause, but was known to have had recurrent disease prior to death, he/she was considered to have died of or with disease. If a follow-up note and/or radiologic assessment was available documenting no evidence of disease within 6 weeks of death, he/she was considered to have died of other cause, and freedom from failure was censored at date of death. Deaths beyond 6 weeks of last follow-up (without evidence of disease recurrence/progression) were categorized as died

of unknown cause; freedom from failure was censored as without evidence of disease at date of last follow-up. Patterns of failure were recorded by initial site(s) of disease recurrence.

Prognostic factors assessed for association with overall survival included age, sex, race, number of previous head/neck cancers, medical operability, surgical resectability, recurrent tumor location, local failure versus second primary, interval since completion of previous RT, prior RT dose >65 Gy, recurrent AJCC clinical stage, primary versus postoperative salvage reirradiation, completion of ≥58 Gy reirradiation, chemotherapy regimen, completion of ≥3 and 4 cycles of chemotherapy, hospitalization during reirradiation, and clinical tumor response at completion of reirradiation.

Statistical Analysis. Overall survival and freedom from progression for the entire cohort were estimated using the Kaplan–Meier method. Patient- and treatment-related factors from the research database were analyzed to determine prognostic factors for overall survival. Stepwise univariate logistic regression analyses of the patient-, disease-, and treatment-related factors were performed in order to identify factors statistically significantly associated with overall survival. Multivariate analysis was not performed due to small cohort size. All p values $<.05$ were considered statistically significant. All analyses were performed using Statistical Analysis Systems, version 9.1 (SAS Institute, Cary, NC).

RESULTS

Between March 1997 and April 2007, 39 patients were identified for inclusion in the present study. Three additional patients were ineligible due to ongoing reirradiation ($n = 2$) or insufficient follow-up without recurrence or survival data ($n = 1$). Within the study cohort, reirradiation was initiated as primary salvage in 30 patients and adjuvant to salvage resection in 9 patients. Adverse pathologic features within the latter group included involved nodal extracapsular extension ($n = 5$), involved surgical margin ($n = 2$), or both ($n = 2$). Patient demographics and previous treatment characteristics are shown in Table 1. Within rationale for use of salvage concurrent chemoradiotherapy, all 13 patients who declined surgical intervention ("patient decision" in Table 1) were medically operable with technically resectable disease. In addition, all 7 medically inoperable patients had technically resectable disease. Recurrent tumor clinical and pathologic staging are demonstrated in Table 2.

Table 1. Patient characteristics.

	Reirradiation cohort ($n = 39$)	
	%	No.
Age		
Median (range)	57 yrs (39–75)	
≥60 y	46.2	18
Sex		
Male	74.4	29
Race		
White	76.9	30
Prior head/neck cancers		
1	74.4	29
2	17.9	7
3	5.1	2
4	2.6	1
Present recurrence site		
Oral cavity	10.3	4
Oropharynx	46.2	18
Larynx	7.7	3
Hypopharynx	5.1	2
Nasopharynx	2.6	1
Nasal cavity	2.6	1
Neck	25.6	10
Interval since prior RT completion		
Median (range)	2.3 years (0.5–19)	
Prior RT characteristics*		
Median dose (dose range)	6680 cGy (5400–7600)	
Standard fractionation	88.2	30
Hyperfractionation	8.8	3
Standard + brachytherapy	2.9	1
Relation to prior RT field		
In-field, primary	48.7	19
In-field, neck	17.9	7
Field margin	33.3	13
Recurrence type		
Primary (local)‡	30.8	12
Second primary	20.5	8
Irradiated neck	23.1	9
Local + neck	17.9	7
Second primary + neck	7.7	3
Intervention		
Reirradiation only	76.9	30
Postoperative reirradiation	23.1	9
Rationale for nonsurgical salvage†		
Medically inoperable	23.3	7
Unresectable disease	33.3	10
Patient decision	43.3	13

Abbreviation: RT, radiotherapy.
**For 34 patients with available prior RT records.*
†For 30 patients treated with primary reirradiation.
‡Includes 3 patients with extensive submucosal failures and contiguous unresectable disease in the neck.

Table 2. Recurrent tumor stage characteristics.*†

	cT0	cT1	cT2	cT3	cT4a	cT4b
cN0		4	2	2	5	7‡
cN1	2	1		1	2	3
cN2a	3					
cN2b	1		3			1
cN2c				1	1	
cN3						
	pT0	pT1	pT2	pT3	pT4a	pT4b
pN0						1
pN1	1				1	1
pN2a					1	1
pN2b		1	2			
pN2c						
pN3						

*Includes clinical staging for all 39 patients and pathologic staging for 9 patients with initial attempted surgical salvage.
†Clinical and pathologic staging include 1 patient with c/pT0N1M1 disease (synchronous independent dermal and intracapsular nodal disease within irradiated neck).
‡Three patients with cT4bN0 disease had unresectable parapharyngeal and/or retropharyngeal masses unable to characterize as primary tumor versus nodal disease with significant extracapsular spread.

Twenty-seven patients (69.2%) completed the full prescribed course of reirradiation (≥60 Gy) RT, and 31 of patients (79.5%) completed all 4 cycles of intended chemotherapy. Detailed treatment-associated characteristics are outlined in Table 3.

Acute treatment-associated toxicities are profiled in Table 4. Of note, fatal treatment-associated acute toxicity occurred in 4 patients (10.3%). Three patients died of neutropenic fever while on treatment and 1 patient died of carotid artery rupture 54 days following completion of reirradiation. Median weight change (from pretreatment baseline) was −3.4% (range, −22.1% to +3.8%) in 25 patients with available data. Fifteen patients (35.9%) required hospitalization while on treatment for a median of 7 days (range, 2–28), most commonly for neutropenia, bleeding, nausea/vomiting, and dehydration (Table 5). Late radiation-associated toxicities were common and are profiled in Table 6. Of note, 1 patient experienced late carotid artery hemorrhage 3 months after postreirradiation salvage laryngectomy, 17 months after completion of reirradiation.

At a median survivor follow-up of 24.5 months (range, 3.0–63.9), 12 patients were alive (10 without evidence of disease) and 27 patients have died (16 of/with disease, 5 treatment toxicity, 1 other cause, and 5 unknown cause). Estimated median overall and disease-free survivals for the entire population were 19.0 months and 13.4 months, respectively. Product-limit survival estimates for 1-, 2-, and 3-year overall survivals

Table 3. Treatment characteristics.

	Reirradiation cohort (n=39)		
		%	No.
Time tissue diagnosis to reirradiation start			
Median (range)	49 days (18–182)		
% >45 days		56.4	22
% >60 days		30.8	12
Time reirradiation start to finish†			
Median (range)	48 days (47–75)		
Reirradiation dose completed			
Median (range)	60 Gy (20–68.4)		
≥ 60 Gy		69.2	27
56–58.5 Gy		10.2	6
45–51 Gy		5.1	2
<45 Gy		10.3	4
Chemotherapy regimen			
Median cycles (range)	4 cycles (2–4)		
% 4 Cycles		79.5	31
Cisplatin/paclitaxel		69.2	27
Cisplatin only		2.6	1
5-FU/hydroxyurea		28.2	11

Abbreviation: 5-FU, 5-fluorouracil.
*For 30 patients treated with primary reirradiation.
†For 33 patients completing ≥56 Gy.

Table 4. Acute treatment-associated toxicities.

	Toxicity grade*		
	3	4	5
Mucositis	2	1	–
Pharyngitis	2	–	–
Neutropenia	5	3	3
Hemorrhage	–	–	1

*RTOG acute toxicity scale used for radiation-associated toxicities, NCI-CTC (version 3.0) acute toxicity scale used for chemotherapy-associated toxicities.

Table 5. Duration and causes of on-treatment hospitalization.

	Reirradiation cohort (n = 15)
Days inpatient	
Median	7 days
Range	(2–28)
Reason for hospitalization	
NPF	3
Bleeding	2
Nausea/vomiting	32
Non-NPF infection	4
Dehydration	1
Facial edema	

Abbreviation: NPF, Neutropenic fever.

Table 6. Late radiation-associated toxicities.*

Toxicity†	RTOG grade 3	4	5
Xerostomia	2	3	–
Trismus	5	–	–
Esophageal stricture	4	–	–
Osteoradionecrosis	2	2	–
Tracheomalacia	1	–	–
Hemorrhage	–	1	1‡
Facial nerve palsy	1	–	–

**Late toxicities defined as occurring >3 months following conclusion of reirradiation course, scored as highest severity for each individual patient.*
†For 23 patients with >3 months postreirradiation survival, excluding those insufficient follow-up records (due to transfer of care, early disease recurrence, and/or transfer to hospice).
‡Excludes 1 patient with fatal carotid hemorrhage at 54 days following completion of reirradiation, scored as an acute toxicity.

were 60.1%, 45.1%, and 22.7%, respectively (Figure 1). Estimated 1-, 2-, and 3-year freedom from failure were 55.1%, 40.3%, and 31.4%, respectively (see Figure 2). Initial site(s) of failure were predominantly locoregional in nature, with no patient experiencing isolated distant failure. Recurrence sites with respect to reirradiation fields are profiled in Table 7. In 18 patients with known disease recurrence, salvage therapy involved chemotherapy in 5 patients, resection ($n = 1$), radiotherapy ($n = 1$), trimodality therapy ($n = 2$), no salvage ($n = 7$), or unknown ($n = 2$).

Univariate analysis of factors associated with improved overall survival demonstrated male gender, reirradiation dose completed (particularly >58 Gy), chemotherapy cycles completed (particularly ≥3), and clinical tumor response as statistically significant (Table 8).

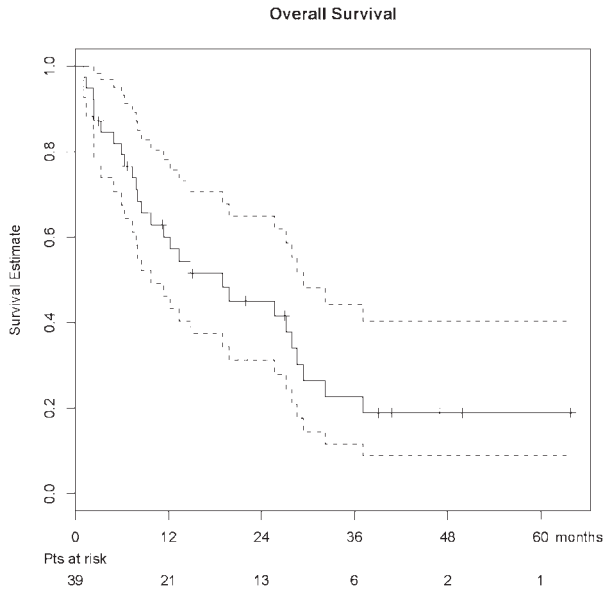

FIGURE 1. Kaplan-Meier curve for overall survival.

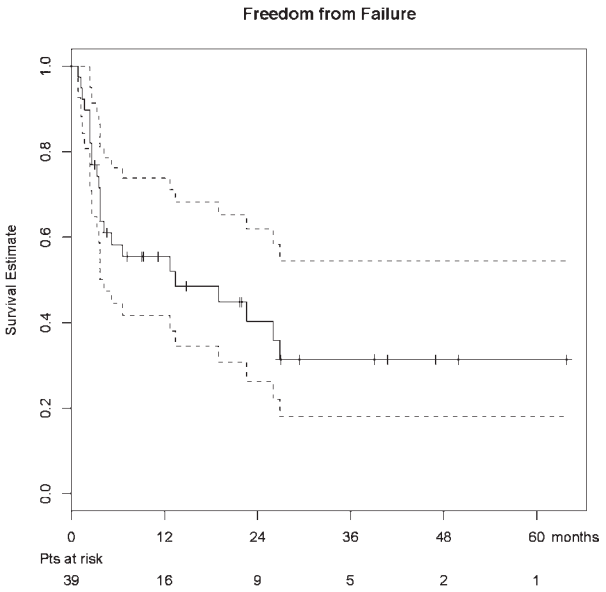

FIGURE 2. Kaplan-Meier curve for freedom from failure.

DISCUSSION

Locoregionally advanced head and neck cancer remains a challenging clinical entity. Following optimal definitive therapy, approximately half of all failures occur within previously irradiated fields.[1,2] For recurrence within a previously irradiated field, surgery has long been the mainstay of salvage therapy for appropriate patients

Table 7. Initial sites of disease recurrence for reirradiated patients.

	Reirradiation cohort ($n = 30$)*
None	12
In-Field	
Primary target	12†
Field margin	
Neck	1
Skin	1
Out of field	
Neck	3
In-Field + distant	1
Distant only	0

**Initial site(s) of recurrence for 30 patients with known pattern of failure; note that 9 patients were not evaluable for pattern of failure (4 patients died of treatment-related acute toxicity and 5 patients died of unknown cause without prior evidence of disease recurrence).*
†One patient discontinued treatment early due to declining performance status and was considered to have had an in-field failure due to uncontrolled disease at this site.

Table 8. Univariate analysis of factors associated with overall survival.

Variable	Model	Hazard ratio	*p* value
Sex	Cox	0.394	.039*
Race	Cox	0.713	.53
Age at diagnosis (continuous)	Cox	1.010	.61
Recurrent tumor site (neck versus mucosal)	Cox	2.121	.13
Local failure (versus 2nd primary)	Logrank	–	.091
rcT-Stage	Logrank	–	.57
rcN-Stage	Logrank	–	.42
Recurrent AJCC clinical stage	Logrank	–	.13
Number of prior head/neck cancers	Cox	1.409	.26
Prior RT Dose (continuous)†	Cox	1.001	.13
Prior RT Dose (>6500)†	Cox	2.351	.084
Time between RT completion	Cox	0.951	.30
Time between RT completion (categorical)	Logrank	–	.28
Therapy (salvage resection followed by reirradiation versus reirradiation alone)	Cox	1.779	.25
Reirradiation days on-treatment‡	Cox	0.947	.20
Time tissue diagnosis to reirradiation start	Cox	0.999	.88
Treatment planning	Cox	0.765	.55
Total reirradiation dose delivered	Cox	0.999	.00014
Completed reirradiation dose > 58 Gy	Cox	0.322	.0071
Completed reirradiation dose > 56 Gy	Cox	0.266	.011
Chemotherapy regimen	Cox	1.086	.69
Chemotherapy cycles (≥3)	Cox	0.166	.002
Chemotherapy cycles (≥4)	Cox	0.387	.044
Hospitalization on-treatment	Cox	1.520	.29
Relative weight change (<10%)	Cox	1.132	.85
Clinical tumor response	Cox	7.329	.00037

**Male sex associated with favorable survival.*
†RT dose within previously irradiated field.
‡For patients completing >56 Gy.

(resectable disease and medically fit for resection).[4–6] Considering all patients with locoregionally recurrent, operable head/neck cancers, salvage resection alone is considered standard of care and provides 55% local control and 32% to 39% survival at 5 years.[4–6] For patients who are unable or unwilling to pursue salvage resection, reirradiation with concurrent chemotherapy can offer an opportunity for disease cure. Early single institution reports demonstrated the feasibility of such an approach, using a variety reirradiation regimens.[7–13] Subsequently, the RTOG prospectively evaluated the toxicity and efficacy of hyperfractionated, split-course radiotherapy (1.5 Gray per fraction, twice daily, 5 days per week, every other week) with concurrent low-dose, daily 5-FU (300 mg/m^2/day), and hydroxyurea (1500 mg/m^2/day) in 86 patients with unresectable recurrence.[14] In 79 evaluable patients, a median survival of 8.5 months was achieved, with estimated 2- and 5-year survivals of 15.2% and 3.8%, respectively. More recently, RTOG 99-11 evaluated the same radiotherapy schedule with concurrent low-dose daily cisplatin (15 mg/m^2/day) and paclitaxel (20 mg/m^2/day). Median survival in 99 evaluable patients was 12.1 months, with estimated 1- and 2-year survivals of 50.2% and 25.9%, respectively.[15] Single institution experiences of hyperfractionated split-course radiotherapy with concurrent chemotherapy have described similar to more favorable results, with 2- to 3-year survival rates of 21% to 37%.[11,12] These findings are similar to the present study cohort, reflecting both population heterogeneity and a possible selection bias for patients with more favorable performance status and tumor-related factors. For example, only 10 of 39 patients (25.6%) in the present study presented with technically unresectable disease, possibly representing population likely to have a more favorable outcome than that seen in other single- or multi-institutional experiences.

Previously described analyses for factors associated with locoregional control and/or survival have identified increasing reirradiation dose (≥58 Gy,[7] ≥50 Gy,[11] or continuous[12]), recurrence beyond 1 year from prior radiotherapy,[10] development of second primary (versus primary recurrence),[10] use of IMRT,[11] nonnasopharyngeal recurrence,[11] prereirradiation surgical salvage,[12] and smaller recurrent disease volume[13] as favorable.

At present, there are no specific recommendations concerning the role of reirradiation following salvage resection. A trial jointly coordinated by the Groupe d'Etude des Tumeurs de la Tete Et du Cou (GETTEC) and Groupe Oncologie Radiotherapie Tete Et Cou (GORTEC) randomized 130 patients to 60 Gy over 12 weeks with concurrent 5-FU and hydroxyurea versus no further therapy following salvage resection of previously irradiated head/neck cancers.[16] Treatment arms were balanced with respect to T- and N-stage, tumor site, "histologic gravity signs" (involved surgical margin and/or nodal extracapsular extension), and second primary versus locally recurrent disease. The reirradiation arm demonstrated significant improvement in progression-free survival (hazard ratio 1.6;

$p = .01$) but without overall survival benefit. Toxicity was considered acceptable, with significantly higher grade ≥ 3 mucositis and moderately increased late grade 3 toxicities (trismus, xerostomia, and fibrosis). A criticism of this study was inclusion of all previously irradiated patients undergoing surgical salvage, irrespective of pathologic features which may have demonstrated a high-risk subpopulation that benefits from trimodality salvage. A cohort series by Kasperts et al[17] described 3-year locoregional control overall survivals of 74% and 44% in patients reirradiated following salvage resection with extranodal spread and/or involved surgical margins. Our present institutional policy is to offer reirradiation following salvage resection when high-risk pathologic features are present (involved surgical margin, nodal extracapsular extension, and dermal neck recurrence).

A major concern of reirradiation to the head and neck is severe toxicity, including treatment-associated mortality. In both RTOG 96-10 and 99-11, 8% of patients died of treatment-related toxicities.[14,15] Single-institution rates (including the present series) demonstrate similar rates, with infection/sepsis (with or without neutropenia) and subacute or late carotid artery hemorrhage as the major causes of treatment-related mortality.[12] Of note, within the present series, all 5 patients who died of treatment toxicity were treated with cisplatin/paclitaxel. In RTOG 99-11, 5 of 8 patients who died of treatment-associated toxicity did so during the acute period (neutropenia, dehydration, pnuemonitis, and stroke), whereas 4 of 5 patients with our series died during the acute period (within 90 days of reirradiation completion).

Late toxicities are also of primary concern in reirradiation of the head and neck. Combining the present study findings with previously described series, the frequency of osteoradionecrosis is approximately 0% to 12%,[9,11,12,15] carotid artery hemorrhage 0% to 5%,[9,11,12,15] and fistula rate 0% to 5%.[9,11] These toxicities are likely related to the inter-relationship of factors, including the previous RT dose, reirradiation regimen (fractionation, schedule, and total dose), concurrent chemotherapy (agent, dose, and schedule), pre- and/or postreirradiation surgical manipulation, reirradiation target structures (mucosal versus neck, oral cavity/pharyngeal versus laryngeal), and reirradiation target cumulative dose. No studies have yet correlated these factors to development of acute and/or late toxicities, thus specific recommendations cannot presently be made.

The more recently investigated cisplatin/paclitaxel regimen is our current institutional regimen, though formal prospective data comparing it to other regimens or chemotherapy are lacking at this time. A retrospective cohort comparison of the two RTOG reirradiation trials demonstrated a significant improvement in survival for patients treated on RTOG 99-11,[18] though the hydroxyurea regimen from 96-10 (1500 mg/m^2/day) differed from twice-daily regimens (1000 mg/m^2/day) used in some institutions.[16] We could not confirm a significant survival difference between treatment cohorts in our experience, though the small size and population heterogeneity limit the ability to detect small survival differences. Although cisplatin-based chemotherapy has become the standard of care for initial definitive and postoperative treatment of locally advanced head and neck cancers, it remains to be determined whether recurrent tumors remain as sensitive to the effects of platinum compounds. Retrospective evidence suggests a benefit when a third chemotherapy agent is added to reirradiation.[12] In particular, recent evidence suggests that gemcitabine concurrent with reirradiation, paclitaxel, and 5-FU can also provide long-term overall survival, albeit at the expense of increased rates of severe toxicity.[19]

Regardless of salvage therapy, the predominant pattern of failure following reirradiation continues to be local. Considering hyperfractionated, split-course reirradiation regimens (including the present study cohort), local recurrences constitute 83% to 100% of initial failures (isolated in 65%–100%).[9,11] These patterns and rates appear to be similar whether reirradiation is administered primarily or following salvage resection with high-risk pathologic features.[11,17] As such, it is not surprising that locoregional control following salvage therapy has been correlated to overall survival for recurrent head/neck cancer.[11]

At the present time, there remains some hesitancy to recommend reirradiation due to the described toxicities, with some clinicians favoring chemotherapy alone. In recurrent head and neck cancer, multi-agent platinum-based chemotherapy is considered standard of care, as this approach has demonstrated improved clinical response rates (but not survival benefit) over historic rates of single-agent chemotherapy in the setting of unresectable recurrent and/or metastatic disease.[20] No platinum doublet has demonstrated superiority over another in this

setting, with cisplatin/5-FU and cisplatin/paclitaxel demonstrating similar efficacy.[21] Preliminary results of a recent phase III randomized trial demonstrated improved survival of platinum-based chemotherapy with cetuximab over platinum plus 5-FU in patients with recurrent and/or metastatic head/neck cancer, though further follow-up is necessary to confirm durable benefit.[22] In addition, investigations of toxicity and outcomes of platinum/cetuximab versus other platinum doublets are required. Few reports have focused specifically on the subgroup of previously irradiated patients with isolated locoregional recurrence, though a retrospective analysis of 2 cooperative group studies evaluating chemotherapy in the setting of recurrent/metastatic disease found prior irradiation to be significantly associated with worse survival (2-year survival of 10%).[23]

The superiority of reirradiation with chemotherapy over chemotherapy alone in recurrent, previously irradiated head and neck cancer remains speculative at this time. The RTOG 04-21 was designed to answer that question, randomizing patients to receive chemotherapy alone (cisplatin/5-FU, cisplatin/paclitaxel, or cisplatin/docetaxel) versus reirradiation as per RTOG 99-11. The trial was designed to enroll 240 patients with unresectable recurrent disease (or who refused salvage resection), with the primary endpoint of overall survival benefit and secondary endpoints of progression-free survival, toxicity, quality of life and performance status measures, and quality-adjusted survival. Unfortunately, this question will remain unanswered for the time being, as the study closed in January 2007 due to poor accrual.

In conclusion, the present series demonstrates the toxicity and survival outcomes of reirradiation in a cohort of previously irradiated patients with locoregionally recurrent head and neck cancer. Although aggressive surgical intervention is considered the standard salvage for appropriately selected head and neck cancer recurrences, reirradiation remains an alternative option with the possibility of long-term survival. Regardless of salvage intervention, further improvements in locoregional control must be made, as the recurrent tumor site(s) predominate postsalvage failures.

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