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ORIGINAL REPORT

Phase II Study of Low-Dose Paclitaxel and Cisplatin in Combination With Split-Course Concomitant Twice-Daily Reirradiation in Recurrent Squamous Cell Carcinoma of the Head and Neck: Results of Radiation Therapy Oncology Group Protocol 9911

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ABSTRACT

Purpose
Recurrent squamous cell carcinoma of the head and neck (SCCHN) or new second primary tumor (SPT) in a previous radiation field, if not curable by surgery or radiation, is almost always fatal. Chemotherapy alone yields a median survival time (MST) of no more than 10 months and 1-year overall survival (OS) of 35% at best. Concurrent reirradiation and chemotherapy is an alternative strategy.

Patients and Methods
Eligibility for Radiation Therapy Oncology Group (RTOG) protocol 9911 stipulated recurrent SCCHN or SPT in a previous radiation field. Patients received twice-daily radiation (1.5 Gy per fraction bid × 5 days every 2 weeks ×4), plus cisplatin 15 mg/m^2 intravenously (IV) daily × 5 and paclitaxel 20 mg/m^2 IV daily × 5 every 2 weeks ×4. Granulocyte colony-stimulated factor was administered days 6 through 13 of each 2-week cycle.

Results
One hundred five patients were enrolled from March 2000 through June 2003; 23% had SPT. Oropharynx (40%) and oral cavity (27%) were the predominant primary sites. Median prior radiation dose was 65.4 Gy. Seventy-four percent of patients completed chemotherapy. Grade 4 or worse acute toxicity occurred in 28%, grade 4 or worse acute hematologic toxicity in 21%. Eight treatment-related deaths (8%) occurred: five in the acute setting, three late (including two carotid hemorrhages). MST was 12.1 months, with estimated 1- and 2-year OS rates of 50.2% and 25.9%.

Conclusion
Despite a high incidence of grade 5 toxicity, 1- and 2-year OS rates for split-course bid radiation therapy and concurrent cisplatin/paclitaxel exceed results generally seen with chemotherapy alone.

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INTRODUCTION

Local recurrence or second primary tumor (SPT) after curative radiation therapy (RT), alone or combined with surgery, is a major dilemma in the management of locally advanced squamous cell carcinoma of the head and neck (SCCHN). Fifty percent to 60% of patients die directly as a result of locally recurrent disease.[1,2] Although surgical salvage is occasionally successful, disease extent and involvement of adjacent critical structures frequently preclude it.

When surgery is not feasible, therapeutic options for local recurrence are limited. Chemotherapy alone is suboptimal. Combination platinum-based regimens generally yield response rates of only 20% to 35%, and median survival time (MST) seldom exceeds 8 to 10 months.[3-6] Except in nasopharyngeal cancer and other selected clinical situations, the size and location of most recurrences does not readily permit the optimal use of interstitial radiotherapy or salvage RT alone (reirradiation).[7-12]

However, reirradiation combined with chemotherapy may be a viable option. In treatment-naïve locally advanced SCCHN, concurrent chemotherapy and radiation have demonstrated a clear survival advantage compared with radiation alone.[13-15] On the basis of pilot trials at the Universities of Alabama and Chicago (Tuscaloosa, AL, and Chicago, IL, respectively),[16-18] Spencer et al mounted a phase II

trial (Radiation Therapy Oncology Group [RTOG] protocol 9610) evaluating concurrent split-course twice-daily radiation, fluorouracil (FU) infusion, and hydroxyurea in patients with unresectable recurrence or SPT within a prior RT field.[19] Patients received RT 1.5 Gy/fraction (fx) bid for 5 days every other week ×4 combined with hydroxyurea 1.5 g orally (PO) and FU 300 mg/m^2 intravenously (IV), daily ×5, each administered before the second fx of RT. Between August 1996 and April 1999, 86 patients were accrued. Median prior RT dose was 64.8 Gy. Twenty-five percent of patients had second primary tumors. Seventy-three percent of patients received all four cycles. Grade 3 or worse mucositis occurred in 21%, and grade 3 or worse neutropenia in 24%. There were six treatment-related fatalities: four from sepsis and two from tumor hemorrhage. MST was 8.8 months, with 1- and 2-year survival rates of 41.7% and 16.9%. The 1-year survival rate was 47.8% in those who relapsed 3 or more years after prior RT compared with 36.4% in those who relapsed within 3 years ($P = .18$).

Because cisplatin and paclitaxel are established radiosensitizers with proven activity in SCCHN, investigators at Fox Chase Cancer Center (FCCC; Philadelphia, PA) mounted a phase I trial combining these agents with bid RT in the salvage setting.[20] They employed a split-course schedule to facilitate optimal integration of chemotherapy with RT, and allowed the integration of hematopoietic growth factors (HGFs) between cycles to potentially mitigate mucositis and myelosuppression and to avoid the paradoxical toxicity of concurrent RT and HGF. FCCC 96-006 established a maximum-tolerated dose (MTD) of split-course RT of 1.5 Gy/fx bid ×5 days every other week for four cycles (60 Gy), in combination with cisplatin 15 mg/m^2/d ×5 and paclitaxel 20 mg/m^2/d ×5 every other week. Without HGF, the second and subsequent cycles were delayed at least 1 week almost routinely. With HGF support, 13 of 18 cycles were delivered on schedule at full dose. The rates of grade 3 or worse neutropenia and anemia were 17% and 23%, respectively. Grade 3 mucositis occurred in only 6% of patients. Of 22 patients with measurable, recurrent SCCHN, the response rate was 54%. Median locoregional freedom from progression was 10 months, and the 1-year progression-free survival (PFS) rate was 28%. MST was 9.5 months; 1-and 2-year survival rates were 41% and 27%, respectively.

On the basis of these encouraging results, RTOG initiated a phase II trial formally testing this regimen in a multicenter setting.

PATIENTS AND METHODS

Objectives

The primary objective of this study was to determine the median and 1-year disease-free and overall survival rates of SCCHN patients treated with split-course bid reirradiation with concurrent cisplatin and paclitaxel. Secondary end points included (1) evaluating the incidence of acute and late toxicities and (2) determining the patterns of disease progression.

Patients

Eligibility stipulated recurrent, unresectable SCCHN or SPT in a previously irradiated field. Additional eligibility requirements included measurable tumor; more than 6 months elapsed since completion of prior chemotherapy and RT; at least 75% of the tumor volume having received prior RT at doses between 45 and 75 Gy; Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 to 1; and absence of significant comorbidities. The protocol stipulated that the entire tumor volume be included in a treatment field without exceeding a total spinal cord dose of 50 Gy (past and current). Adequate physiologic indices were mandated: absolute neutrophil count (ANC) of at least 1,500/mL; platelets at least 100,000/mL; bilirubin no more than 1.5 mg/dL; and creatinine not to exceed 1.5 mg/dL. All patients were required to have liver function tests (LFTs) no more than 2× upper limits of normal (ULN), with ultrasound or computed tomography (CT) of the liver negative for metastases, if LFTs proved 2× ULN or more. All patients signed informed consent in accordance with institutional standards.

Exclusion criteria included distant metastases; primary tumor in the nasopharynx or salivary gland; other invasive malignancies within the preceding 2 years; preexisting grade 2 or worse peripheral sensory neuropathy; or ongoing lactation or gestation.

Treatment

Patients received RT at a dose of 1.5 Gy/fx bid ×5 days every other week for four cycles; interfraction interval was 4 to 6 hours. Chemotherapy consisted of cisplatin 15 mg/m^2/1 hour and paclitaxel 20 mg/m^2/1 hour each daily ×5 every other week ×4. Standard premedication included antihistamines, corticosteroids, H2 blockers, and serotonin antagonists. Granulocyte colony-stimulating factor (G-CSF), either 300 μg subcutaneously daily (patients $<$ 60 kg), or 480 μg daily (patients $\geq$ 60 kg), was administered days 6 through 13 every other week. Intravenous fluid was administered before and during platinum infusion with appropriate electrolyte replacement.

Treatment fields encompassed recurrent tumor with adequate margins ($\geq$ 2 cm) whenever possible. Margins of less than 2 cm were considered acceptable only in instances of spinal cord encroachment. Elective treatment to regional lymph nodes was not required. Individualized treatment planning with CT or conventional simulation was mandated. Positron emission tomography (PET) or PET/CT imaging was not used for treatment planning. Review of the previous RT records (including simulation films, treatment plans, and dosimetry data) was required to avoid total spinal cord radiation in excess of 50 Gy. All fields were treated daily; custom blocking with multileaf collimation or Cerrobend (Cerro Metal Products, Bellefonte, PA) was used with each beam to limit radiation to the surrounding normal tissue. Conventional three-dimensional conformal (3DCRT) and intensity-modulated RT (IMRT) techniques were used at the discretion of the individual investigators. For 3DCRT and IMRT treatment plans, isodose calculations in the axial, sagittal, or coronal planes were required. In addition, dose volume histograms for the gross tumor volume and the spinal cord were required.

The doses of cisplatin and paclitaxel were reduced 25% during the second and subsequent cycles for any of the following: neutropenic fever; delay in resuming radiation more than 1 week; thrombocytopenia requiring platelet transfusion; grade 4 mucositis requiring total parenteral nutrition or hospitalization; and grade 3 or worse fatigue, which, in the opinion of the treating physician, precluded full-dose therapy. In addition, the dose(s) of the implicated agents were reduced 25% for grade 3 neurotoxicity or other attributable grade 4 nonhematologic toxicity, excluding nausea and vomiting. Persistent creatinine elevations of 1.6 to 2.0 mg/dL mandated 50% reduction in cisplatin dose. Cisplatin was withheld for creatinine elevations exceeding 2 mg/dL.

Treatment was delayed 1 week or more for mucositis precluding hydration or intake; grade 2 or worse neurotoxicity, ANC less than 1,500/mL, or platelets less than 80,000/mL; or other grade 3 or worse nonhematologic toxicities.

Statistical Considerations

Using the method of Dixon and Simon[21] a sample size of 90 assessable patients followed during a 12-month period ensured at least 80% probability of detecting a minimum 15% improvement in 1-year survival rate compared with the prior RTOG 9610 trial, with a significance level (one-sided test) of .05. Allowing up to 10% of patients to be deemed retrospectively ineligible and/or nonassessable, the targeted sample size was 100 patients. Median, 1- and 2-year overall survival (OS) and PFS rates were estimated using the Kaplan-Meier method,[22] and OS on RTOG 9911 was compared to a historical control (RTOG 9610) using a one-sided log-rank test.[23] With regard to PFS, "failure" included local, regional, or distant progression, second primary tumor, or death. Systemic and acute RT effects were scored using the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0, whereas late RT

effects were scored according to the RTOG/European Organisation for Research and Treatment of Cancer (EORTC) criteria.

RESULTS

One hundred five patients were enrolled at 36 separate institutions between March 2000 and June 2003. Ninety-nine were deemed eligible: in four patients, less than 6 months had elapsed from completion of prior radiation to recurrence; one died before starting treatment; another individual had distant metastases at study entry.

Baseline Demographics

Baseline patient demographics are shown in Table 1. Of the remaining 99 patients, median age was 60 years (range, 27 to 83 years). Seventy-seven percent were male, 90% white, and 66% ECOG PS 1. Twenty-three percent had SPTs, and 77% had locoregional recurrences. The predominant site of recurrence was oropharynx (40%); oral cavity was the second most common site (27%). Median time from prior radiation to study entry was 39.6 months; 52% relapsed more than 3 years after prior RT. The median prior RT dose was 65.4 Gy (range, 45 to 75 Gy). Twenty percent received prior chemotherapy.

Table 1. Distribution of Patient and Tumor Characteristics (n = 99)

Characteristic	No. of Patients	%
Age, years		
Median	60.0	
Range	27.0-83.0	
Sex		
Male	76	76.8
Female	23	23.2
Zubrod performance status		
0	34	34.3
1	65	65.7
Recurrence type		
Second primary	23	23.2
Locoregional recurrence	76	76.8
Primary site at study entry		
Oral cavity	27	27.3
Oropharynx	40	40.4
Hypopharynx	12	12.1
Larynx	10	10.1
Other	10	10.1
Months from prior RT		
Median	39.6	
Range	6.1-317.9	
< 36	48	48.5
> 36	51	51.5
Prior RT dose, Gy		
Median	65.4	
Range	45.0-75.0	
Prior chemotherapy		
None	79	79.8
Lomustine	1	1.0
Fluorouracil	3	3.0
Platinum	2	2.0
Procarbazine	1	1.0
Carboplatin	2	2.0
Multiple	9	9.1
Administered, but drug unknown	2	2.0

Abbreviations: RT, radiotherapy.

Toxicity

Worst grade toxicity reported per patient per CTC category is shown in Table 2. Five percent experienced early grade 5 toxicities. Causes included neutropenic sepsis in two individuals, with death occurring 9 and 23 days from start of treatment; dehydration and shock (71 days); pneumonitis (20 days); and cerebrovascular accident (55 days). Twenty-one percent experienced grade 4 or worse myelosuppression, including 18% with grade 4 or worse neutropenia. Twenty-one percent experienced grade 3 or worse anemia, 6% grade 3 or worse thrombocytopenia. Eleven percent required platelet or red cell transfusions. Grade 3 or worse infection or febrile neutropenia occurred in 15%. Grade 3 or worse mucositis occurred in only 14%, with 2% grade 4. Forty-eight percent had grade 3 or worse GI toxicity.

Eighty-three patients were assessable for late radiation toxicity (Table 3).[24] Late grade 5 toxicities included two carotid hemorrhages 272 and 427 days from start of treatment and one death attributable to oral-cutaneous fistula and soft tissue necrosis (116 days).

Figure A1 (online only) shows cumulative incidence estimates for grade 3 to 5 toxicity and for grade 4 nonhematologic or grade 5

Table 2. Chemotherapy and Acute Radiotherapy Toxicities (n = 99)

Toxicity	Grade 3	Grade 4	Grade 5
Auditory/hearing	1	0	0
Blood/bone marrow	24	20	1
Neutropenia	6	17	1
Leukopenia NOS	11	19	0
Anemia	19	2	0
Thrombocytopenia	5	1	0
Platelet transfusion	1	0	0
Packed RBC transfusion	10	0	0
Cardiovascular (arrhythmia)	2	0	0
Cardiovascular (general)	6	0	0
Constitutional symptoms	11	0	0
Dermatology/skin	9	1	0
GI	44	4	1
Radiation mucositis or stomatitis	12	2	0
Hemorrhage	3	1	0
Hepatic	4	0	0
Infection/febrile neutropenia	11	3	1
Febrile neutropenia (fever of unknown origin)	3	2	0
Infection without neutropenia	5	0	0
Infection with grade 3 or 4 neutropenia	3	1	1
Infection with unknown ANC	1	0	0
Metabolic/laboratory	23	9	0
Neurology	3	0	1
Pain	5	0	0
Pulmonary	5	0	2
Renal/genitourinary	6	0	0
Worst nonhematologic	48	23	5
%	48.5	23.2	5.1
Worst overall	49	23	5
%	49.5	23.2	5.1

Abbreviations: NOS, not otherwise specified; ANC, absolute neutrophil count.

Table 3. Late Radiotherapy Toxicities (n = 83)

Toxicity	Grade 3	Grade 4	Grade 5
Skin	1	2	0
Mucous membrane	0	6	0
Subcutaneous tissue	5	4	1
Salivary gland	6	0	0
Esophagus/pharynx	12	3	0
Larynx	1	1	0
Bone	0	4	0
Joint	2	0	0
Other	5	1	2
Worst overall	14	14	3
%	16.9	16.9	3.6

toxicity. In the first 2 years, an estimated 84.9% of patients experienced grade 3 to 5 toxicity, whereas an estimated 31.8% experienced grade 4 nonhematologic or grade 5 toxicity.

Dose Delivery

Seventy-four percent of patients completed four cycles of chemotherapy; 92% completed at least two cycles. Treatment was administered per protocol or with minor deviations in 82%. Seventeen percent failed to complete chemotherapy in the absence of significant toxicity. Of the 26 patients who stopped chemotherapy early, five died, three because of toxicity, one because of medical comorbidities, and one because of underlying cancer. Six patients were removed from treatment because of toxicity: five because of medical comorbidities; one because of disease progression; and one because of physician failure to follow protocol guidelines. Eight patients refused further treatment. Targeted dose delivery among those continuing treatment is shown in Table 4.

The definitions of protocol adherence for radiation are shown in Table A1 (online only). Radiation was administered per protocol to 46% of patients. Minor, acceptable variations occurred in 23% and unacceptable deviations in 10%; 7% died before they completed radiation, 1% progressed, and 12% refused further radiation. The median RT dose delivered was 60 Gy; 76% received more than 52.5 Gy.

Survival and Patterns of Recurrence

At a median follow-up for surviving patients of 23.6 months, 75 have died: 71% as a result of underlying cancer, 11% as a result of direct or related toxicities, 1% as a result of second primary tumors, and 11% as a result of comorbidities or intercurrent illnesses. One percent of the study patients have died as a result of complications of other treatment, and 5% for unknown reasons.

Figure 1 shows estimated OS and PFS. MST is 12.1 months, with a 1-year OS of 50.2% and a 2-year OS of 25.9%. Median PFS is 7.8 months with a 1-year PFS of 35% and a 2-year PFS of 15.8%. Nineteen percent of patients are alive without progression. Thirty-eight percent died as a result of underlying cancer, but without clear documentation of progression. The first site of progression was local in 23%, regional in 7%, distant in 8%, and both in 1%. Three percent had SPT, including pyriform sinus, esophageal carcinoma, and bladder carcinoma as the first manifestation of treatment failure.

Compared with RTOG 9610,[19] outcome in RTOG 9911 appears superior ($P = .0444$; Fig 2). MST was 12.1 compared with 8.8 months in RTOG 9610, with respective 1- and 2-year survival rates of 50.2% versus 41.7% and 25.9% versus 16.9%.

MST for patients relapsing within 36 months is 14.1 versus 10.8 months for those relapsing more than 36 months after initial definitive treatment; relative 1-year survival rates are 56.3% and 44.6%. PFS curves for these two groups are superimposable. MST for those with recurrent disease is 14.1 versus 6.8 months for those with SPTs ($P = .042$); relative median PFS are 8.0 and 5.4 months, respectively.

OS was compared by treatment delivery for patients who survived at least 3 months to eliminate bias from patients not completing treatment because of early death. Patients scored by the study chairs as "per protocol" for both chemotherapy and RT had an MST of 1.5 compared with 1.0 year for the remaining patients ($P = .15$). Patients who received all four chemotherapy cycles had an MST of 1.2 compared with 0.6 years for the remaining patients ($P = .20$). Patients who received all four chemotherapy cycles with at least 80% of protocol dose had an MST of 1.6 compared with 0.9 years for the remaining patients ($P = .0026$).

DISCUSSION

The MST and 1- and 2-year survival rates for our approach appear promising, and generally exceed results previously observed with chemotherapy alone. ECOG trials 1393 and 1395 tested chemotherapy alone in this setting. Of nearly 400 patients accrued, 153 had local disease, of whom 124 were previously treated with radiation.[6,25] The 2-year survival rate in this group was only 10.5%. In addition, the results appear superior to historical RTOG controls employing split-course RT, hydroxyurea, and infusional FU,[19] although the usual caveats regarding selection bias and possible stage migration over time apply.

Table 4. Dose Delivery and Delays (n = 99)

Cycle	% Did Not Receive Cycle (% of all patients enrolled)	% Delay ≥ 1 Week (patients continuing) during cycle	% ≥ 80% of Protocol Dose During Cycle	% ≥ 80% of Protocol Dose (all patients as denominator)
1	1.0	1.0	93.9	92.9
2	8.1	7.7	83.5	76.8
3	16.2	8.4	78.3	65.7
4	26.3	9.6	71.2	52.5

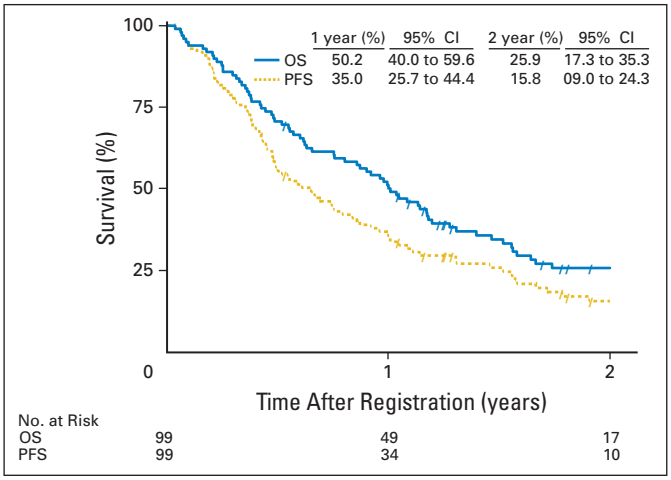

Fig 1. Kaplan-Meier estimates of overall survival (OS) and progression-free survival (PFS) for Radiation Therapy Oncology Group protocol 9911.

Toxicity on RTOG 9911 was substantial, with a relatively high incidence of treatment-related deaths, and late grade 4 or worse toxicity rates. Patients with SPTs and those whose head and neck cancers relapsed more than 36 months after prior treatment fared no better than did patients with recurrent disease and those who relapsed within 3 years. These observations are discordant with our previous experience in RTOG 9610,[19] wherein those who relapsed more than 3 years after prior radiation had a 12% improvement in 1-year survival rate; a similar trend favored those with SPTs as opposed to recurrent disease.

Sixteen percent of patients on RTOG 9911 remain alive and progression free beyond 2 years, with long-term survival, if not cure, potentially achievable. Whether reirradiation and concurrent chemotherapy are superior to chemotherapy alone can only be addressed by a properly conducted prospective phase III trial. RTOG 0421 randomly assigned patients identical to those enrolled onto RTOG 9911 to split-course bid radiation with concurrent cisplatin and paclitaxel and G-CSF support, or to three separate cisplatin-based standard chemotherapy regimens. The primary objective of this study was OS.

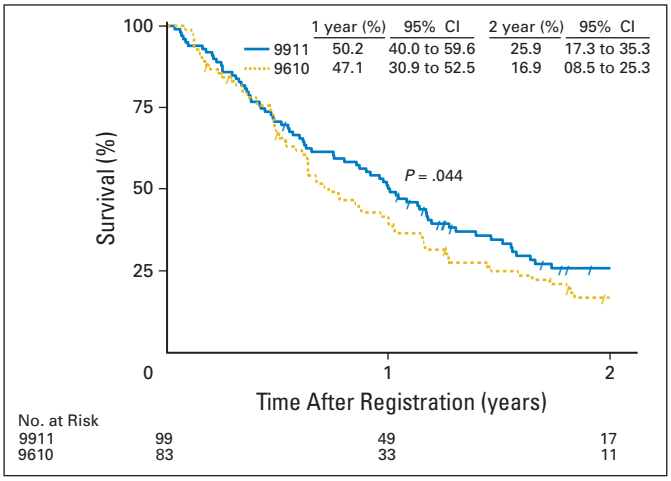

Fig 2. Kaplan-Meier estimates of overall survival for Radiation Therapy Oncology Group protocols 9911 and 9610.

The eligibility criteria were identical to RTOG 9911. The study, which targeted 240 patients for enrollment, had an 80% power and 0.025 type-I error (one-sided test) to detect a 33% reduction in risk of death. Unfortunately, this trial closed because of poor accrual; the history of this ill-fated effort makes it unlikely that similar trials in the future will ever be mounted. Acknowledging the preconceived notions that frequently exist, it may be inherently difficult, if not impossible to mount a trial comparing chemotherapy alone with combination chemotherapy and RT in this setting.

As concurrent chemotherapy and radiation emerge as standard treatment in newly diagnosed, locally advanced SCCHN, the utility of reirradiation and further chemotherapy in the salvage setting may be compromised, especially in patients whose disease has relapsed relatively quickly ($\leq$ 1 year). How monoclonal antibodies targeting epidermal growth factor receptor factor into this paradigm remains uncertain. Regardless, an increasing proportion of relapsed patients will have received radiosensitization as part of their initial treatment.

In addition, the MTD of reirradiation is unclear. Although older studies have suggested limited tolerance to repeat administration of radiation, more recent preclinical experiments have indicated that soft tissue can tolerate repeat doses as high as 90% of the original dose if the second treatment is applied more than 6 weeks after the first has concluded.[26] Subsequent tissue tolerance depends on both fraction size and field size.[27,28] Langlois[28] has shown that reducing size of the reirradiation volume can substantially decrease the probability of complications; risk of toxicity is further reduced by split-course approaches and smaller fraction sizes: 1.8 to 2.0 Gy/fx.[27,28] The incidence of soft tissue necrosis in various series ranges from 0% to 40%. In our series, grade 4 and 5 soft tissue necrosis occurred in less than 5%. As others have demonstrated, total reirradiation doses of 60 Gy can be given with serious toxicity rates of less than 25%.

Vokes et al[16,17] previously employed split-course radiation with hydroxyurea and infusional FU. They observed substantial local toxicity, but a relatively high locoregional response rate, and gratifying long-term survival; MST was 12 months, with 15% of enrollees disease free in the long term.

In a pilot effort, investigators at the University of Alabama at Birmingham treated 35 patients with recurrent, previously irradiated SCCHN with hydroxyurea 2 g PO bid $\times$5, and FU 300 mg IV bolus daily $\times$5, weeks 1, 3, 5, and 7 in combination with bid RT to a total dose of 60 Gy.[18] Median prior RT dose was 62.8 Gy. Fourteen (40%) of 35 had previously received chemotherapy. Because of significant myelosuppression in the first 11 patients, subsequent treatment was modified, reducing RT to 1.2 Gy/fx and hydroxyurea from 2 to 1.5 g bid. As a result, hematologic tolerance improved substantially. The 1-year survival rate was 59%. However, four deaths occurred, one from aspiration pneumonia, one from neutropenic fever/sepsis, and two secondary to carotid artery rupture.

The subsequent RTOG effort (RTOG 9610) employed a treatment schema virtually identical to the last cohort of the Alabama series; 60 Gy RT was administered over 4 treatment weeks (7 elapsed weeks).[19] Acute grade 3 or worse mucositis occurred in 21% of patients, a higher percentage than observed in the 9911 trial. Six grade 5 adverse events occurred, two caused by neutropenic sepsis; OS appeared inferior to that found in RTOG 9911.

Considerable reluctance to investigate reirradiation persists. Toxicity is substantial. However, appropriate patient selection restricting this approach to patients with excellent performance status

should help mitigate this concern. In addition, adequate nutrition is imperative; those with compromised nutritional integrity should receive gastronomy tubes. Outside of formal studies, concurrent chemotherapy and reirradiation are not ready for routine implementation.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).