

OUTCOMES FOLLOWING REIRRADIATION OF PATIENTS WITH HEAD AND NECK CANCER

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Abstract: *Background.* This study reports the outcomes for patients with head and neck cancer who received reirradiation with palliative or curative intent.

Methods. A retrospective review of 41 patients treated with curative ($n = 28$) or palliative ($n = 13$) reirradiation was conducted. Survival was calculated from the start of the reirradiation. Radiation-related toxicities were classified according to Radiation Therapy Oncology Group criteria. Disease-related problems included adverse events during or after reirradiation that were not directly related to reirradiation.

Results. The observed 1-year survival for all patients was 39.0% (23.0% palliative, 46.3% curative). Median survival for all patients was 10.2 months. Seventy-five percent of curative and 53.8% of palliative patients had grade 3 or 4 radiation-related toxicities and/or major disease-related problems.

Conclusion. A second course of radiotherapy in patients with head and neck cancer should be offered with a clear understanding that survival is poor and many of these patients will suffer severe radiation-related or disease-related insults to their quality of life during and after treatment. ©2008 Wiley Periodicals, Inc. *Head Neck* 30: 765–770, 2008

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In patients with squamous carcinoma of the head and neck, local and regional recurrence accounts for the majority of failures.^{1–4} Over 50% of these patients will die as a direct result of their locoregional recurrence.⁵ Management of recurrent carcinoma or a new primary within a previously radiated area of the head and neck poses a therapeutic challenge because of the limitations imposed on potentially curative interventions.^{6,7} A number of factors influence the treatment options available including tumor resectability, prior radiation dose to surrounding normal tissues, time from the initial radiation, the patient's ability to undergo surgery, and the anticipated treatment toxicities.

Surgery is generally regarded as the first choice of salvage treatment in cases of recurrent head and neck cancer in which radiation was previously used.^{8–11} When surgery is not an option or when salvage surgery is undertaken and the pathologic findings demonstrate a high risk of failure, reirradiation with or without the addition of chemotherapy may be considered for salvage

treatment.^{7,9,12–15} Reirradiation may also be used for palliation in cases where the disease is not felt to be curable.^{11,16}

The major concern with reirradiation that uses an effective tumor dose (>50–60 Gy^{17,18}) is the anticipated toxicity to normal tissues.^{7,12,15,19} There are limited data on toxicity following reirradiation, particularly late toxicity, because the majority of patients do not survive long enough to be at risk for these toxicities.⁵ The rate of acute complications for reirradiation alone has been reported to be similar for primary radiation in a number of series.^{13,14,20} The reported rates of severe late complications following reirradiation range from 7% to 24%.^{7,11,13,14,16–18,20–26}

The primary objective of this study was to investigate both the survival outcomes and adverse events in patients managed with reirradiation for head and neck cancer at the University of Iowa. Patients treated with palliative intent were assessed separately from patients treated with curative intent because survival rates and adverse events have clearly different implications for these 2 patient groups.

MATERIALS AND METHODS

Patients. This study included patients with head and neck cancer who underwent reirradiation for either locoregional recurrence or a second primary within a previously irradiated field between January 1998, and December 2003. Eligible patients were identified through radiation oncology records and the University of Iowa Cancer Registry after ethical approval was obtained from the University of Iowa's Institutional Review Board.

A retrospective chart review was then performed on these patients who underwent reirradiation for head and neck cancer. The data were analyzed by the intent of the second course of radiation based on a categorization of patients as potentially curable or palliative made during a multidisciplinary tumor board prior to reirradiation. Curative intent included postoperative, reirradiation therapy following surgical salvage in which high-risk pathologic features were identified (eg, positive margins, extracapsular spread in cervical nodes) or primary reirradiation therapy for patients who either declined or were medically unfit for surgical intervention. Palliative radiation therapy was given to treat incurable, locoregional recurrent disease. Patients who did not complete their first or second full course of radia-

tion were excluded unless reirradiation was terminated because of disease-related problems or radiation-related toxicities. Because the study was confined to reirradiation outcomes, patients who received chemotherapy as a component of salvage therapy were not included.

Treatment. All patients in this study were treated with external beam radiation for their first and second course of radiation. Thirty-two received intensity-modulated radiotherapy delivered with the Peacock system with multivane intensity modulating collimator (MIMiC) planned with the CORVUS system (NOMOS, Sewickley, Pennsylvania). Target volumes included the tumor (or the tumor bed in cases of postoperative reirradiation) and high-risk areas. A total dose of 60 to 70 Gy at 1.8 to 2 Gy per fraction was prescribed (around 60–66 Gy for postoperative cases and 66–70 Gy for nonsurgical cases). Five patients terminated treatment after receiving only 20 to 41.4 Gy.

Of the remaining 9 patients, 7 were treated with standard fractionation at 1.8 to 2.0 Gy per fraction, 1 received en face electron for dermal metastases to 51 Gy at 3 Gy per fraction, and 1 with a skull base recurrence in a retropharyngeal lymph node received stereotactic radiosurgery under optical guidance to a dose of 15 Gy in 1 treatment.

Toxicity. Radiation-related toxicities were assigned a grade based on the Radiation Therapy Oncology Group (RTOG) scoring system for acute and late toxicities. Because of the poor survival in this patient group, both acute and late toxicities were combined. Disease-related problems were events with a detrimental effect on quality of life that were not clearly definable as radiation-related toxicities. Disease-related problems were grouped as minor or major. Minor disease-related problems were defined as those managed with conservative, outpatient measures such as wound dressings or medication. Major disease-related problems were defined as those that required hospital admission, in-hospital intervention, or surgery (eg, gastrostomy-tube placement, tracheostomy, pharyngocutaneous fistula) and those that resulted in substantial morbidity (eg, stroke, vascular rupture, death). When an adverse event was not clearly related to the radiation therapy, it was designated as a disease-related problem.

Statistics. The data were analyzed using SPSS statistical software. Chi-square analyses were used to determine significant differences in the proportion of patients in the palliative and cura-

Table 1. Case-mix and treatment characteristics for patients who had a full initial course of radiation therapy for a head and neck carcinoma followed by a second course of radiation therapy ($n = 41$).

Characteristic	Count	%
Age*		
<50	9	22.0
50-65	18	43.9
≥66	14	34.1
Sex		
Male	32	78.0
Female	9	22.0
Anatomic site		
Oral cavity	11	26.8
Pharynx	13	31.7
Larynx	9	22.0
Other	8	19.5
Histologic type		
SCC	34	82.9
Other carcinoma	7	17.1
Intent to treat status		
Palliative	13	31.7
Curative	28	68.3

*Mean = 60.4 years.

tive groups with radiation-related toxicities or disease-related problems. Actuarial, observed survival (reflecting death from all causes) and median survival were calculated from the date the second course of irradiation was initiated to the outcome of interest. The survival rates of patients in the 2 treatment groups were compared using the Wilcoxon statistic.

RESULTS

Of the 41 patients eligible for inclusion, 13 (31.7%) received palliative reirradiation and 28 (68.3%) received reirradiation with intent to cure. Within the curative group, 12 received reirradiation only and 16 received reirradiation following surgical resection.

Most of the patients were men (78.0%), and the mean age at diagnosis was 60.4 years (Table 1). Squamous cell carcinoma was the most common histological type. The most frequently reirradiated site was the pharynx, which included the oropharynx, nasopharynx, and hypopharynx.

The reirradiation dose and the total radiation dose received by the 13 patients in the palliative group tended to be lower than that received by the 28 patients in the curative group (Table 2). However, the difference was not statistically significant.

Four of the 41 patients were alive at last contact, resulting in a crude survival rate of 9.8%. The mean follow-up for these 4 patients was 37.7

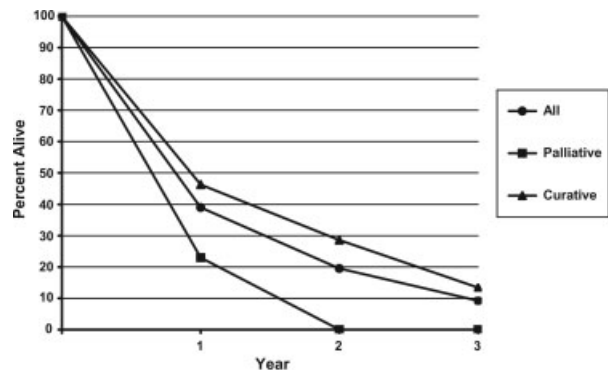
Table 2. Mean radiation doses (Gy) for reirradiation (second course) and total radiation dose by intent to treat status ($n = 41$).

Course of irradiation	Intent to treat status		<i>p</i> value
	Palliative	Curative	
Reirradiation (second course)	54.5	61.1	.198
Total irradiation (all courses)	119.9	123.2	.563

months (ranging from 30.6 to 46.8 months). Actuarial, observed survival (death from all causes) was 39.0% at 1 year and 19.5% at 2 years for all patients in the study (Figure 1).

The curative group's survival rate was significantly higher ($p = .039$) than that of the palliative group. The 1-year survival rate for the patients treated with palliative reirradiation was 23.0%, and none of these individuals was alive 2 years after reirradiation. The survival rate for the patients who received reirradiation with curative intent was 46.3% at 1 year, 28.6% at 2 years, and 13.4% at 3 years. The median duration of survival was 6.2 and 11.5 months for the palliative and curative groups, respectively.

Thirty-three of these reirradiated patients (80.5%) had 1 or more documented radiation-related toxicity and/or disease-related problems. Twenty-eight (68.3%) had a grade 3 or 4 radiation-related toxicity and/or a major disease-related problem (Table 3). The curative group had



Cases	Year			Median Survival, months	N
	1	2	3		
All cases	39.0	19.5	9.2	10.2	41
Palliative	23.0	0	0	6.2	13
Curative	46.3	28.6	13.4	11.5	28

FIGURE 1. Annual, observed survival and median survival by intent to treat status for patients who had a full initial course of radiation therapy for a head and neck carcinoma followed by a second course of radiation therapy ($n = 41$).

Table 3. Documented radiation-related toxicities and disease-related problems for the curative intent and palliative intent patients.

Outcome	Palliative, <i>n</i> = 13		Curative, <i>n</i> = 28		<i>p</i> value
	Patients	Percent	Patients	Percent	
Radiation-related toxicity					
Grades 1 or 2	2	15.3	7	25.0	.692
Grades 3 or 4	3	23.1	16	57.1	.052
Disease-related problem					
Minor	4	30.8	3	10.7	.181
Major	6	46.2	15	53.6	.744
Grade 3 or 4 radiation-related toxicity and/or major disease-related problem	7	53.8	21	75.0	.280

Note: Some patients had more than 1 type of adverse event.

a larger proportion of patients with these adverse events (21 of 28, or 75.0%) compared with the palliative group (7 of 13, or 53.8%), although the difference was not significant ($p = .280$). The percentage of patients in the 2 treatment groups with a major disease-related problem was similar, with 46.2% in the palliative group and 53.6% the curative group (Table 3 and Figure 2). However, the curative group (57.1%) had substantially more documented grade 3 or 4 radiation-related toxicities than the palliative group (23.1%) ($p = .052$).

DISCUSSION

Reirradiation is generally not considered the first line approach for managing recurrent head and neck cancer.⁸ However, it has gained acceptance as a potential management alternative in patients with surgically unresectable, recurrent disease or with unfavorable pathologic findings following surgery for recurrent disease. Although there is evidence to warrant substantial concern regarding the toxicity resulting from reirradiation of the head and neck, a number of studies addressing survival and disease control rates with reirradiation (with or without chemotherapy) have demonstrated long-term survival in a small percentage of patients.^{7,11,13,16,24–27}

In the current study, palliative patients were assessed separately from patients treated with curative intent because the survival rates and adverse events have clearly different implications for these 2 patient groups. The survival rate for our palliative patient group was poor, with a median survival of 6.2 months and no 2-year survivors. This survival outcome is similar to the survival outcomes reported in patients with advanced, unresectable disease treated with chemotherapy alone, which have shown survival rates ranging from 6 to 9 months.^{28–33} Unfortu-

nately, although the primary goal of using reirradiation for palliative purposes was to lessen patients' symptoms, a substantial percentage of patients (53.8%) in this study developed 1 or more grade 3 or 4 radiation-related toxicity and/or major disease-related problem during the follow-up. Based on this rate of severe, adverse events, reirradiation in patients with incurable, recurrent head and neck cancer did not provide palliation (lessening of pain or symptoms) in over half of these patients.

It is difficult to compare results across different reirradiation series because outcomes vary substantially based upon patient selection, treatment technique, and the differentiation between curative or palliative intent of the treatment. Large ranges of 5-year survival rates, from 13% in unselected series to 93% in highly selected series, have been reported.^{10,20} Reports that include only laryngeal or nasopharyngeal cancers, early-stage recurrences, or second primaries arising within a previously radiated field report substantially better survival outcomes compared with the series with unselected patient populations.^{11,12,14,24,34}

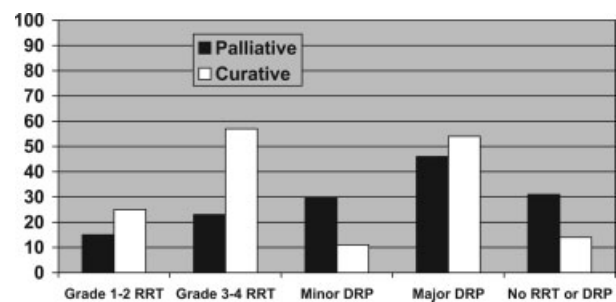


FIGURE 2. Radiation-related toxicity or disease-related problem by intent to treat status for patients ($n = 41$). The percentage of palliative intent and curative intent patients with each class of adverse event is shown. Some patients had more than 1 type of adverse event.

The survival rate of the unselected patients who received reirradiation with intent to cure, either alone or as postsurgical adjuvant therapy, was also relatively poor (with an 11.5-month median survival and observed survival rates of 46.3%, 28.6%, and 13.4% at 1, 2, and 3 years, respectively). Our results were similar to previous studies that included unselected patients treated with external beam reirradiation.^{11,14,21,35} Stevens et al¹⁴ followed 85 patients with recurrent head and neck carcinoma managed with reirradiation and found a 27% 2-year and 17% 5-year actuarial survival.

The use of concurrent chemotherapy in the reirradiation setting has paralleled its use in the primary setting in an attempt to increase locoregional control and survival. In a recent review, Kasperts et al⁷ reported a 2-year overall survival rate ranging between 5% and 45% with the use of chemotherapy during reirradiation. As with the series assessing outcome with reirradiation alone, survival rates following treatment with chemotherapy and reirradiation vary substantially with patient selection. Phase I and II studies of concurrent chemotherapy and reirradiation for incurable, recurrent head and neck cancers have been reported by Haraf et al¹⁶ with a 5-year overall survival rate of 14.6%. Interestingly, in this report, survival was related primarily to the radiation dose, with those patients who received more than 58 Gy having a better 5-year overall survival rate (22%).¹⁶

The reported reirradiation series frequently classify radiation-associated complications as either acute/early or late effects. We did not find it very helpful to characterize radiation-related toxicities into late or acute. Because of the short lifespan of most of these patients, any major disease-related problem or grade 3 or 4 radiation-related toxicity occurring during or after reirradiation was felt to represent a significant insult to quality of life during the patients' remaining life, regardless of this designation. In this article, we evaluated all adverse events, including both radiation-related toxicities and disease-related problems. In some cases it was difficult to separate out radiation-related toxicities, particularly late radiation complications, from problems related to progression of the disease itself (eg, the need for tracheostomy or gastrostomy developing in the face of increased tumor size during reirradiation).

In our series, adverse events occurred relatively frequently in both the palliative and curative groups, with 68% of all patients developing a

major disease-related problem and/or grade 3 or 4 radiation-related toxicity. This high percentage demonstrates how difficult reirradiation can be on patients with recurrent head and neck cancer.

Reported rates of late complications in the literature, such as Kasperts et al's⁷ 14% rate for grade 3 and 4 late complications in 3 reirradiation series, are often lower than those reported in the current article. But previous results need to be interpreted with caution. Complication rates vary between studies as a result of the length of survival and type of treatment (eg, external beam vs brachytherapy vs IMRT, total dosage, site irradiated, time from initial radiation, addition of chemotherapy).¹² More importantly, these rates vary depending on the definition of complications. Often, the early and anticipated complications such as severe mucositis are not reported, and many patients are never at risk for developing late complications due to the short survival of the majority of patients with recurrent head and neck carcinoma receiving reirradiation.^{11,12} It is important to compare the prevalence of late complications with the number of patients who are actually at risk.⁷

Our relatively high rate of radiation-related toxicities likely reflects the inclusion of all radiation-related toxicities, including both acute and late, in the analysis. This approach is appropriate in a population of patients for whom survival is likely to be very short and for whom any radiation-related toxicity or disease-related problem is likely to have a substantial, detrimental effect on the quality of life during their remaining life.

CONCLUSIONS

The survival prognosis for patients treated palliatively is very poor. The desire to offer palliative reirradiation to provide some form of treatment should be tempered by the extremely poor prognosis in these patients and the high rate of adverse events that are detrimental to their quality of life. The prognosis for patients treated with curative intent is also poor. Reirradiation in these cases with potentially curable disease should be performed cautiously, with a clear understanding by both physician and patient of the relatively poor survival and quality of life outcomes. Inclusion of disease-related problems in addition to acute and late radiation-related toxicities provided a more comprehensive evaluation of the severely compromised quality of life experienced by many patients

who undergo reirradiation due to recurrent head and neck cancer.

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