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Beyond reirradiation: Efficacy and safety of three or more courses of radiation for head and neck malignancies

Amy J. Xu [1], Leo Luo [1], Jonathan E. Leeman, Paul B. Romesser, Daniel Spielsinger, Christopher Sabol, Todd Waldenberg, Thomas Brinkman, Nadeem Riaz, Sean McBride, Julie Kang, Nancy Lee, Chiaojung Jillian Tsai *

Memorial Sloan Kettering Cancer Center, Department of Radiation Oncology, 1275 York Ave, New York, NY 10065, United States

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ABSTRACT

Purpose: Recurrent head and neck cancers are associated with significant morbidity and mortality. Outcomes of multiple courses of radiation have not yet been described.
Methods and Materials: A single institution database was queried to retrospectively review treatment plans and select patients who underwent ≥ 3 courses of radiation to the head and neck region.
Results: Thirty-three patients were found to have ≥ 3 courses of radiation with overlapping fields. Median local recurrence free survival after last course of reirradiation was 9.1 months and median overall survival was 10 months. Grade 3 and above toxicities were reported in 15 patients (45%). Grade 4 and above toxicities were reported in seven patients (21%). There was no grade 5 toxicity. 20 patients (61%) underwent subsequent therapies following completion of repeat reirradiation.
Conclusions: Repeat reirradiation to the head and neck region is feasible and carries significant risks that are most appropriately managed with a multi-disciplinary team and must be balanced against the potential for local control and opportunities for emerging systemic therapies.

1. Introduction

Radiation is a critical and curative treatment modality for locally advanced head and neck cancers. Despite advances in local and systemic treatment, locoregional recurrence remains a significant problem [1]. As outcomes of head and neck cancer patients continue to improve, locoregional failures or second primary malignancies in the head and neck region can present significant morbidity and management challenges.

Curative treatment options for locally recurrent head and neck cancer are limited to surgical resection and reirradiation therapy. Surgical resection with postoperative reirradiation is preferred for operative candidates with resectable disease. The benefit of reirradiation was demonstrated in a randomized trial of 130 patients in France, where reirradiation to 60 Gy with concurrent chemotherapy improved loco-regional control and disease-free survival compared to surgery alone [2]. For unresectable recurrent head and neck cancers, two single-arm trials by Radiation Therapy Oncology Group (RTOG 96-10 and RTOG 99-11) investigated the feasibility and efficacy of salvage reirradiation with chemotherapy. Higher overall survival rates were seen with salvage reirradiation compared to chemotherapy alone, however patients suffered significant toxicities, including 85% grade 3–5 toxicities within 2 years, and eight (8%) treatment-related deaths [3,4].

More recent studies of salvage reirradiation with modern radiation techniques report significantly reduced severe toxicity profiles [5]. A multi-institutional collaborative reviewed the safety and efficacy of IMRT-based reirradiation in 412 patients and found overall rates of severe (grade ≥ 3) toxicity to be 19% [6]. Multiple studies have reported favorable toxicity profiles with proton therapy. A series of 76 patients from MD Anderson Cancer Center reported 30% acute and 16.7% late grade 3 toxicities [7]. Similarly, a multi-institutional analysis of 92 patients reported 31.4% acute and 18.6% late grade 3 or greater toxicity [8].

Given the promising outcomes of modern radiation techniques and advancements in systemic therapy, loco-regional disease con-

* Corresponding author.
E-mail addresses: xua@mskcc.org (A.J. Xu), luol1@mskcc.org (L. Luo), romessep@mskcc.org (P.B. Romesser), spielsid@mskcc.org (D. Spielsinger), sabolc10@gmail.com (C. Sabol), waldenbt@mskcc.org (T. Waldenberg), brinkmat@mskcc.org (T. Brinkman), riazn@mskcc.org (N. Riaz), mcbrides@mskcc.org (S. McBride), kangj1@mskcc.org (J. Kang), leen1@mskcc.org (N. Lee), tsaic@mskcc.org (C.J. Tsai), tsaic@mskcc.org (C.J. Tsai).
[1] A.J.X. and L.L. contributed equally to this article

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trol is of paramount importance in recurrent and metastatic head and neck cancer. To date there is no published report on three or more courses of radiation to the head and neck region. In this study, we report the first experience on the toxicity and efficacy of delivering three or more courses of radiation for recurrent head and neck cancers.

2. Methods and materials

2.1. Patients and pretreatment evaluation

Approval for this study was provided by a waiver of informed consent for retrospective analysis of patient data provided by the Institutional Review Board. A single institution department database of 3063 patients who underwent head and neck radiation at the institution between February 2011 and July 2018 was retrospectively queried for multiple courses of radiation. Dates of radiation therapy spanned 1984–2018 (some patients were previously treated at outside institutions). 55 patients underwent three or more courses of radiation to the head and neck region. Detailed treatment plans, including isodose distributions, were thoroughly reviewed by Head and Neck Radiation Oncology experts to select patients who underwent multiple courses of radiation to completely overlapping regions in the head and neck. Twenty two patients were excluded for receiving treatment to non-overlapping regions of the head and neck, yielding 33 patients used for final analysis.

All patients underwent multidisciplinary pretreatment evaluation, includingcomplete medical history, focused head and neck physical exam(fiberoptic nasopharyngoscopy when appropriate), and imaging studies (computed tomography [CT], magnetic resonance imaging [MRI]and/or positron emission tomography [PET]). Personalized treatment plans were formulated from multidisciplinary tumor boards, comprised of medical oncologists, head and neck surgeons, dentists, speech and swallow pathologists, and head and neck radiation oncologists.

2.2. Radiation therapy

Patients received CT-based simulation in supine position with personalized head and neck immobilization. Fusion of MRI or PET images to the primary simulation CT scan was performed when feasible. Gross tumor volume was delineated based on physical exam and imaging findings. For postoperative cases, the entire postoperative bed was delineated as the clinical target volume. A 3–5 mm margin was typically added for planning target volume.

Photon radiation was delivered with either 3D conformal radiation or intensity modulate radiation therapy (IMRT). Proton radiation was delivered with uniform scanning beams. A relative biological effect (RBE) of 1.1 was used to calculate biological effective doses for proton treatments. Setup accuracy was confirmed using daily orthogonal imaging verification based on bony anatomy. A verification CT scan was also performed in selected cases to verify isocenter or assess any changes in anatomy. Cumulative radiation dose was calculated by converting to all courses of radiation to 2 Gy-equivalent biologically effective dose (EQD2) through the linear-quadratic model using α/β ratios of 3 and 10 to reflect normal tissue and tumor, respectively.

2.3. Prior treatment review

Previous radiation was thoroughly reviewed prior to each course of radiation therapy. Prior treatment was evaluated by performing a rigid registration of beams with anatomic adjustments made as necessary to match the divergence of prior treatments. Cumulative dose to organs at risk were calculated and peer review obtained for any patient for which there was concern for exceeding organ tolerance, especially for the brainstem, cord, optic structures, and optic chiasm.

2.4. Acute and late toxicity management and follow-up

During treatment, patient underwent weekly assessments by a radiation oncologist. After completing treatment, patients were evaluated every 2 to 3 months of the first year and 4–6 months thereafter. Toxicities were assessed with clinic visits and routine surveillance imaging. Late toxicity was assessed beginning 90 days after completing the last course of radiation. Toxicity was assess using Common Terminology Criteria for Adverse Events version 4.0. Follow-up visits consisted of physical examination and flexible fiberoptic nasopharyngoscopy when appropriate. Posttreatment surveillance imaging including CT, MRI, and PET scans were performed 2–3 months after completing treatment.

2.5. Statistical methods

Time to event was determined from the last date of repeat reirradiation treatment to an overlapping region. Local disease control and overall survival was estimated using Kaplan-Meier survival analysis. Statistical significance was assessed using the Gehan-Breslow/Wilcoxon test with a significance level of $p < 0.05$. Statistical analyses were performed with GraphPad Prism (version 7.04).

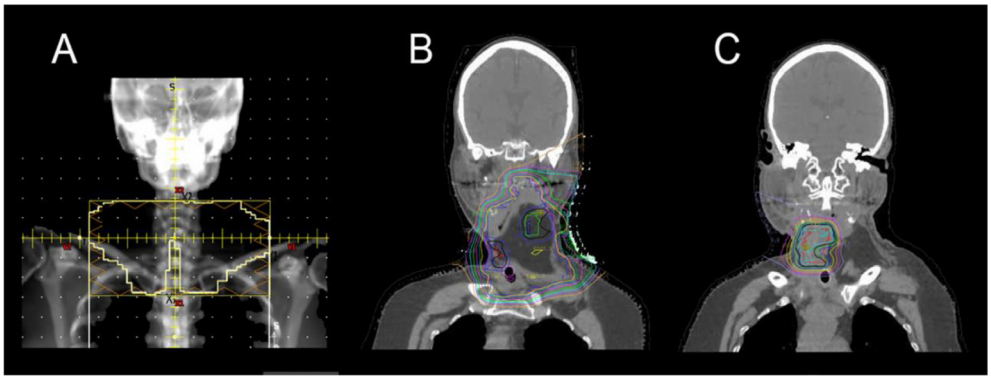

Fig. 1. Example plan for patient undergoing repeat reirradiation. A) Chemoradiation to larynx and bilateral neck to 72 Gy (extra fraction delivered for a 4 day treatment break) for cT2N2b SCC of supraglottic larynx in 2013. B) First recurrence treated with total laryngectomy followed by proton radiation to 76 Gy (RBE) in 2016. C) Third course of radiation delivered 7 months later as 27 Gy in 3 fractions to recurrent disease in right neck.

Table 1
Patient and tumor characteristics.

Characteristics	n	Percent
Total patients	33	100%
Gender		
Male	22	67%
Female	11	33%
Initial disease site		
Oral cavity	4	12%
Oropharynx	2	6%
Nasopharynx	4	12%
Larynx	5	15%
Nasal cavity/paranasal sinuses	4	12%
Salivary	3	9%
Base of skull	1	3%
Skin	10	30%
New primary		
Yes	4	12%
No (recurrent)	29	88%
Histology		
SCC	24	73%
Melanoma	2	6%
Nasopharyngeal carcinoma	2	6%
Salivary duct carcinoma	2	6%
Merkel cell	1	3%
Adenoid cystic	1	3%
Plasmacytoma	1	3%
# courses head and neck radiation		
Three	23	70%
Four	8	24%
Five	2	6%

3. Results

3.1. Patient and tumor characteristics

Thirty-three patients were identified with three or more courses of overlapping radiation to the head and neck region. An example of treatment overlap is provided in Figure 1. Median follow-up time after repeat reirradiation was 9.2 months (range 0.4–65.1 months) in all patients and 37.6 months (range 3.4–65.1 months) in surviving patients.

Twenty nine patients underwent treatment for multiply recurrent disease and four patients were treated for metachronous head and neck primary tumors (Table 1). Primary tumor sites included skin (30%), larynx (15%), oral cavity (12%), nasopharynx (12%), nasal cavity/*para*-nasal sinuses (12%), salivary gland (9%), oropharynx (6%) and base of skull (3%). Squamous cell carcinoma was the most common histology (73%). Median Karnofsky performance score (KPS) was 80 prior to third course of radiation.

Radiation therapy included external beam radiation with photons, electrons and protons, as well as intraoperative brachytherapy (Table 2). Concurrent chemotherapy was delivered with 49%, 52% and 39% of first, second and third radiation courses, respectively. 18% of reirradiation courses and 70% of repeat reirradiation courses were delivered with palliative intent.

3.2. Reirradiation characteristics

The median cumulative dose for overlapping radiation was 155.3 (range 107.5–220.0) cobalt gray equivalents (CGE) with biologic effective dose in two gray equivalents (BED 2 Gy) of 176.7 and 163.8 assuming α/β ratios of 3 and 10, respectively (Table 2). Median age at the start of the third radiation course was 64 years of age. Median time intervals were 22.9 months between first and second courses of radiation, and 14.5 months between second and third courses of radiation. Median doses for the first, second, and third courses of radiation were 65, 57 and 44 CGE, respectively.

Eight patients (24%) underwent four courses of head and neck radiation and two patients (6%) underwent five courses of head and neck radiation. Proton radiation was increasingly used for repeat reirradiation, comprising 24% of second radiation courses and 61% of third radiation courses. 48% of third reirradiation courses were delivered as quad shot therapy. Quad shot is a hypofractionated, palliative regiment consisting of 3.7 Gy, delivered twice-daily over two consecutive days per cycle, with adaptive planning and 2–4 week rest between each cycle [9]. Of note, all quad shot cycles (up to 4 cycles of 4 fractions each) were counted as a single course of reirradiation.

3.3. Local control

Fifteen patients (45%) developed local recurrence following third course of repeat reirradiation therapy. Median local recurrence free survival after last course of reirradiation was 9.1 months (Figure 2A). Median time to failure was 8.4 months for the 19 patients who did not receive salvage surgery prior to third course repeat reirradiation. For the 13 patients who received salvage surgery, fewer than half experienced a local failure. This difference in time to disease failure trended towards statistical significance ($p = 0.07$) (Figure 2B).

Table 2

	1st RT	2nd RT	3rd RT	
Age(median, range)	56 (30, 85)	62 (30, 85)	64 (30, 87)	
Interval surgery prior to each RT course	67% (22)	58% (19)	39% (13)	
Concurrent chemotherapy	49% (16)	52% (17)	27% (9)	
Palliative intent	0% (0)	18% (6)	70% (23)	
Time interval since previous radiation (months)		22.9 (1.5–157.6)	14.5 (0.2–84.3)	
Modality				
Photons/electrons	94% (31)	67% (22)	33% (11)	
Protons	3% (1)	24% (8)	61% (20)	
IORT	3% (1)	9% (3)	6% (2)	
Quad Shot	0	9% (3)	48% (16)	
				Cumulative dose
Dose (CGE)	65 (21.0–72.0)	57.1 (8.0–80.0)	44.4 (10.0–76.3)	155.3 (107.5–220.0)
BED (2GY, α/β = 3)	66.0 (36.0–117.3)	64.8 (11.2–114.8)	59.5 (19.8–104.0)	176.7 (121.3–281.9)
BED (2GY, α/β = 10)	66.0 (29.8–89.7)	60.6 (9.3–80.0)	50.9 (16.7–76.3)	163.8 (97.3–213.6)

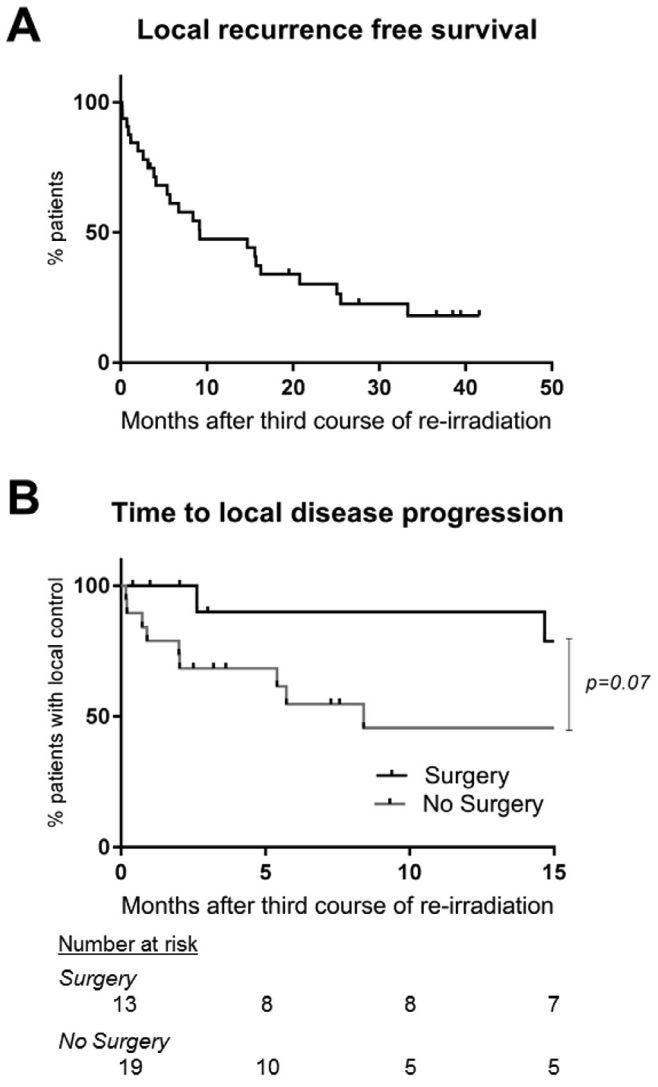

Fig. 2. Local control with repeat reirradiation and salvage surgery. Local control was assessed based on review of imaging and clinical documentation. A) Median local recurrence free survival after last course of reirradiation was 9.1 months. B) Actuarial local control rates stratified by the presence or absence of salvage surgery prior to third course of overlapping radiation. Fourteen patients underwent salvage surgery prior to third course of repeat reirradiation (black). Local control trended towards significance amongst this cohort compared to local control rates for the 22 patients who did not undergo salvage surgery (p = 0.07). Median time to local disease progression for patients who did not undergo surgery was 9.5 months and not reached amongst the patients who underwent salvage surgery.

3.4. Overall survival

Median overall survival was 10 months after last course of reirradiation (Figure 3). Amongst the four patients treated for metachronous head and neck primaries, median overall survival was 6.7 months, compared to 11.2 months for the 29 patients treated for recurrent disease of the same primary. At one-year, overall survival was 47% for patients with second malignancies, 25% for patients with recurrent disease, and 44% for the entire cohort.

3.5. Toxicities

Fifteen (45%) patients experienced grade 3 or above treatment toxicities. Of these patients, 33% (5 of 15) had pre-existing toxicities prior to third course RT. Specifically, four patients had pre-existing percutaneous endoscopic gastrostomy (grade 3 toxicity) and one had tracheoesophogeal fistula (grade 4 toxicity).

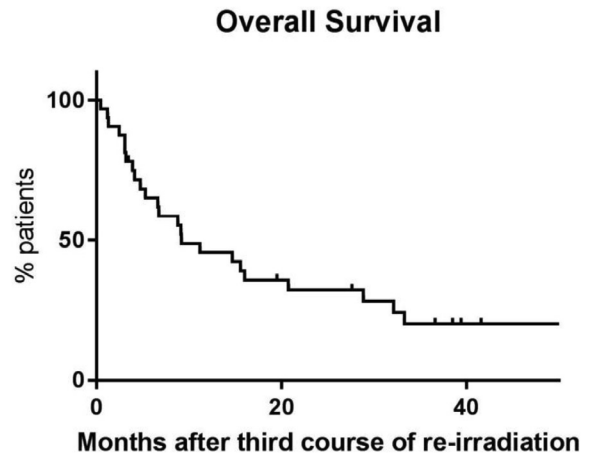

Fig. 3. Actuarial overall survival rates. Median overall survival was 10 months. Overall survival at 12 months was 44%.

Other grade 3 and above acute toxicities included dermatitis, dysphagia, trismus, fatigue, mucositis, soft tissue necrosis, and fibrosis. Grade 3 or above late toxicities included dysphagia, soft tissue necrosis, dermatitis, fibrosis, and trismus. Grade 4 toxicities were reported in seven patients (21%) and included osteoradionecrosis, cutaneous fistula, osteomyelitis, and paraspinal soft tissue necrosis. These complications required surgical management, including skin graft, debridement, and flap reconstructions.

Assuming an α/β ratio of three, patients who experienced grade three or above late toxicities had a mean dose in 2 Gy equivalents of 184 Gy (range 144–225 Gy), which was not statistically different from the mean dose of 179 Gy (range 121–282 Gy) in patients who only experienced grade 1 or 2 toxicities.

3.6. Additional therapies

Twenty patients (61%) underwent subsequent therapies following completion of three or more courses of reirradiation. Three patients underwent additional surgery, eleven patients underwent additional chemotherapy, and nine patients underwent immunotherapy.

4. Discussion

We present the first report of three or more courses of radiation to overlapping regions in the head and neck. Reirradiation for recurrent or second primary head and neck cancer was previously studied in prospective and retrospective settings. Two phase II clinical trials of salvage reirradiation, RTOG 96-10 and RTOG 99-11, demonstrated overall survival benefit with concurrent reirradiation and chemotherapy compared to chemotherapy alone [3,4]. However, significant side effects were reported, with 90% of patients experiencing grade 3 to 5 toxicity in first 2 years after reirradiation in RTOG 99-11 [3].

Modern radiation techniques have enabled better tumor coverage and sparing of normal tissue. Multiple studies have reported single or multi-institutional experience with IMRT-based reirradiation [6,10–14]. One of the largest single-institutional cohort was 105 patients treated with definitive or postoperative reirradiation. The study demonstrated superior loco-regional control with IMRT compared to 3D-conformation radiation technique (52% vs. 20%, at 2 years, $p < 0.001$ [12]. A multi-institutional cohort study included 412 patients treated with re-IMRT achieved 60% loco-regional control and 40% overall survival at 2 years [6].

Proton therapy has also been adopted for salvage reirradiation for its advantage of minimal exit dose delivered to surrounding

normal tissues [7,8,15,16]. Romesser et al. reported a cohort of 92 patients treated with proton reirradiation with curative intent. At 1 year, 75% locoregional control and 65% overall survival were achieved, with 31% acute grade 3 or greater toxicity [8].

Three or more courses of reirradiation has not been previously described in the head and neck region, but has been reported for other disease sites such as brain, spine, lung, and pelvis [17]. Katsoulakis et al. reported 10 patients with multiply recurrent spine metastases treated with third course of radiation using image-guided IMRT [18]. The median spinal cord maximum dose was 70.7 Gy in 2 Gy equivalent (range 51.9–101.7 Gy) and the crude rate of local control was 80% with 1 in-field failure and 1 marginal failure. We report comparable rates of local disease control, with local control achieved in 63% of surviving patients at 1 year.

As expected, three or more courses of head and neck radiation was associated with significant toxicities, with 45% of patients experiencing grade 3 or above toxicities. Seven patients (21%) experienced toxicities of grade 4 and above. These complications highlight the importance of working with a truly multi-disciplinary team of specialists to help manage complications that may arise from these complex cases.

Similar to findings for a second course of reirradiation, patients who had salvage surgery prior to postoperative third course reirradiation had improved local control compared to salvage reirradiation alone [6,12]. After repeat reirradiation, 61% of patients were treated with subsequent therapies such as immunotherapy. Within an academic center where such promising therapies continue to evolve, reirradiation can be considered as a bridge to additional therapies to potentially improve outcomes.

This study is limited by a relatively small cohort of heterogeneous patients, as well as the standard limitations of retrospective review. Toxicity data were collected by reviewing available medical records which may underestimate the incidence of adverse effects. In addition, it is difficult to discern toxicities from the last radiation course versus from prior two courses of radiation, or from other treatment modalities such as surgery, chemotherapy, or immunotherapy. The safety and quality assurance for treatment of these patients are also specific to our tertiary referral institution. Patients considered for reirradiation should be referred to a high volume center with expertise in reirradiation and multi-disciplinary specialists that can work together to manage the significant risks.

5. Conclusions

Repeat reirradiation to the head and neck region is feasible and carries significant risks that are most appropriately managed with a multi-disciplinary team and must be balanced against the potential for local control and opportunities for emerging systemic therapies.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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