Scientific Article

Adjuvant Reirradiation With Proton Therapy in Head and Neck Squamous Cell Carcinoma

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Purpose: For patients with head and neck squamous cell carcinoma (HNSCC), locoregional failure and second primary tumors are common indications for adjuvant reirradiation (re-RT). Given an absence of clear consensus on the role of adjuvant re-RT, we sought to assess histopathologic risk factors of patients with HNSCC and their resulting outcomes after adjuvant re-RT with proton therapy.

Methods and Materials: We conducted a retrospective analysis of patients with HNSCC who underwent salvage surgery at our institution followed by adjuvant re-RT with proton therapy over 1.5 years. All included patients received prior radiation therapy. The Kaplan-Meier method was used to evaluate locoregional recurrence-free survival and overall survival.

Results: The cohort included 22 patients, with disease subsites, including oropharynx, oral cavity, hypopharynx, larynx, and nasopharynx. Depending on adverse pathologic features, adjuvant re-RT to 66 Gy (32% of cohort) or 60 Gy (68%), with (59%) or without (41%) concurrent systemic therapy was administered. The majority (86%) completed re-RT with no reported treatment delay; 3 patients experienced grade ≥3 acute Common Terminology Criteria for Adverse Events toxicity and no patient required enteral feeding tube placement during re-RT. Median follow-up was 21.0 months (IQR, 11.7-25.2 months). Five patients had biopsy-proven disease recurrences a median of 5.9 months (IQR, 3.8-9.7 months) after re-RT. Locoregional recurrence-free survival was 95.2%, 70.2%, 64.8% at 6, 12, and 24 months, respectively. OS was 100%, 79.2%, and 79.2% at 6, 12, and 24 months, respectively. Four patients had osteoradionecrosis on imaging a median of 13.2 months (IQR, 8.7-17.4 months) after re-RT, with 2 requiring surgical intervention.

Conclusions: Adjuvant re-RT for patients with HNSCC was well-tolerated and offered reasonable local control in this high-risk cohort but appears to be associated with a risk of osteoradionecrosis. Additional study and longer follow-up could help define optimal patient management in this patient population.

Introduction

As the incidence of human papilloma virus increases, rates of tobacco and alcohol use decrease, and the population ages, the landscape of head and neck squamous cell carcinoma (HNSCC) is evolving.[1,2] In addition, there have been significant advances in radiation therapy technology. Thus, the treatment paradigm for HNSCC continues to evolve.[3] The standard of care of HNSCC includes radiation therapy either as definitive or adjuvant therapy for most disease sites and stages. Presently, radiation therapy (RT) doses for the treatment of HNSCC include definitive RT to a dose of 70 Gy or postoperative RT to a dose ranging from 60 to 66 Gy given via intensity modulated radiation therapy (IMRT).[4]

Even with optimal management, up to half of the patients may develop disease recurrence.[5] Patients with prior head and neck cancer are also at increased risk of developing a second primary cancer (SPC), with the incidence of SPC risk ranges from 3% to 7% per year[6,7]; however, it increases exponentially over time.[8] Treatment options are limited in a previously irradiated field.[9] Treatment of SPCs varies by tumor subsite and stage, and thus are treated similarly to a primary HNSCC. For recurrent disease, salvage surgery with curative intent is the preferred treatment when feasible because reirradiation (re-RT) is associated with substantial acute and late toxicity.[10-12] Re-RT with or without concurrent chemotherapy is an alternative option for patients who are not candidates for resection or for patients who undergo surgical salvage and found to have high-risk features, such as positive margins, perineural invasion, lymphovascular invasion, or extracapsular extension.[13,14]

Adjuvant re-RT after surgical salvage has shown promising outcomes in retrospective as well as early phase randomized trials.[15,16] Although IMRT is the most common approach for re-RT of the head and neck, re-RT with more advanced technology, such as protons and heavy ions, may offer improved dose distributions leading to increased normal tissue sparing and less toxicity.[17,18] However, to date, the data on proton use as an adjuvant, curative treatment in reirradiation settings for recurrent or second primary HNSCC is limited.[17,19-21] Given that there is no clear data or consensus on the role of adjuvant re-RT with proton therapy for patients with HNSCC, many of whom present in the recurrent setting with high-risk features, additional data are needed to help guide the use of adjuvant re-RT with proton therapy. We sought to evaluate outcomes and toxicity after adjuvant re-RT with proton therapy for recurrent HNSCC or second primary HNSCC.

Methods and Materials

Study cohort inclusion criteria

A retrospective chart review of patients with HNSCC from our institutional database, approved by the Institutional Review Board, was conducted. Given the retrospective aspect of this research, informed consent was waived. Consecutive patients with HNSCC who underwent salvage surgery at our institution followed by adjuvant re-RT with proton therapy from June 2019 to November 2022 were included. All included patients had received prior radiation therapy, either in the definitive or adjuvant setting, and had biopsy-proven recurrence or a SPC with pathology reviewed in-house before re-RT. The study was approved by the Institutional Review Board (IRB#: HS 19-00863).

Definition of variables and terminology

Common Terminology Criteria for Adverse Events, version 5.0 toxicity scale was used to evaluate acute toxicity during re-RT. A treatment interruption was defined as missing at least one unexcused radiation treatment, and federal holidays and facility issues are excused absences. A premature treatment termination was defined as premature treatment discontinuation resulting in not receiving the full prescribed treatment. Time interval between initial course of RT and re-RT is calculated from last date of initial RT course and first date of re-RT course. For patients whose first or last date of initial RT course is unavailable to calculate age at first RT or time interval between RT, respectively, the simulation date, if available, or the year of initial RT course is used as the substitute. Follow-up duration was defined as the time from end of re-RT to last follow-up. Locoregional recurrence-free survival (RFS) was defined as the time from end of re-RT to biopsy-proven disease recurrence or death from any cause, censored at the date of patient's last contact. Overall survival (OS) was defined as the time from end of re-RT to death from any cause, censored at the date of patient's last contact. In-field recurrence after re-RT is defined as recurrence within re-RT field.

Re-RT target volume delineation

Given prior RT in the head and neck region, the volumes of re-RT fields are purposefully smaller than those applied in standard adjuvant cases.[4] The treatment intent is to limit field size and extent to reduce toxicity by targeting the area closest to the tumor and thus at the highest

risk of disease recurrence. Preoperative imaging and prior RT plan, if available, were fused to the re-RT simulation scan. For patients without available prior RT plan, we assumed the critical structures, such as the spinal cord, received the maximal allowed dose and thus planned for these structures to receive doses as low as reasonably achievable. For patients with grossly resected disease, the clinical treatment volume is based on preoperative imaging and included the postoperative bed. The clinical treatment volume-to-planned treatment volume margin is usually 5 mm. Our institution uses pencil beam scanning with multifield optimization intensity modulated proton therapy, which accounts for proton beam arrangement and proton range uncertainty. Figure 1 shows a multiview sample external beam planning for reirradiation with proton therapy to treat primary site alone.

Statistical analysis

Data were provided as medians with IQR. The Kaplan-Meier method was used for RFS and OS. All tests were performed using R version 4.1.1.

Results

Of the cohort of 22 patients, most patients were males (81.8%) with 100% receiving prior RT to primary site and 72.7% also to bilateral necks and had recurrent HNSCC (90.9%). The median prior RT dose was 68 Gy (range, 45-72 Gy); 2 patients with no prior RT record available. The median time between RT courses was 5 years (IQR, 2.5-7.6 years) between the 2 courses of RT. The distribution of patient demographics with prior disease characteristics and RT treatments are shown in Table 1.

Depending on adverse pathologic features seen in the surgery before re-RT (Table 2), adjuvant re-RT of 66 or 60 Gy, with or without concurrent systemic therapy, was

given (Table 3). Of the 9 patients who did not receive concurrent chemotherapy, 2 were recommended for chemotherapy but did not receive it by choice or because of poor performance status.

Three patients developed grade ≥3 acute Common Terminology Criteria for Adverse Events toxicity: 1 patient each with grade 3 radiation dermatitis, grade 3 oral mucositis, and grade 3 dysphagia (Table 3). No patient required enteral feeding tube placement during re-RT. Of the 22 patients, 2 experienced re-RT interruption (1 due to pneumonia that was not deemed to be related to RT or aspiration and that resulted in hospitalization and 1 due to several missed appointments); 1 terminated treatment early given concern for out-of-field disease progression (patient to be excluded from further analysis); all others completed the re-RT with no reported treatment delay. There was no other hospitalization during re-RT.

Four patients (19%) developed osteoradionecrosis after treatment based on CT imaging. Median time to development of osteoradionecrosis was 13.2 months (IQR, 8.7-17.4 months). Two patients required surgical intervention for osteoradionecrosis. These 4 patients received a median prior RT dose of 63 Gy (IQR, 60-67 Gy) to primary site and bilateral necks with 3 of the 4 also receiving concurrent chemotherapy, with a median maximal dose of 65.3 Gy (IQR, 64.9-66.2 Gy) to the mandible. They subsequently received re-RT dose of 63 Gy (IQR, 60-66 Gy) with 3 of the 4 also receiving concurrent chemotherapy, with a median maximal dose of 64.56 Gy (IQR, 63.1-66.8 Gy) to the mandible. One of the 4 patients did not have an available DICOM file for the first course of RT, and we are unable to provide the composite dose to the site of the mandible where osteoradionecrosis developed. For the other 3 patients, the maximal composite doses to the mandible are 125.70, 131.02, and 134.35 Gy. The re-RT fields included primary site only for 1 patient, primary site and ipsilateral neck for 1 patient, and primary site and bilateral necks for 2 patients. There was no grade 3+
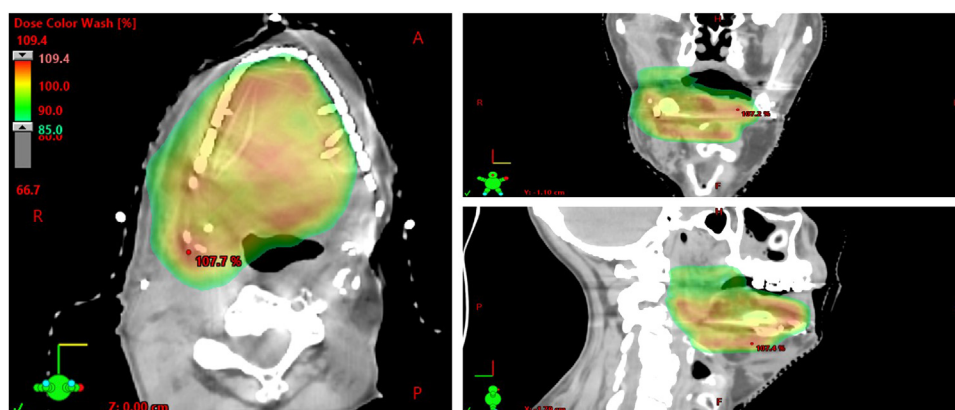

Figure 1   Sample external beam planning for reirradiation with proton therapy to treat primary site alone to 60 Gy with a hotspot present.

Table 1   **Patient demographic with prior disease characteristics and RT treatments (N = 22)**

Characteristic	N	%
Sex		
Female	4	18.2
Male	18	81.8
Age* (in years at prior RT, median [IQR])	55.9 [51.6, 63.9]	
Age (in years at re-RT, median [IQR])	64.0 [58.4, 71.2]	
Time interval between RT (in years, median [IQR])	5.0 [2.5, 7.6]	
Prior disease site		
Oropharynx	11	50.0
HPV associated	6	
Non-HPV associated	3	
Unknown HPV association	2	
Oral cavity	5	22.7
Hypopharynx	2	9.1
Larynx	2	9.1
Nasopharynx	1	4.5
Unknown	1	4.5
Prior RT dose (median [IQR]), Gy	68.0 [60, 70]	
<60[†]	3	13.6
60	4	18.2
64	1	4.5
66	2	9.1
≥70	10	45.5
Unknown[‡]	2	9.1
Prior RT field		
Primary site alone	1	4.5
Primary site + ipsilateral neck	3	13.6
Primary site + bilateral necks	16	72.7
Unknown[‡]	2	9.1
Disease recurrence at the time of re-RT[‡,§]		
In prior RT field	11	50.0
Out of prior RT field	7	31.8

Abbreviations: HPV = human papilloma virus; RT = radiation therapy.
*The year, but not the exact start date, of the first course of RT are known for 6 patients. The age was calculated using a start date of July 1.
†Clinical trial doses: 45 Gy, 50 Gy, 56 Gy.
‡Two patients' prior RT dose and field are unknown.
§Two patients had second primary cancer.

toxicity for brachial plexopathy, flap failure, optic toxicity, or central nervous system toxicity.

Median duration of follow-up for patients still alive was 21.0 months (IQR, 11.7-25.2). Locoregional RFS was 95.2%, 70.2%, 64.8% at 6, 12, and 24 months, respectively (Fig. 2). OS was 100%, 79.2%, and 79.2% at 6, 12, and 24 months, respectively (Fig. 3). Five patients had biopsy-proven disease recurrence a median of 5.9 months (IQR, 3.8-9.7 months) after re-RT, specifically 4 patients with

locoregional recurrence and one patient with metastatic recurrence: 1 patient with a close surgical margin received adjuvant re-RT of 60 Gy alone had an in-field recurrence 5.9 months after re-RT; 1 patient with a close surgical margin received adjuvant re-RT of 60 Gy with concurrent systemic therapy had an out-of-field local recurrence 3.2 months after re-RT; 1 patient with a positive surgical margin received adjuvant re-RT of 66 Gy with concurrent systemic therapy had an out-of-field nodal recurrence 9.7

Table 2 Histopathologic factors warranting adjuvant reirradiation (n = 22)

Adverse pathologic feature	Patients (no. and %)	Patients with disease recurrence (no.)
Extracapsular extension	4; 18%	1
Positive surgical margin	8; 36%	3
Close (<5 mm) surgical margin	5; 23%	2
pT3/4 disease	14; 64%	2
Perineural invasion	14; 64%	1
Lymphovascular invasion	4; 18%	1
Lymph node involvement	5; 23%	1
No. of adverse pathologic feature(s)	**Patients (no. and %)**	**Patients with disease recurrence (no.)**
1	3; 14%	2
2	9; 41%	1
3	4; 18%	1
4	5; 23%	1
5	0	0
6	0	0
7	0	0

Table 3 Adjuvant re-RT and concurrent systemic therapy (n = 22)

		Concurrent systemic therapy	
re-RT of 66 Gy in 33 fractions for 7 patients (32%)		**Yes**	**No**
re-RT field	Primary site alone	0 (0%)	1[‡] (5%)
	Primary site and ipsilateral neck	1 (5%)	1 (5%)
Primary site and bilateral necks		4[*] (18%)	0 (0%)
Re-RT of 60 Gy in 30 fractions for 15 patients (68%)		**Concurrent systemic therapy**	
		Yes	**No**
Re-RT field	Primary site alone	7 (32%)	5[†] (23%)
	Primary site and ipsilateral neck	1 (5%)	1 (5%)
	Primary site and bilateral necks	0 (0%)	1 (5%)

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; re-RT = reirradiation.
*1 patient with CTCAE grade 3 radiation dermatitis.
†1 patient with CTCAE grade 3 dysphagia.
‡1 patient with CTCAE grade 3 oral mucositis.

months after re-RT; 1 patient with a positive surgical margin received adjuvant re-RT of 60 Gy with concurrent systemic therapy had an out-of-field local recurrence 20.0 months after re-RT; 1 patient with a positive surgical margin and lymph node involvement received adjuvant re-RT of 66 Gy with concurrent chemotherapy had an out-of-field metastatic recurrence 3.8 months after re-RT.

Discussion

Because of the need for multimodality therapy and the proximity to critical organs, initial treatment of HNSCC can be challenging, with radiation therapy potentially contributing to rates of acute grade 3 or higher toxicity up to 80% and severe late toxicity rates up to 35% with resulting decreased quality of life.[22-24] Locoregional failure and SPC are common indications for definitive or adjuvant re-RT in patients with HNSCC, although there are fewer reported outcomes and toxicities for this patient population and for adjuvant re-RT with proton therapy.[25] In the context of these findings, this study sought to assess the role of adjuvant re-RT with proton therapy for HNSCC, specifically whether a reasonable locoregional control can be achieved with an acceptable toxicity profile. To our knowledge, this is the first study to assess the
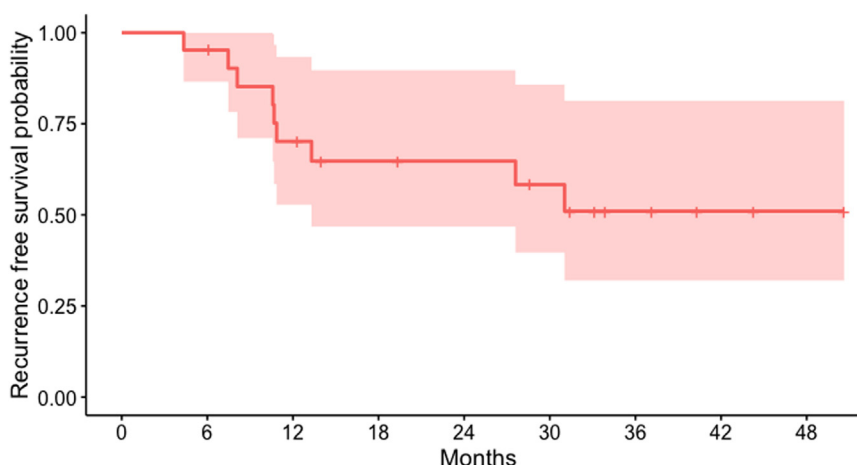
Figure 2   Locoregional recurrence free survival after adjuvant proton reirradiation for head and neck squamous cell carcinoma (n = 21).

histopathologic risk factors, toxicity, and outcome of patients receiving adjuvant re-RT with proton therapy for HNSCC.

It is well known that exposure to radiation therapy may be associated with various malignancies. Out of our cohort of 22 patients, most of the patients had disease recurrence. Only 2 patients had SPC, neither of which developed in prior RT field. Given the retrospective aspect of this study and the focus of adjuvant re-RT in locoregional control, additional risk factors associated with recurrent or SPC were not further explored.

Close monitoring with regular follow-up is required for early detection of recurrent or SPC.[4] In a study looking at SPCs, nearly 50% of patients were asymptomatic and they were detected on routine examination.[8] Even though risk of recurrence decreases over time, the risk of SPC increases over time, therefore continued surveillance beyond 5 years from the index cancer is recommended.

In our cohort, there is a median of 5 years between the 2 courses of RT. Some patients may have their disease recurrence detected via routine examination, such as physical examination or radiologic imaging, and others may have gotten expedited office visit or imaging due to concerning clinical findings. Some patients in our cohort may have other salvage treatment, such as salvage surgery alone, during the interim. Although the purpose of this study is to evaluate the effectiveness and tolerability of adjuvant re-RT with proton therapy, this is a limitation of this study.

Surgical resection depends on the primary site of disease and is classically the preferred initial management for cancers of the oral cavity, salivary gland, nasal cavity, and paranasal sinus, as well as select oropharyngeal and larynx cancer cases.[4] Certain adverse pathologic features after surgical resection may warrant adjuvant treatment, and they include large tumor size, nodal disease,
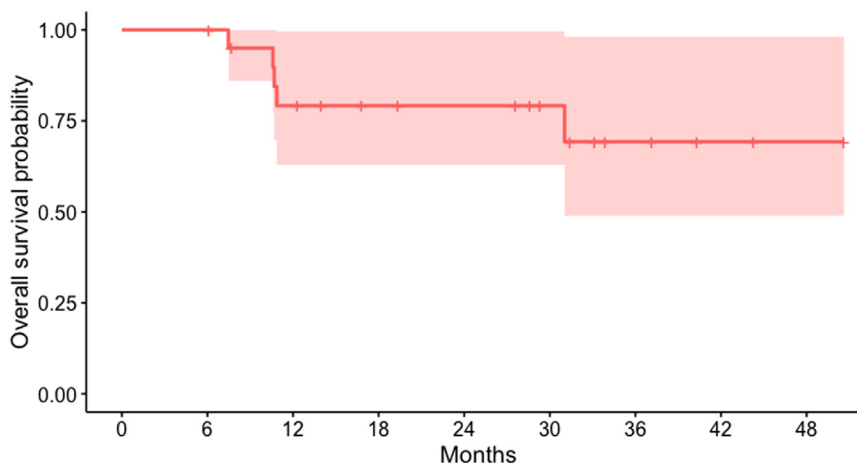

Figure 3   Overall survival after adjuvant proton reirradiation for head and neck squamous cell carcinoma (n = 21).

perineural invasion, lymphovascular invasion, and close margins (<5 mm).[26-28] Given limited data on adverse pathologic risk features for recurrent HNSCC after salvage surgery, the criteria for adverse pathologic risk features in an index cancer was also used for recurrent cancer or SPC to identify patients in our institution who would benefit from adjuvant re-RT. Because of an absence of any standardized guideline for adjuvant re-RT in this population, our institution's preferred adjuvant re-RT treatment is 60 to 66 Gy with the exact dose dependent on the prior RT treatment, the particular adverse histopathologic features, the patient's overall clinical status, and the physician's preference. All 7 patients in our cohort who received re-RT of 66 Gy had certain high-risk features, such as multiple risk factors or at least extracapsular extension (ECE) or microscopic positive margins. Of the 5 patients who had disease recurrence after re-RT, all 5 had either positive or close surgical margin and only one had ECE.

Certain adverse histopathologic feature portend worse overall and disease specific survival and warrant adjuvant chemoradiotherapy.[28,29] In a prospective randomized trial, patients were randomized to adjuvant re-RT of 60 Gy with concurrent chemotherapy after surgery versus observation alone after surgery, with the adjuvant treatment arm showing an improvement in progression-free survival but not OS.[30] Although the role for adjuvant therapy is demonstrated, the exact adjuvant therapy for specific patient populations is further explored. A randomized controlled study showed that postoperative RT of 60 Gy with concurrent chemotherapy improved locoregional control in cases with ECE and positive margins, and there was no statistically significant difference in locoregional control when chemotherapy was omitted for tumors without ECE or positive margins.[31] When selecting adjuvant treatments for patients with high-risk pathologic features after surgical salvage, there may be a benefit to adding chemotherapy to postoperative re-RT. One prospective nonrandomized trial showed a 3-year OS of 44% with adjuvant re-RT alone, and another such trial showed a 4-year OS of 43% with adjuvant re-RT with concurrent chemotherapy.[32,33] Although these 2 trials may not definitely prove that concurrent chemotherapy in the setting of adjuvant re-RT has an overall survival benefit, further research is warranted.

Patient selection is critical when evaluating for salvage treatment.[34,35] In early randomized trials looking at re-RT in recurrent head and neck cancers, there were high rates of grade 4 or worse acute and late toxicities while using conventional re-RT techniques, such as 3-dimensional conformal RT.[36] IMRT has emerged as the preferred RT modality for re-RT in head and neck cancer as it demonstrated an improved 2-year locoregional control ranging from 50% to 60%, with a decrease in acute and late toxicities with rates of acute grade 3, 4, and 5 toxicities reported to be 10% to 30%, <10%, and 1% to 3%,

respectively.[37-39] Although IMRT is a common approach for re-RT of the head and neck, RT using protons or other charged heavy particles is advantageous due to a rapid dose falloff beyond the target, thereby sparing the surrounding normal structures. In a retrospective study of 60 patients undergoing curative proton beam re-RT, 58% of whom had had salvage surgery, the 2-year rates of locoregional control and OS were 79.8% and 69.7%, respectively, and the late grade 3 toxicity was 26.0%, which was lower than those in published reports of 3-dimensional conformal RT and IMRT.[20] In another retrospective analysis of 92 patients treated with curative proton beam re-RT, 39% of whom had had salvage surgery, 1-year locoregional failure was 25% and OS was 65.2%.[19] Both of these aforementioned curative proton beam re-RT studies reported outcomes and toxicities for all their patients, including those who received definitive radiation therapy alone or definitive chemoradiotherapy. Our study focusing on the patients with HNSCC who had received adjuvant proton re-RT had a comparable locoregional control and an improved OS at 1 year and 2 years compared with the 2 previously mentioned studies. The purpose of this article is to share our institution's early experience with proton re-RT, not to suggest specific recommendations of patient selection for adjuvant re-RT based on their histopathologic features.

The toxicity profile of our cohort is comparable to prior proton re-RT studies of head and neck. Acute grade 3 or greater toxicities were experienced by 3 patients: 1 each with radiation dermatitis (5%), mucositis (5%), and dysphagia (5%). A prior study of proton re-RT reported acute grade 3 or greater toxicities, including dermatitis (3%), mucositis (10%), dysphagia (9%), and esophagitis (9%).[19] Our study found 4 patients (19%) with osteonecrosis on CT imaging, with 2 of them requiring surgical intervention. In a prior study focusing on 50 patients with proton re-RT with a median follow-up time of 13.6 months after re-RT, 8% of patients had necrosis: 1 patient had soft tissue necrosis and 3 had osteoradionecrosis with 2 dying shortly thereafter.[20] In another study with 69 out of 75 patients having a follow-up time >3 months after re-RT and a median follow-up of 13.3 months among surviving patients, 6% of the patients had necrosis: 2 patients had soft tissue necrosis requiring intervention, 1 had osteoradionecrosis of the mandible requiring surgical intervention, and 1 had temporal necrosis not requiring surgical intervention.[19] Compared with these 2 studies, our study appeared to have a higher rate of osteonecrosis although that may be due to having the longest median follow-up after end of re-RT, specifically 21.0 months among surviving patients with our 4 patients developing necrosis a median of 13.2 months after re-RT. Our institution's early experience with adjuvant proton re-RT was not designed to assess late toxicities. Additional research is warranted to assess the long-term side effects of adjuvant reirradiation and

determine the optimal management in this patient population.

Conclusion

Although patients with HNSCC generally tolerated adjuvant proton re-RT well while experiencing a reasonable local control, there appears to be a risk of osteoradionecrosis. Additional research into selecting patients for adjuvant re-RT based on their histopathologic findings and tailoring adjuvant re-RT dose and target volume are warranted to help optimize patient management in this high-risk patient population.

Disclosures

Marshall Posner reports royalties or licenses from Beth Israel Deaconess Medical Center; consulting fees from Naveris, Hookipa, Cel-SCI; participation on a Data Safety Monitoring Board or Advisory Board with Merck, Calliditas, Frizent, and Vivant Therapeutics. The remaining authors declare that they have no conflict of interest.

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