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Critical Review

Palliative Radiation Therapy for Head and Neck Cancers

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Patients with advanced head and neck cancers who are not eligible for curative treatment represent a challenging cohort of patients to manage given the complexity and severity of their presenting symptoms. Palliative radiation therapy, along with other systemic and surgical measures, has the potential to significantly improve the quality of life of such patients. There is little high-level evidence and a lack of consensus to direct the selection of an optimal palliative radiation regimen.

An ideal palliative radiation regimen should alleviate symptoms secondary to the cancer with minimal treatment toxicity and side effects while improving a patient's quality of life. This review presents the treatment approaches, outcomes, and toxicities associated with different radiation regimens and proposes a multidisciplinary framework for the selection of an individualized treatment regimen for patients that centers around patient prognosis, goals of care, logistics of treatment, and the availability of other surgical and systemic therapies.

Introduction

Head and neck cancers represent the sixth most common cancer worldwide, with approximately 630,000 new patients receiving diagnoses annually.[1] Although many advances within the field of head and neck cancer have improved curative-intent treatment, a lack of universal guidelines remains for palliative treatment. Disease- and health-related factors associated with the delivery of palliative-intent treatment include the presence of distant metastatic disease at the time of initial presentation, very advanced locoregional disease, prior extensive surgery or radiation therapy to the head and neck, patient comorbidities and poor performance status precluding tolerance of curative-intent therapy, and patient choice. In such patients, definitive, curative-intent treatment with cancer-directed therapy is thought to be associated with significant treatment-related toxicity, including the burden of daily treatments over many weeks. Such toxicity negatively affects the health and quality of life of these patients and outweighs the benefit of potentially curative therapy.

Supportive care measures used in patients with head and neck cancer focus on managing the disease-associated symptoms, including pain, dysphagia, dyspnea, bleeding, and ulceration. Given the critical importance of the tissues of the head and neck to basic life function, such symptoms significantly affect quality of life. Pain management with medications, anticholinergic blockade of secretions, tracheostomy for airway protection, and feeding tube placement for nutritional supplementation represent some of the common forms of care provided. For more symptomatic patients, palliative surgery or embolization

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Table 1 Studies of palliative radiation therapy for H&N cancers, organized chronologically by year published

Study	Type of study	n	Population	Treatment regimen	Fx size, Gy	Modality	BED, Gy†	EQD2, Gy†	Response Rate	Median OS, mo*	Toxicity
Paris et al[9]	Prospective	37	27% stage IVC; 63% inoperable	3 cycles of 14.8 Gy/4 fx, bid over 2 d, with a 3- to 4-wk break between cycles	3.7	2D	61	51	28% CR; 49% PR; 85% subjective palliative response	3	—
Minatel et al[30]	Prospective	62	16% recurrent; 74% stage IV	2 cycles of 25 Gy/10 fx, with a 2-wk midtreatment break; concurrent bleomycin	2.5	2D	63	52	28% CR; 41% PR; 81% symptom palliation	7	43% G3 mucositis, 3% G3 dyphagia
Mohanti et al[22]	Retrospective	505	78% stage IVA; 22% stage IVB	20 Gy/5 fx in 1 wk	4	2D	28	23	37% PR; 47-59% symptom response rate	6.7	100% patchy mucositis at 1-mo follow-up
Ghoshal. et al[24]	Prospective	25	72% stage IV	30 Gy/10 fx in 2 wks	3	2D	39	33	100% with >50% patient reported pain relief at 4 wks	—	32% G2 mucositis
Corry et al[10]	Prospective	30	35% stage I-III; 65% stage IV	3 cycles of 14 Gy/4 fx, bid over 2 d, with a 4-wk break between cycles	3.5	3D	57	47	6% CR; 47% PR; 44% improved QOL	5.7	33% G1; 11% G2, 0% G3 mucositis
Carrascoca et al[17]	Retrospective	7	14% stage III; 86% stage IV	3 cycles of 14.8 Gy/4 fx, bid over 2 d, with a 3- to 4-wk break between cycles. (+chemotherapy)	3.7	2D	61	51	14% CR; 71% PR	4	14% G3 mucositis
Porceddu et al[18]	Prospective	35	35% stage I-III; 65% stage IV	30 Gy/5 fx, twice weekly	6	—	48	40	56% CR and 9% PR for primary and 44% CR and 19% PR for nodes; 62% QOL and 67% pain improvement	6.1	26% G3 mucositis; 11% G3 dysphagia
Agarwal. et al[28]	Retrospective	110	78% T4	40 Gy/16 fx	2.5	2D	50	42	10% CR; 63% PR	12 (55% PFS)	14% G3 dermatitis, 3% G4, 63% G3 mucositis
Al-mamgani et al[29]	Prospective	158	81% stage IV	50 Gy/16 fx	3.125	2D	65	54	45% CR; 28% PR	17	45% and 65% G3 + dermatitis and mucositis
Siddiqui et al[33]	Retrospective	44	48% recurrent; 23% stage I-IVB; 30% stage IVC	13-18 Gy/1 fx or 36-48 Gy/5-8 fx	6-18	SBRT	30-86	25-72	7% CR; 80% PR in patients with stage IVC disease	5.6 (stage IVC)	G4 mucositis, dysphagia, EC fisutla, OC fistula
Ali et al[25]	Prospective	30	70% stage IV	30 Gy/10 fx in 2 wks	3	2D	39	33	26% CR; 47% PR	Not reported	37% G2 mucositis
Kancherla et al[26]	Retrospective	33	91% stage IVA-IVB	2 cycles of 20 Gy/5 fx, with a 2-wk break between cycles	4	3D	56	47	39%CR; 33% PR, 79% symptom palliation	12 (42% OS)	6% and 9% G3 mucositis and esophagitis, 18% IH*
Paliwal et al[23]	Retrospective	50	All patients with fixed nodes, stage IV; 46% T4	20 Gy/5 fx in 1 wk	4	2D	28	23	8% CR; 92% PR; 60-70% symptom palliation	—	4% G3 mucositis
Kawaguchi et al[32]	Retrospective	14	7% N1; 0% stage IV	35-42 Gy/3-5 fx	—	SBRT	—	—	36% CR; 64% PR	3 year OS: 79%	100% G1/2 oropharyngitis

(*continued on next page*)

Table 1 (*continued*)

Study	Type of study	n	Population	Treatment regimen	Fx size, Gy	Modality	BED, Gy†	EQD2, Gy†	Response Rate	Median OS, mo*	Toxicity
Lok et al[13]	Retrospective	75	55% stage IVC	3 cycles of 14.8 Gy/4 fx, bid over 2 d, with 3- to 4-wk break between cycles	3.7	3D/ IMRT	61	51	66% subjective pain response	5.7	5% G3 mucositis/ dermatitis
Nguyen et al[20]	Retrospective	110	62% stage IV	24 Gy/3 fx, 1 fraction/wk	8	3D/ IMRT	43	36	31% CR; 50% PR; 82% symptom palliation	6.2	3 inpatient hospitalizations
Khan et al[34]	Retrospective	21	81% de novo primary H&N cancers, 19% recurrent	35 Gy/5 fx to 48 Gy/6 fx	7-8	SBRT	60-86	50-72	25% CR; 67% PR	12 (60% OS)	—
Fortin et al[21]	Prospective	32	66% T4, N3, or M1	25 Gy/5 fx in 1 wk	5	IMRT	38	31	3- and 6-mo improvement in QOL: 59% and 58%; pain response: 71% and 83%;	6.5	13% G3 toxicity
Murthy et al[19]	Prospective	126	70.6% stage IVB	32 Gy/8 fx, twice weekly	4	—	45 Gy	37 Gy	3.2% CR and 41% PR for primary and 3.2% CR and 62% PR for nodes; 76% subjective pain improvement	5.5	1.2% G3 mucositis
Bledsoe et al[31]	Retrospective	65	15% stage III; 56% stage IVA/IVB; 14% stage IVC	60 Gy/20 fx or 72 Gy/24 fx with 4- to 6-wk midtreatment break	3	3D/ IMRT	78/94	65/78	50% CR, 41% PR among non-stage IVC patients	8.9	42% feeding tube requirement
Gamez et al[16]	Retrospective	21	19% recurrent; 52% stage III-IVB; 29% Stage IVC	3 cycles of 14.8 Gy/4 fx, bid over 2 d, with a 3- to 4-wk break between cycles. (+chemotherapy)	3.7	3D/ IMRT	61	51	24% CR; 62% PR; >76% symptom palliation	7	34.8% G2 mucositis/ xerostomia

Abbreviations: 2D = 2-dimensional; 3D = 3-dimensional; BED = biologically effective dose; CR = complete response; EC = enterocutaneous; EQD2 = equivalent dose in 2 Gy; H&N = head and neck; IMRT = intensity modulated radiation therapy; OC = oral cutaneous; OS = overall survival; QOL = quality of life; PFS = progression-free survival; PR = partial response; SBRT = stereotactic body radiation therapy.

* Other survival data reported in studies in which median OS is not reported.

† For $\alpha/\beta = 10$ (tumor).

of bleeding vessels can also be performed.[2,3] Multidisciplinary management of the supportive care these patients receive remains essential. Best supportive care is associated with a median survival of between 3 to 5 months—shorter for patients who have received prior therapy.[4] The use of palliative systemic therapy has the potential to improve survival over supportive care alone, as demonstrated by the median survival of 10.1 months with the EXTREME regimen (cisplatin/carboplatin, 5-fluorouracil, and cetuximab) and of 14.9 months with Pembrolizumab.[5,6]

A subset of patients not eligible for radical curative-intent therapy may still be candidates for palliative cancer-directed therapy with radiation therapy. The goal of a palliative treatment is to alleviate symptoms secondary to the cancer with minimal treatment toxicity and side effects.

Palliative radiation therapy

There have been many studies on the use of radiation therapy to mitigate disease-related symptoms and to improve patients' speech, swallowing, breathing, and pain and to mitigate ongoing bleeding and tumor ulceration. Although such studies advocate for the use of radiation

therapy in the palliative setting, there is little high-level evidence to direct the selection of an optimal palliative radiation regimen.

Curative-intent radiation therapy is delivered with doses from 6000 to 7000 cGy divided into 180 to 200 cGy fractions and is often delivered with concurrent chemotherapy. Such regimens, although curative, are often highly toxic.[7] Common side effects of treatment that are secondary to radiation damage to normal soft tissues include mucositis, dysphagia, xerostomia, dysgeusia, and radiation dermatitis. Many palliative regimens aim to reduce the dose of radiation administered to below the threshold for producing severe side effects to optimize the balance between risk and benefit when cure is not the goal. Maintaining the delicate balance of providing a sufficient dose for durable local control without causing significant morbidity is fundamental to the selection of each treatment regimen.

Overview of Palliative Regimens

The treatment of head and neck cancers with palliative radiation therapy has been studied in retrospective institutional studies and small phase 2 trials, as seen in Table 1. The treatment schedules used in these studies range from short courses with simple techniques to stereotactic radiation to conventionally fractionated, standard-length courses. Treatment durations range from 1 to 7 weeks, with many regimens including predetermined breaks between cycles of radiation. Some regimens include the use of chemotherapy. Treatment response rates, changes in quality of life, and toxicity profiles vary significantly based on treatment regimen. We reviewed the literature to identify evidence to guide the development of a patient-centric framework for selection of an optimal regimen for the palliative treatment of head and neck cancers. PubMed, EMBASE, MEDLINE, and Cochrane Library databases were searched for published studies on palliative radiation for head and neck cancers from 1993 to 2018.

QUAD Shot

One popular approach in the palliative treatment of head and neck cancers in North America is the "QUAD shot" regimen. This approach was introduced in the palliation of pelvic malignancies in RTOG 8502.[8] The regimen consists of 370 cGy delivered twice daily for 2 consecutive days (total of 1480c Gy/cycle), repeated every 3 to 4 weeks for a total of 4400 cGy in 3 cycles. For patients who tolerate the cycles well and who continue to respond, more than 3 cycles can be delivered. The cyclic nature of the regimen allows for disease response assessment after each course, at which time a decision is made regarding whether to proceed with another course. The biologically equivalent dose administered in QUAD shot is below the threshold for producing mucositis, and the separation between subsequent cycles of radiation allows for depleted mucosal stem cells to repopulate before the next cycle. In addition, this regimen allows patients to complete all radiation for 1 cycle within 2 days, limiting the travel burden and time required in a health care facility for palliative treatment.

The regimen was first studied in the head and neck setting by Paris et al in 37 patients with head and neck cancer.[9] Patients included were medically inoperable, failed chemotherapy, or had metastatic disease. Twenty-one patients completed all 3 cycles of radiation. An objective response rate of 77% was seen, with an improvement seen in those who completed more cycles. Average survival after therapy was 4.5 months. The majority of patients (85%) endorsed subjective improvement in presenting symptoms. No major toxicities were seen, and expected side effects including skin changes, dysphagia, and xerostomia peaked 12 days after completion of each cycle. No late complications were observed.

A similar QUAD shot approach was used by Corry et al.[10] In this study of 30 patients, 1400 cGy was administered over 2 days in twice-daily fractions. Patients received up to 2 additional cycles if they demonstrated no tumor progression at the time of follow-up. All but 1 patient had metastatic disease, and two-thirds of the patients had an Eastern Cooperative Oncology Group performance status of 2 to 3 at baseline. Fifty-three percent of patients completed all 3 cycles, and 50% of all patients had an objective response. Median overall survival was 5.7 months, and 44% of patients endorsed improved quality of life after completion of therapy. Patients also endorsed improvements in dysphagia (33%) and pain (56%). No patients developed grade 3 toxicities, and the most common grade 1 and 2 toxicities were dermatitis (52%) and mucositis (67%). Similarly, low rates of grade 3 toxicities using the QUAD shot approach have been shown in other retrospective analyses.[11,12]

The significance of completing more cycles of the QUAD shot regimen was reported by Lok et al in the largest retrospective study using QUAD shot.[13] The study included 75 patients with pain, dysphagia, and bleeding secondary to head and neck cancer, 40% of whom had prior radiation at the site of palliation. Thirty-seven percent of patients completed at least 3 cycles of 1480 cGy, and some patients who tolerated and continued to respond to therapy received 5 cycles. Palliative response was significantly correlated with increasing number of cycles but not with prior radiation, chemotherapy, surgery, or disease stage. Palliative response was seen in 65% of patients, and median overall survival was 5.7 months. Grade 3 dermatitis and functional mucositis were reported in 4 patients.

The properties of protons allow for significant dose sparing of neighboring tissues and organs at risk and have been studied in cases of head and neck reirradiation.[14] Proton therapy has been used to deliver the QUAD shot regimen in a cohort of 26 patients, as described by Ma et al.[15] Eighty-eight percent of these patients had prior head and neck radiation. Overall palliative response was 73%, and the grade 1 acute toxicity rate was 58%.

Addition of Concurrent Chemotherapy to QUAD Shot

There have been efforts to formally determine the response of radiosensitizing chemotherapy combined with the QUAD shot regimen. Gamez et al similarly demonstrated the tolerance of concurrent chemotherapy in a retrospective study of 21 patients with metastatic or recurrent head and neck cancer.[16] The 2 most common indications for treatment in this cohort were pain and dysphagia. All patients received at least 1 cycle of QUAD shot radiation therapy with carboplatin (AUC = 2) or cetuximab 250 mg/m^2 before each radiation cycle. Seventy-six percent of patients completed all 3 cycles of radiation. Objective response was high (85.7%), and the majority of complete responders (80%) completed all 3 cycles of radiation. Patients who completed all 3 cycles of radiation also had a 100% rate of presenting symptom resolution. Treatment was well tolerated with no grade 3 acute toxicities. All patients had at least a grade 1 toxicity, distributed among dermatitis, mucositis, and xerostomia. Thirty-five percent of patients had acute grade 2 toxicities, split between mucositis and xerostomia. Two cases of late grade 2 xerostomia and dysgeusia were reported. Carrascosa et al similarly showed a high response rate (95%) in 7 patients with head and neck cancer treated with QUAD shot and concurrent paclitaxel 60 mg/m^2.[17]

30-32 Gy in 5-8 Fractions

The "Hypo Trial" conducted by Porceddu et al was a prospective multicenter trial of a hypofractionated palliative regimen for head and neck cancers in which patients were given 3000 cGy in 5 fractions, with 2 fractions administered at least 3 days apart weekly.[18] Of the 37 patients enrolled in the study, the majority (51%) had a World Health Organization performance status of 1. The most common presenting symptom was dysphagia, seen in 18 of 39 patients. Overall, 80% of patients had an objective response after treatment. Median survival was 6.1 months. Grade 3 mucositis was observed in 26% of patients, and 11% of patients experienced grade 3 dermatitis and dysphagia. Two patients had grade 4 dysphagia. Late grade 3 toxicities of skin, mucosa, fibrosis, and xerostomia (all n = 1) were also observed in this cohort.

Murthy et al studied a regimen with similar biological dose equivalency and biweekly administration.[19] Their regimen of 3200 cGy with 400 cGy fractions given twice a week had a treatment completion rate of 74% in their prospective study of 126 patients. Forty-two percent of patients had a response at the primary site of disease, and three-quarters of patients endorsed improvement in pain from baseline. Only 1 case of grade 3 mucositis was reported, and no long-term follow-up was reported owing to significant travel burden for the majority of patients.

24 Gy in 3 Fractions

Higher-dose-per-fraction hypofractionated regimens have been studied in larger retrospective studies. The "0-7-21" regimen from Canada delivered 24 Gy in 3 weekly fractions and was studied in 110 patients, the majority of whom had stage IV disease.[20] This approach yielded high response rates of 82% and 81% for symptoms and tumor size, respectively. However, toxicities from this regimen were not reported.

20-25 Gy in 5 Fractions

Short-course daily radiation regimens have been proposed and described in studies, including a phase 2 trial by Fortin et al.[21] In their study of 32 patients with advanced head and neck cancer, patients received 2500 cGy in 5 fractions over the course of 1 week. Patients were treated with intensity modulated radiation therapy (IMRT), and the majority of patients expressed improvement in global quality of life, physical functioning, swallowing, and pain compared with baseline. Thirteen percent of patients experienced a grade 3 toxicity.

Mohanti et al described a similar weeklong treatment in a large retrospective study of 505 patients.[22] Patients were treated with 2000 cGy in 5 fractions. Compared with Fortin et al, this regimen showed a lower objective response rate at 37% and a symptom response rate of 50%. In addition, all patients in this cohort experienced patchy mucositis when examined 1 month posttreatment. Paliwal et al used this same regimen of 2000 cGy in 5 fractions in a 50-patient retrospective study.[23]

30 Gy in 10 Fractions

Ghoshal et al studied a more conventional palliative regimen of 3000 cGy in 10 fractions.[24] Seventy-two percent of the 25 patients in this study had metastatic disease, with pain and dysphagia as the main indications for delivery of palliative-intent radiation therapy. After treatment, symptoms were relieved by at least 50% for 90% of patients. All patients had either grade 1 or 2 mucositis after treatment.

Ali et al reported similar outcomes with the regimen of 3000 cGy in 10 fractions in a prospective study of 30 patients with symptomatic disease.[25] All patients had >50% pain relief and improvement in baseline dyspnea. A similar toxicity profile was also observed, with all patients having grade 1 or 2 mucositis. Twenty-seven percent of patients in the cohort went on to receive further radiation in 200-cGy fractions to a cumulative biologically effective dose of 6600 cGy.

40 Gy in 10 Fractions

Two radiation regimens of 4000 cGy delivered over 10 fractions have been studied, each with slight variations in

the design of treatment delivery. The first, studied by Kancherla et al, administered 2000 cGy over 5 days, followed by a 2-week break and then a second cycle of 2000 cGy in 1 week.[26] There was a 72% objective response rate and a 79% symptom response rate at 4 to 6 weeks after treatment completion among the 33 patients in this cohort. One- and 2-year overall survival were 42% and 35%, respectively. Grade 3 skin toxicity, mucositis, and esophagitis were seen in 3%, 6%, and 9% of patients, respectively, and 20% of all patients required hospitalization for toxicity management.

Das et al prospectively studied 36 patients with stage IV or recurrent head and neck cancer.[27] Patients received 4000 cGy in 10 fractions, with 2 fractions given each week. Sixty percent of patients had an improvement in performance status after treatments, and 88% of patients endorsed pain relief greater than 50%. No significant changes were noted in head and neck–specific quality-of-life scores after treatment. Similar to the toxicity profile seen by Kancherla et al, 21% of patients experienced grade 3 mucositis or dermatitis. Forty-eight percent of patients were recommended a nasogastric tube during treatment owing to oropharyngeal odynophagia. In an effort to reduce such early mucosal toxicity, groups have studied the use of smaller fractions with similar cumulative doses.[28,29]

40-50 Gy in 16 Fractions

The Tata Group has reported on the delivery of 4000 cGy in 250-cGy fractions to 110 patients with incurable disease and limited life expectancy.[28] The most common baseline symptoms in this cohort were pain (99%) and dysphagia (88%). Seventy-three percent of patients had an objective response, and 74% of patients had >50% symptom relief. With the use of smaller fractions of radiation, 63% and 3% of patients still developed grade 3 and grade 4 mucositis, respectively.

A higher dose per fraction of 312.5 cGy was used in the "Christie scheme," in which patients were treated to a cumulative dose of 5000 cGy.[29] A 73% response rate was seen in the cohort of 158 patients unsuitable for curative treatment. Seventy-seven percent of the 62 patients surviving past 1 year had pain relief, and 47% of such patients had improvement in their performance status. Grade 3 skin and mucosal toxicities were seen in 45% and 65% of patients, respectively, with severe late toxicity seen in 5% of patients.

Higher-Dose (50-72 Gy) Regimens

Higher cumulative dose palliative regimens administered in small fraction sizes have been studied in patients with good performance status but are not amenable to curative intent therapy. Minatel et al treated 58 patients with 5000 cGy in 20 fractions with a 2-week break after the first 2500 cGy.[30] Patients received bleomycin during the first 3 weeks of treatment. Objective and symptom response rate were high at 69% and 81%; however, toxicity levels were on par with rates associated with curative intent therapy, with 43% of all patients experiencing grade 3 mucositis.

A similar high-dose, split-course accelerated hypofractionated regimen was studied by Bledsoe et al.[31] This approach used a regimen in which 6000 cGy to 7200 cGy was given in 20 to 24 fractions with a midtreatment 4- to 6-week break. The majority of the 65 patients had a Karnofsky performance score of greater than 70 (74%). Eleven percent of patients were unable to complete both courses of treatment owing to disease progression, patient decline, or patient refusal. Ninety-one percent of evaluable patients had an objective response at 3-month follow-up, and approximately 35% of patients continued to have local control at 4-year follow-up. Forty-two percent of patients required a feeding tube at some point during treatment secondary to mucositis and dysphagia, and 20% of patients remained on tube feeds at their last follow-up. One patient developed late mucosal ulceration and necrosis 1.5 years after the completion of treatment.

Stereotactic Body Radiation Therapy

In recent years, growing literature has emerged on the use of stereotactic body radiation therapy (SBRT) for the treatment of recurrent head and neck cancers given the severe toxicity profile associated with conventionally fractionated radiation therapy. There remain few studies investigating the role of SBRT in patients with untreated primary head and neck cancers who are unable to tolerate standard curative treatment. The few studies published consist of asymptomatic patients with early-stage disease who are treated to provide local control rather than symptom palliation. A retrospective series from Japan showed local control of 71% and overall survival of 79% in a cohort of 14 elderly patients treated with 3500 to 4200 cGy in 3 to 5 fractions.[32] All patients had an objective response. These patients all had nonmetastatic disease, and only 1 patient had N1 nodal involvement.

Similarly, Siddiqui et al used SBRT to treat 10 patients with primary head and neck cancer with 1300 to 1800 cGy in a single fraction or 3600 to 4800 cGy in 5 to 8 fractions.[33] Median overall survival was 29 months for these patients. A number of patients treated with SBRT developed grade 4 toxicities including mucositis, dysphagia, esophagocutaneous and orocutaneous fistulas, and osteonecrosis. Khan et al similarly showed high response rates in a cohort of 21 patients receiving SBRT for de novo head and neck cancers.[34] No toxicity data was reported in their cohort of patients treated with SBRT.

In the setting of reirradiation, a multi-institutional review of SBRT for recurrent or second primary head and

neck cancers showed a 2-year overall survival rate of 16.3% for patients.[35]

Comparative Studies of Palliative Radiation Regimens

In examining the comparisons among these distinct palliative regimens, 2 single-institutional studies have highlighted differences between response and toxicity based on fractionation scheme. Chen et al reviewed 60 patients treated with palliative intent for incurable and recurrent head and neck cancers.[5] The regimens used to treat patients included QUAD shot, 7000 cGy in 35 fractions, 3000 cGy in 10 fractions, 3750 cGy in 15 fractions, and 2000 cGy in 5 fractions. Rates of palliative response for these regimens were 83%, 77%, 67%, 86%, and 60%, respectively. Although these regimens yielded similarly high response rates, the toxicity profiles varied significantly, with 9% grade 3 toxicity in the QUAD shot−treated patients compared with 38%, 42%, 29%, and 20% in patients treated with 7000 cGy in 35 fractions, 3000 cGy in 10 fractions, 3750 cGy in 15 fractions, and 2000 cGy in 5 fractions, respectively.

Stevens et al compared outcomes of 148 patients treated with palliative radiation therapy.[36] The most common radiation schedule was 5000 cGy in 20 fractions; however, other patients received 2400 cGy in 3 fractions, 6000 cGy in 25 fractions, 3000 cGy in 10 fractions, 6000 cGy in 30 fractions, and 7000 cGy in 35 fractions. Radiation regimens were prescribed based on provider judgment of patient tolerability. Only 58% of patients scheduled to receive 7000 cGy in 35 fractions were able to complete this course. On multivariate analysis, radiation dose was found to be an independent predictor of treatment response and survival. This analysis was unable to capture the reasoning behind provider dose selection, including judgment of patient performance status and expected dose tolerance for each patient at initial consultation.

Immunotherapy

Along with the palliative radiation regimens noted earlier, many patients ineligible for definitive concurrent chemoradiation and with metastatic or recurrent head and neck cancers may be candidates for immunotherapy with or without radiation therapy. The role of immunotherapy in the second-line treatment of metastatic and recurrent head and neck cancers was established in the KEYNOTE-040 and CheckMate 141 trials.[37,38] Pembrolizumab, studied in KEYNOTE-040, showed a modest improvement in overall survival over standard-of-care second-line systemic therapy (investigator's choice of methotrexate, docetaxel, or cetuximab), with a median overall survival of 8.4 versus 6.9 months. This benefit was most evident in patients with PD-L1 expression levels greater than 50%. Similarly, nivolumab was shown to improve overall survival (median overall survival 7.7 vs 5.1 months) in CheckMate-141, a phase 3 trial comparing nivolumab to a single-agent investigator's choice of second-line therapy (methotrexate, docetaxel, or cetuximab). Post hoc exploratory analyses from Checkmate-141 indicated significantly increased overall survival in patients with human papillomavirus (HPV)-positive tumors treated with nivolumab (median overall survival of 9.1 vs 4.4 months), and PD-L1 expression greater than 1%. Both trials showed reduced toxicity of immunotherapy over conventional systemic therapy in the second-line recurrent or metastatic setting. Based off these promising results, pembrolizumab was moved to the frontline recurrent or metastatic setting and compared with the EXTREME regimen (cisplatin or carboplatin, 5-fluorouracil, and cetuximab) in KEYNOTE-048.[6] Initial results from KEYNOTE-048 showed single-agent pembrolizumab prolonging survival in patients with a PD-L1 combined positive score of greater than 1 (median overall survival 12.3 vs 10.3 months) and 20 (14.9 vs 10.7 months). Pembrolizumab was associated with fewer grade 3 to 5 adverse events compared with the EXTREME regimen (17% vs 69%) and more durable responses (median 20.9 vs 4.5 months).

Patients receiving palliative radiation therapy for head and neck cancer may also be candidates for immunotherapy. Although there remains a relative paucity of data investigating immunotherapy with palliative radiation therapy, the administration of concurrent and adjuvant immunotherapy with radiation therapy was studied in RTOG 3504, in which nivolumab was deemed to be safe to administer with concomitant cetuximab and radiation therapy.[39] Pembrolizumab has also been shown to be safe to administer with concurrent radiation and cisplatin (40 mg/m^2) in patients with both HPV-positive and HPV-negative head and neck cancers.[40]

Discussion

Patients with advanced head and neck cancers represent a challenging cohort of patients to manage given the complexity and severity of their presenting symptoms. Radiation therapy, along with other measures including chemotherapy, palliative care, and interventional procedures have the potential to significantly improve the quality of life of these patients. Although some studies support the use of radiation therapy in the palliative setting, no consensus exists to guide provider selection of appropriate regimens for individual patients. Radiation regimens vary in treatment length from 3 days to conventional 7-week courses. Providers often select regimens based off a holistic assessment of a patient. Performance status, comorbidities, disease burden, risk of acute toxicity, prior treatment, delivery of concurrent systemic therapy, logistics regarding the delivery of treatment, and patient goals

of care are all important considerations in determining regimen selection.

Performance status

Patients with a poorer performance status are likely to have difficulty with protracted courses of radiation therapy, which are associated with the burden of daily trips for treatment. Patients with a poor performance status may also suffer more from toxicities from a protracted and high cumulative dose course of radiation treatment, as demonstrated by studies showing high rates of nasogastric tube requirement and mucositis in such patients.[24-27] Likewise, concurrent administration of systemic therapy can exacerbate known and introduce new toxicities of radiation therapy, making this combination more challenging in patients with poorer performance status.[12] SBRT in the upfront de novo palliative radiation setting, although an attractive approach for treatment given the short treatment course, deserves additional investigation regarding safety in this tenuous population given the high rates of grade 4 toxicities seen in retrospective studies.[29]

Patient prognostication

Patient prognosis is another piece of information that providers should consider when selecting dose. Patient prognostication remains a challenge for providers, who often overestimate survival by a factor of 3 of more.[41] Different tools, including nomograms, are now available to aid in making prognostication more objective.[42] Patient prognosis aids in determining the desired duration of palliation from radiation treatment. Patients treated with protracted courses tend to have more durable responses to treatment, as seen by median survivals in the 6- to 17-month range.[25-27] These patients are also more likely to experience higher rates of toxicity from treatment; however, with a greater predicted longevity, the toxicity may represent an inconvenience more than a significant detriment in quality of life, as it may be for patients with limited life expectancy. For patients with good performance status who are believed to have a favorable prognosis (life expectancy >1 year), a more protracted course of radiation may be beneficial because late toxicity may be exacerbated by hypofractionated courses.[22,24]

Adaptive treatment

A practical feature offered with some palliative regimens is the flexibility offered with cyclic and split courses. Regimens with this built-in break, such as QUAD shot or 8 Gy x 3 delivered weeks apart, allow providers to assess a patient's response and tolerability to an initial course of radiation therapy and determine whether the patient would benefit from additional treatment. This break also provides an opportunity for patients with mucosal toxicity to recover before further insults are caused by additional radiation therapy. Patients deemed to be unsuitable for additional radiation therapy may still benefit from the initial cycle of treatment, as demonstrated in prior studies.[7,11]

Option of nonradiation palliative therapies

The discussion of patients in a multidisciplinary environment allows for the assessment of whether other nonradiation palliative treatments, such as surgery or systemic therapy, are options if radiation therapy does not achieve the desired effect. Patients who are candidates for systemic therapy may benefit from shorter courses of radiation therapy so that the toxicities of radiation do not delay the start of systemic therapy. Patients eligible for immunotherapy may receive immunotherapy before, during, or after radiation therapy, as demonstrated by the safety profile of both pembrolizumab and nivolumab with concurrent therapy.[39,40] There is some suggestion of improved efficacy of immunotherapy when administered closely with radiation therapy.[43,44] Those patients without other treatment options and with survival anticipated to be many months to a year may benefit from more protracted courses of radiation that provide a higher total dose.

Goals of care

One potential structured approach to elicit patient values and priorities and determine and personalize treatment plans involves asking patients 4 questions: (1) "What are your most important goals if your health situation worsens?"; (2) "What do you value most?"; (3) "What abilities are so critical to your life that you can't imagine living without them?"; and (4) "If you become sicker, how much are you willing to go through for the possibility of gaining more time?"[45] The answers to these questions have the potential to allow providers to ensure that a shared decision is made that is concordant with a patient's outlook and goals. Other approaches, including more general conversations with patients and their families, may also help both providers and patients.

Best practices to consider

As seen in Figure 1, radiation regimen selection for palliation cannot be based on patient prognosis alone. Consideration of advanced care planning, goals of care, and an assessment of other palliative treatment options is paramount to shared decision-making between the patient and the multidisciplinary care team.

For patients with symptomatic disease and with poorer prognoses of less than 4 months, the QUAD shot regimen, 2400 cGy in 3 fractions, or 2000 cGy in 5 fractions allow for symptom palliation, are associated with less severe treatment toxicities, and reduce travel burden for patients.

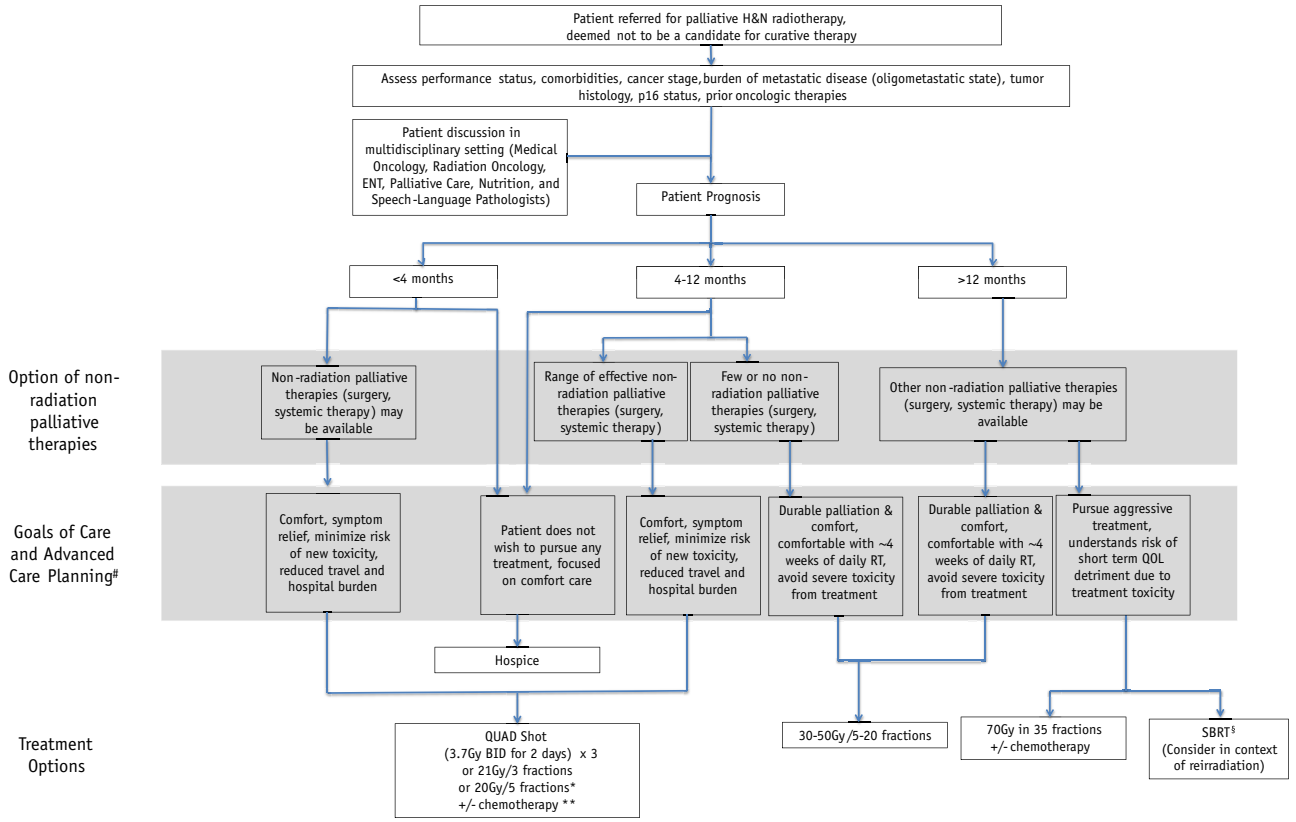

Fig. 1. Framework incorporating patient prognostication, goals of care, and nonradiation palliative therapy options in selecting appropriate palliative regimens for patients with head and neck cancers. ∗Can be explored with 4 questions of values and priorities. †Useful for short-course palliation for symptoms (ie, bleeding) when patient is eligible for systemic therapy. ‡Possible increase in treatment toxicity without a proven benefit. §Only if neighboring organs at risk can allow additional dose from such a treatment.

Patients with good responses to the initial cycle of QUAD shot should proceed with additional cycles, but patients who experience difficulty with the first cycle can opt to forego additional radiation therapy. These regimens are also better suited for patients who have difficulty with the positioning required for radiation treatment (ie, difficulty breathing or severe, difficult-to-control pain while lying flat in a thermoplastic mask). Longer courses are inappropriate for this cohort of patients because they are likely to cause greater harm secondary to treatment-related toxicity.

Patients with an intermediate prognosis of 4 to 12 months who don't have other treatment options may benefit from a conventional palliative course of 2000 cGy in 5 fractions or a more protracted course of 5000 cGy in 20 fractions. 2000 cGy in 5 fractions can be used to provide patients with cancer-related symptoms, such as bleeding with palliation, and if they are eligible, can allow them to proceed with systemic therapy without a significant delay. Such regimens, when administered without scheduled treatment breaks, allow patients to complete therapy within a relatively short period of time and offer tumor and symptom responses with less toxicity than higher-dose regimens. Those patients whose goals of care align with treatments that provide comfort with minimal risk of additional treatment-related toxicity might instead benefit from the QUAD shot or 2400 cGy in 3 fractions approach.

A more protracted regimen of 7000 cGy in 35 fractions may be suitable for patients with a prognosis of greater than 1 year who have goals of care that align with aggressive palliation. Although QUAD shot and 3000 Gy in 10 fractions can be used for patients whose goals of care align better with such regimens, these regimens are unlikely to provide durable responses in patients with better prognoses and may necessitate additional treatments in the future. Although high-dose regimens are associated with higher rates of acute toxicity, concerns of late toxicity are important to consider when hypofractionation is used in this subset of patients. Such regimens should also be considered for patients with untreated or previously treated HPV-positive oropharyngeal cancers and those with oligometastatic disease to address the primary tumor, as discussed below.

HPV-associated head and neck cancer

The rise of HPV-associated oropharyngeal cancers has led to an increase in the number of patients younger than 60

years of age with better performance status presenting for care.[46] Although many patients presenting with HPV-positive cancers are treated with curative intent therapy, some patients present with metastases or locally advanced disease and are only candidates for palliative-intent therapy. For such a patient with good performance status and a radiosensitive tumor, a protracted course of radiation therapy, similar to that which is offered in a definitive approach (70 Gy in 35 fractions), offers the potential for durable cancer control.

Although it is known that the risk of cancer progression for patients with HPV-positive oropharyngeal carcinoma is reduced compared with patients with HPV-negative disease, approximately 10% to 25% of patients with HPV-positive disease will experience a recurrence.[47] Patients with HPV-positive oropharyngeal cancer recurrences have improved survival compared with patients with HPV-negative recurrences (2-year overall survival 55% vs 28%), and hence durable control is similarly required for patients with HPV-positive recurrences.[48] Such patients respond well to immunotherapy, as demonstrated by the CHECKMATE-141 trial, and treatment options include immunotherapy followed by palliative radiation at progression, palliative radiation followed by immunotherapy at progression, or the use of a concurrent therapy approach.[38] Reirradiation for HPV-positive cancers is associated with improved overall and progression-free survival.[49] Given the improved prognosis of such patients, a reirradiation course of 70 Gy in 35 fractions can be considered if organs at risk are within reirradiation dose constraints.

Reirradiation

Patients with a history of head and neck radiation may benefit from reirradiation in the palliative setting for recurrences and new primary cancers. Although there is a paucity of data regarding palliative-intent reirradiation, RTOG 96 to 10 and RTOG 99 to 11, trials of curative-intent salvage reirradiation, assessed the outcomes of patients after 1.5 Gy bid to 60 Gy, with 5-FU and hydoxyurea, and cisplatin and paclitaxel, respectively.[50,51] Eligible patients had a minimum 6-month interval from their prior course of radiation. Results from these studies highlight the guarded prognosis for patients with recurrent disease treated with reirradiation, with a 2-year overall survival rate of 15.2% in RTOG 96 to 10 and 25.9% in RTOG 99 to 11. In this cohort of patients, better outcomes were observed in patients with an interval of greater than 1 year from the first course of radiation. A separate multi-institutional review of 412 patients treated with reirradiation with IMRT similarly found improved outcomes (2-year overall survival 61.9%) in patients with resected tumors and an interval of than 2 years between radiation courses.[52] Adverse events from these trials of reirradiation included fatal oropharyngeal hemorrhages and carotid blowout in RTOG 99 to 11, highlighting the potential severity of toxicity associated with reirradiation. Carotid blowout is an infrequent but serious complication of reirradiation for head and neck cancers, with an incidence of 2.6% in a pooled analysis of 1554 patients treated with reirradiation.[53] Such episodes are often fatal, and discussion of such treatment toxicities and death is an integral part of informed consent for reirradiation. Furthermore, discussion of other treatment options, including immunotherapy and salvage surgery, are essential within a multidisciplinary setting.

Patient selection for palliative reirradiation should be based on interval from prior course of radiation and the ability to deliver sufficient dose to control disease while sparing organs at risk from significant toxicity. An interval of 6 months from initial course of radiation, as used in RTOG 96-10 and RTOG 99-11, is a minimum threshold used at many centers. Patients with recurrences that occur earlier than 6 months out from initial radiation course may harbor disease that is relatively radioresistant because the initial course of radiation therapy likely never induced a significant therapeutic response. As such, further radiation therapy is likely to cause more harm than provide benefit. Reirradiation at sites close to serial organs, such as the spinal cord, brain stem, optic chiasm, and optic nerves, requires careful treatment planning to minimize the cumulative dose to such structures. Reirradiation to sites close to these critical organs at risk should be administered using standard fractionation as opposed to accelerated hypofractionation. Regardless of fractionation scheme used, treatment planning in the setting of reirradiation necessitates the calculation of equivalent dose in 2 Gy for all organs at risk to determine whether such a course can be safely administered. To minimize the risk of serious toxicity in patients receiving reirradiation, a conservative cumulative dose constraint of 60 Gy to critical serial organs can be used, as seen in Table 2. Although patients with greater intervals from initial course of radiation therapy may experience some tissue recovery, a cumulative dose constraint greater than 60 Gy has the potential to increase the risk of late toxicity.[54] Minimizing cumulative dose to as low as reasonably achievable is a goal for sequential organs at risk.

Recurrences at areas farther away from critical serial organs at risk may be amenable to SBRT, which should be performed on clinical trial if possible. A multi-institutional comparison of reirradiation with IMRT and SBRT showed worse survival (2-year overall survival 39.1 vs 18.6 months) with SBRT in patients more than 2 years out from treatment with unresected tumors.[35] Furthermore, patients with tumor recurrences less than 2 years out from initial treatment had poor outcomes regardless of treatment with IMRT or SBRT (2-year overall survival 16.8%). As such, all treatment options should be discussed with patients to allow for an informed, shared decision.

Oligometastatic and oligorecurrent disease

Patients presenting with oligometastatic and oligorecurrent head and neck cancer may benefit from aggressive palliation of their limited metastatic disease. Initial findings from

the SABR-COMET trial of stereotactic ablative radiation therapy in patients with up to 5 metastatic sites from any primary tumor site showed improvements in progression-free survival (12 vs 6 months, $P < .01$) and overall survival (41 vs 28 months, $P = .09$) when sites of metastases were treated with radiation.[55] Sun et al similarly reported 5-year survival rates of 20% in select patients with head and neck cancer who underwent oligometastasis-directed surgery of stereotactic radiation to metastases.[56] Given the improved overall survival in patients with oligometastatic disease, treatment to the primary head and neck tumor should provide durable response, and as such, a course of 70 Gy in 35 fractions should be considered in patients with a good performance status. Metastases should also be addressed in patients with oligometastatic and oligorecurrent disease. Given the good life expectancy for such patients, wedge resection, metastectomy, or stereotactic approaches should be considered over conventional palliative radiation doses (30 Gy in 10 fractions or 20 Gy in 4-5 fractions) to sites of metastatic disease.

Treatment volumes

Appropriate volume selection has the potential to minimize treatment-related toxicity. While no consensus guidelines in contouring remain for palliative head and neck cancer, most providers strive to treat both disease that is actively causing symptoms and disease that has the potential to cause symptoms if untreated. Such anticipatory planning is essential in the palliative setting. Elective nodal volumes are excluded in the palliative setting because they increase the radiation field size and introduce the possibility for worse treatment-related toxicity.

Treatment planning

Earlier studies in the palliative setting generally used simpler techniques, such as 2-dimensional and 3-dimensional planning, with parallel-opposed fields. Although such planning is simpler and reduces time to initiation of treatment, this field arrangement can increase mucosal radiation dose. The goal of a palliative course of radiation therapy is to minimize toxicity, and as such, IMRT should be considered, given its greater ability to spare critical structures in the head and neck from radiation dose than less conformal techniques.

Early palliative care

All patients seen in consultation for palliative radiation should be referred to palliative care. Several studies have shown the benefits of earlier involvement of a palliative care team in the treatment of patients with advanced cancer. Shuman et al noted improved scores measuring the end-of-life experience among patients with head and neck cancer who had received support from a palliative care team.[57] Early palliative care integrated within a patient's oncologic care has the potential to improve patient quality of life, reduce depressive symptoms, and improve survival, as shown in a trial of 151 patients with advanced lung cancer.[58] Although it remains uncertain whether similar benefits are seen in patients with other cancers, a known value of early palliative care is the delivery of holistic mental and physical care to patients during a vulnerable time in their lives.

Table 2 Authors suggested maximum dose constraints on H&N organs at risk

	Palliative reirradiation	Palliative de novo RT
Organ at Risk	Cumulative dose (EQD2)	Cumulative dose (EQD2)
Spinal cord	60 Gy	50 Gy
Brain stem	60 Gy	54 Gy
Carotid artery	ALARA	ALARA
Mandible	ALARA	ALARA
Optic nerve	60 Gy	54 Gy
Optic chiasm	60 Gy	54 Gy
Constrictors	Mean dose: ALARA	Mean dose: <50 Gy
Brachial plexus	70 Gy*	60 Gy

Abbreviations: ALARA = as low as reasonably achievable; H&N = head and neck; RT = radiation therapy; EQD2 = equivalent dose in 2 Gy.

* There may be situations when it is appropriate to exceed the cumulative constraint (eg, plexus previously received full dose, and recurrent disease involves or invades plexus). Clinical discussion between provider and patient is recommended to discuss the risks and benefits of reirradiation in this setting, with clinical decision-making based on the results of such a discussion.

Future directions

Current trials under active enrollment include studies of SBRT with concurrent administration of immunotherapy (NCT03539198) and of proton therapy in the setting of reirradiation (NCT03217188).[59,60] Patients with recurrent head and neck cancer should be considered for such clinical trials, with discussion and enrollment as clinically indicated via the patient and the patient's multidisciplinary care team.

There remains a paucity of data regarding the level of treatment toxicity patients are willing to accept to achieve palliation. The role of patient-reported outcomes in the palliative setting will be instrumental in guiding future practitioners because patient-reported toxicity can differ substantially from provider-assessed toxicity. Radiation regimens resulting in significantly worse patient-reported outcomes may need to be modified to ensure that palliation is achieved.

Conclusions

The results from the studies above demonstrate the value of palliative radiation therapy in the treatment of patients with locoregionally advanced and metastatic head and neck cancers. Short, cyclic, hypofractionated courses are promising regimens for patients with poor performance status and worse prognosis, and protracted courses that dose escalate with smaller fraction sizes are advantageous for patients with a better performance status and greater expected longevity. A collaborative approach from the onset with teams from palliative care, hospice, otorhinolaryngology, medical oncology, and radiation oncology is essential to developing a comprehensive plan for patients with advanced and incurable head and neck cancers. Reaching consensus recommendations for patients from such a group allows patients to have contingency options when treatments do not achieve intended results.

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