

Palliative Radiation Treatment for Previously Untreated Head and Neck Cancer - Why, When and How: A Comprehensive Review



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Submission: December 18, 2019; **Published:** January 27, 2020

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Abstract

Currently, there are no evidence-based guidelines regarding palliative radiation for untreated head and neck squamous cell carcinoma (HNSCC) patients who are ineligible for curative treatment. This article reviews the available literature for palliative head and neck radiotherapy. The life expectancy and performance status of patients are used to optimize the treatment recommendations.

Introduction

Head and neck cancer include a diversity of tumor sites including, oral cavity, pharynx, larynx, paranasal sinuses, salivary gland, and thyroid. It includes a wide variety of histologies, the most common being squamous cell carcinomas of the mucosa or skin. The vast majority have locally advanced disease and approximately 3% of patients present with metastatic disease at presentation [1,2].

The current standard-of-care treatment for well-performing (ECOG 0-1) metastatic head and neck cancer patients (American Joint Commission on Cancer [AJCC] Stage IV C) is palliative multi-agent systemic therapy. More specifically, for well-performing patients with non-nasopharyngeal primaries, the Category 1 defined first-line systemic therapy combinations are Cisplatin/Carboplatin and 5 Fluorouracil with Pembrolizumab or with Cetuximab [3-8]. While, for patients with nasopharyngeal primaries, the Category 1 recommendation is a combination of Cisplatin and Gemcitabine [9-11]. However, for selected patients with excellent performance status and limited metastasis, surgery, or a combination of radiation and systemic therapy is recommended [11].

Importance of Palliative Radiation in Head and Neck Cancers

The curative treatment of head and neck cancers may not be possible in many circumstances - especially, in the presence of

distant metastatic disease, poor performance status, significant comorbidities, or significantly extensive local disease [11]. These patients can often suffer from associated symptoms which include pain, trismus, dysphagia, odynophagia, stridor, hoarseness, otalgia, cough, and respiratory distress from advanced locoregional disease, which often impairs their quality of life (QOL). Many patients will benefit from palliative locoregional treatments, which typically involves radiation therapy. These treatments will improve the locoregional control of the disease, quality of life, and possibly improve survival [1]. However, there are only a few evidence-based guidelines specifying dose, fractionation, treatment techniques or volumes. This article reviews the available literature for palliative head and neck radiotherapy to make recommendations based on patient life expectancy and performance status.

Materials and Methods

Articles published between 1980 and 2018 were selected from an English Medline literature search using the following keywords: metastatic head and neck cancer, palliation, palliative radiation, Quality of Life (QOL).

Discussion

Even though several retrospective studies compared palliative radiation dose and fractionation schedules for patients with incurable head and neck cancer, there were only a few phase II studies that had explored the optimal treatment regimen. Most of

these studies included patients with the newly diagnosed disease who were ineligible for curative treatment due to comorbid conditions, poor performance status, or metastatic disease at diagnosis, resulting in a heterogeneous study population. We discuss available phase II and retrospective studies in detail below.

Phase II trials

Paris et al. reported on a phase II trial using the Radiation Therapy Oncology Group (RTOG) 85-02 fractionation scheme [12]. This protocol used 3.7Gy per fraction, twice daily (6 hours apart) for two consecutive days to deliver a total dose of 14.8Gy per course. This course repeated every four weeks for a total of 3 courses and a total dose of 44.4Gy. The reported objective response was 77%, with minimal acute toxicity and without any long-term toxicity [12]. The so-called 'QUAD SHOT' protocol was another phase II trial from Australia which treated patients with incurable head and neck cancer with 14Gy in four fractions: 3.5Gy given twice a day, at least 6 hours apart, and for two consecutive days [13]. This regimen was also repeated at four-week intervals for a further two courses if there was no tumor progression. The treatment was well tolerated. Seventy-seven percent of patients had a significant reduction or stabilization of their disease following treatment, and 44% of the evaluated patients showed improved QOL. The "Hypo Trial" is yet another phase II clinical trial from Australia, which treated patients with advanced HNSCC using a hypofractionated course of radiotherapy consisting of 30Gy in 5 fractions (6Gy/fraction) delivered at 2 fractions/week, with an optional 6Gy boost for small volume disease (<3cm) [14]. Eighty percent of patients had an objective clinical tumor response, and 62% had an improvement in QOL. Another phase II study from Canada by Fortin et al. treated patients with 25Gy in 5 daily fractions using intensity-modulated radiation therapy (IMRT) technique [15]. This treatment regimen was also well tolerated.

Retrospective studies

Retrospective data from Princess Margaret Hospital has shown that the radiation dose used is an independent predictor of both overall survival and treatment response, suggesting that even in the setting of metastatic disease higher doses may benefit certain well-selected patients [16]. The most commonly used fractionation regimen was a split course designed to deliver a total dose of 50Gy in 20 fractions (2.5Gy/ fractions) over six weeks and was composed of two cycles of 25Gy in 10 fractions given daily over two weeks and separated by a 2-week break between cycles.

A large retrospective series from India that included 352 patients, used a palliative radiation regimen of 20Gy in 5 fractions; it showed significant palliation of symptoms in 60% of patients [17]. Another large institutional study from Tata Memorial Hospital in India evaluated a hypofractionated palliative radiation scheme: 40Gy in 16 daily fractions (2.5Gy daily) [18]. The patients

with any response after 40Gy received an additional 10Gy in 4 fractions to a total dose of 50Gy; only 25% of patients were able to receive the additional 10Gy, but 87% of all patients (either 40 or 50Gy) had symptomatic improvement.

Chen et al. [19] retrospectively reviewed patients from the University of California, Davis, who had received palliative radiation treatment. They reported that the most commonly used fractionation regimen was that from the RTOG 85-02 protocol, as described above. They also delivered 70Gy in conventional 2Gy fractions, 30Gy in 3Gy fractions, 37.5Gy in 2.5Gy fractions, or 20Gy in 4Gy fractions and concluded that the RTOG 85-02 regimen provided effective palliation for patients. The Memorial Sloan Kettering Cancer Center (MSKCC) also documented a similar experience using the RTOG 85-02 regimen; 65% of their patients had a positive response in terms of palliation [20].

Erkal et al. [21] from the University of Florida retrospectively reviewed HNSCC patients who received palliative radiotherapy. Patients with relatively better KPS received 30Gy in 10 fractions (3Gy/daily) in once-daily fractions, and patients with poorer KPS received a split course of 20Gy: two 10Gy fractions one week apart. Eighty-eight percent of patients had either complete or partial response to the treatment, and 57% of patients had continued response at 1-year post-treatment. A retrospective series from the Netherlands reported on the use of the "Christie's" regimen for palliative radiation therapy, in which patients were treated to 50Gy in 3.125Gy fractions daily over 16 days [22]. These patients had a 73% response rate with tolerable toxicity. Another study from the United Kingdom used a split course hypofractionated regimen with an initial 20Gy in 5 fractions over one week, followed by a 2-week gap, finally followed by an additional 20Gy in 5 fractions over one week [23]. They found that approximately 80% of patients had symptomatic improvement with tolerable toxicity.

In a case review, Ampil et al. reported improved survival for patients diagnosed with head and neck cancers with synchronous distant metastasis treated with a prolonged "definitive" course of radiation therapy, defined as a total dose >50Gy and daily dose fractions ranging from 1.8 to 3Gy, as opposed to a shorter "palliative" course of radiation [24]. More recently, Laursen et al. [25] from Denmark reported the use of an extended hypofractionated palliative regimen delivering 52-56Gy in 13-14 fractions at 4Gy per fraction twice weekly using IMRT techniques. Seventy-five percent of the patients completed the intended treatment, and 45% of patients had either complete or partial response of their locoregional disease. Acute toxicity was relatively higher, 25% and 15% of patients reported Grade III or IV mucositis and dermatitis, respectively. Patients with poor performance status, however, did not tolerate this regimen well, and the authors concluded that it was not suitable for these patients.

“SCAHR” (Split-Course Accelerated Hypofractionated Radiotherapy) is another palliative radiation regimen, reported from Yale University [26]. This regimen consists of 3Gy daily for 10-12 fractions and repeated after 3-5 weeks to a total dose of 60-72Gy. The authors reported that 89% of the patients completed both treatment courses, with a total tumor response of 91%. A retrospective study from the Netherlands compared 2- and 3-D techniques to IMRT for a palliative regimen of 48Gy in 12 fractions with 3-4 fractions per week and reported a statistically significant difference in the occurrence of mucositis favoring IMRT.43 They concluded that IMRT should be considered the modality of choice, even for purposes of palliation.

A randomized, open-label, parallel study performed in India compared three palliative radiation therapy regimens for head and neck cancer - (i) the QUAD SHOT, (ii) Christie’s regimen, and

(iii) the conventional palliation fractionation scheme used in India (20Gy in 4-Gy daily fractions over 5 days, repeated once after 3 weeks) [27]. They performed a prospective analysis assessing QOL using the University of Washington QOL questionnaire, version 4. There was no significant difference in local control or overall response rate between the regimens. The grade III mucositis and treatment discontinuation rates were found to be higher in patients treated with Christie’s regimen. The quality of life was better, albeit only minimally, in patients who received the “QUAD SHOT” regimen compared to the two other regimens. In conclusion, the authors recommended the “QUAD SHOT” regimen for palliation of head and neck cancers given the comparable response rates, symptom relief, improved toxicities, and post-treatment QOL. These different palliative radiation regimens and studies are summarized in Table 1.

Table 1: Summary of palliative radiation schema.

Name	Total Dose	Fractionation	RT Technique
QUAD SHOT [13]	42Gy	3.5Gy BID x 2 days Repeated q4 weeks interval x 2 times	3-D CRT
Hypo Trial [14]	30Gy	6Gy per fraction x 5 fractions, two fractions per week Optional boost of 6Gy if <3cm	2-D and 3-D CRT
Canadian Fortin et al. [15]	25Gy	5Gy in 5 daily fractions in 1 week	IMRT
Princess Margaret Hospital (Canada) [16]	50Gy	2.5Gy daily x 10 fractions in 2 weeks Repeated once after a 2-week break	2-D
AIIMS (India) [17]	20Gy	4Gy daily in 5 fractions over one week	2-D and 3-D CRT
Tata Memorial (India) [18]	40Gy	2.5Gy daily in 16 fractions 10Gy boost if partial response	2-D and 3-D CRT
RTOG 85-02 [12,19,20]	44.4Gy	3.7Gy BID x 2 days Repeated q2-3 weeks x 2 times	2-D Initially 3-D CRT
Christie’s Regimen [22]	50Gy	3.125Gy daily x 16 fractions	3-D CRT
UK regimen [23]	40Gy	4Gy daily x 5 fractions in 1 week Repeat after a 2-week break	3-D CRT
SCAHR (Yale) [26]	60-72Gy	3Gy daily x 10-12 fractions Repeat after 3-5 weeks	3-D CRT initially IMRT recently
Denmark [25]	52-56Gy	4Gy per fraction, two fractions per week Total 13 - 14 fractions	IMRT
University of Florida [21]	30Gy 20Gy	3Gy daily over two weeks if good KPS 10Gy weekly x 2 fraction	3-D CRT

Conclusion

All incurable head and neck cancer patients should be evaluated in a multidisciplinary tumor board to choose the optimum treatment. The physicians should assess the patient’s performance status and goals of care very carefully. Palliative radiotherapy is a useful tool in improving the symptoms and should be offered as a treatment option. There are multiple-dose fractionation regimens currently being used for palliative radiation treatment, and the decision should be based on the patient’s performance status. For selected patients with limited metastatic disease and excellent performance status (ECOG 0-1),

an aggressive treatment approach with a higher dose of radiation is a valid option. Patients with worse performance status (ECOG 2 or worse) will benefit from a hypofractionated palliative radiation treatment.

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DOI: [10.19080/PMCIJ.2020.03.555607](https://doi.org/10.19080/PMCIJ.2020.03.555607)

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