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High-dose hypofractionated radiotherapy is effective and safe for tumors in the head-and-neck

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ABSTRACT

Objectives: High-dose, hypofractionated radiotherapy (HFRT) is sometimes used to treat malignancy in the head-and-neck (HN), both in the curative and palliative setting. Its safety and efficacy have been reported in small studies and are still controversial.

Materials and methods: We retrospectively evaluated the outcomes and toxicities of HFRT, including ultra-high-dose fractionation schemes ($\geqslant$8 Gray per fraction), for HN malignancies.

Results: A total of 62 sites of measurable gross disease in 48 patients were analyzed. The median follow-up was 54.3 months among five survivors and 6.0 months in the remaining patients. Median RT dose was 30 Gray in 5 fractions; 20/62 lesions (32%) received dose-per-fraction of $\geqslant$8 Gray. Overall response rate at first follow-up was 79%. One-year local-progression free rate was 50%. On multivariate analysis for locoregional control, dose-per-fraction $\geqslant$6 Gray was associated with control ($p = 0.04$) and previous radiation was associated with inferior control ($p = 0.04$). Patients who achieved complete response to RT had longer survival than those who did not ($p = 0.01$). Increased toxicity rates were not observed among patients treated with dose-per-fraction $\geqslant$8 Gray; only re-irradiation increased toxicity rates.

Conclusion: Despite the poor prognostic features noted in this cohort of patients with HN malignancies, HFRT was associated with high response rates, good local control, and acceptable toxicity. Sites that were treated with 6 Gray per fraction or higher and had not been previously irradiated had the best disease control. A prospective trial is warranted to further refine the use and indications of HFRT in this setting.

Introduction

Hypofractionated radiation therapy (HFRT) involves the use of high doses per fraction to achieve improved tumor control. A more desirable therapeutic ratio has been achieved for HFRT in recent years through the use of image-guided RT (IGRT), which allows improved certainty regarding daily treatment setup and dose delivered to organs at risk. IGRT has in turn facilitated the use of stereotactic body radiation therapy (SBRT), which allows delivery of highly conformal, high doses of radiotherapy to a clinical target. Preclinical data show that high-dose single-fraction RT operates via a unique mechanism involving injury of tumor endothelial cells that is distinct from conventionally fractionated RT and independent of tumor histologic subtype [1]. Clinical data show that HFRT improves local tumor control beyond that possible using conventional fractionation, for various scenarios including early-stage lung cancer [2,3], radioresistant histologies such as melanoma and renal cell cancers [4–7], and oligometastatic disease [8–12].

In recent years, a growing body of literature has reported on the safety and feasibility of HFRT for tumors of the head and neck (HN) [13–20]. Most of these series include patients with recurrent, unresectable HN cancers who had been previously irradiated. These studies have found promising overall response rates up to 80% and 1-year local control rates in the range of 50%. Despite promising tumor control, severe toxicities have occurred in

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patients receiving HFRT for re-irradiation, including carotid blowout and hemorrhage [14,19]. Carotid blowout in particular is a severe complication of high-dose radiation therapy in which there is physical rupture of the carotid artery and hemorrhage. This hemorrhage is potentially fatal if not addressed emergently. Several groups have reported on outcomes of HFRT used to treat a heterogeneous group of HN malignancies, including primary, recurrent, and metastatic tumors [20,21]. These studies have also shown high response rates and 2-year local control rates of 30–40%, with limited toxicity in patients who had not been previously irradiated.

In our institution, HFRT is routinely offered to the most challenging HN disease presentations: those with "radioresistant" histologies (such as melanoma and renal cell carcinoma), cases of disease recurrence in a previously irradiated field, or bulky lesions for which rapid palliation is desired. After the year 2004, IGRT became available in our center. In recent years, SBRT has been routinely used for treatment of lesions with proximity to critical structures. As we have gained experience with HFRT in HN cancers, our dose prescribed per fraction has increased over time. In this study, we report on the outcomes and toxicity of HFRT for various malignancies with measurable gross disease in the HN. We also analyze the outcomes of patients who received an ultra-high dose ($\geqslant$8 Gray per fraction) hypofractionated regimen to determine if these more intensive regimens were associated with improved outcomes.

Material and methods

We reviewed all cases of hypofractionated HN RT, which we defined as a dose of 5 Gy or more per fraction, treated at our center from January 1997 to July 2014. We excluded patients who did not complete the prescribed course of radiotherapy and those who were treated to bone-only sites including the clivus. We therefore identified a total of 123 patients treated to 163 lesions in the HN. Within this group, we limited our analysis to patients with measurable gross disease, thereby excluding postoperative treatments following gross total resections, and at least one follow-up visit 30 days or more after completing HFRT.

Patients were offered HFRT to the HN tumor if they had one or both of the following features, as determined by the attending radiation oncologist: (1) radioresistant histology that would benefit from higher doses per fraction, (2) prior RT at the same site and not a candidate for salvage surgical resection or conventionally fractionated external beam RT, or (3) no prior RT at the site, but cannot tolerate surgical resection or conventionally fractionated RT to curative doses. Patients were treated with either "definitive" or "palliative" intent. Patients treated "definitively" did not have evidence of metastatic disease and were technically considered curable despite being ineligible for surgical or other modalities of treatment. Patients treated with "palliative" intent had other metastatic or locoregional disease and were considered incurable even if this course of RT were to lead to a complete response of the treated lesion. Pretreatment evaluation consisted of a complete history and physical examination, comprehensive metabolic panel, complete blood count, computed tomography (CT) of the HN and chest, magnetic resonance imaging (MRI) as indicated, and whole body positron-emission tomography (PET) as indicated. Our institutional review board approved a waiver of written informed consent for this retrospective study.

Radiation treatment design

All patients underwent either CT or PET-CT simulation. CT images were obtained using 2–3 mm slice thickness. Patients were immobilized in either a three-point or five-point thermoplastic face mask. Intravenous contrast was used for the simulation scan when indicated. Following CT-simulation, target volume was defined using available diagnostic CT, MRI, and/or PET images alongside the planning scan. For patients undergoing PET-CT simulation, the target volume was defined using the hypermetabolic tumor volume on the fused PET-CT scan. Treatments were targeted to local disease without elective nodal treatment. Any clinically or radiographically measurable gross disease was defined as the gross tumor volume (GTV). CTV was typically a 3–10 mm three-dimensional expansion on the GTV. The planning target volume (PTV) expansion on the CTV was dependent on the alignment technique, but was typically 2–3 mm for cases receiving IGRT with kV planar imaging or cone beam CT.

Dose was generally fractionated and delivered daily or every other day. Total dose and fractionation was selected by the attending radiation oncologist, based on field size, tumor location, prior radiation dose, and patient functional status. Treatment planning for 3D-conformal and IMRT treatments was performed using our in-house treatment-planning system. Dose was prescribed to the isodose line best covering the PTV, while also protecting normal tissues. The permitted normal tissue doses were defined by the attending radiation oncologist and were a function of fractionation scheme and any prior RT to the HN.

Response assessment

We determined objective response to HFRT using both clinical assessment and follow-up imaging. Patients were followed every 1–3 months on an outpatient basis. Follow-up evaluation consisted of an interval history and clinical examination focusing on the HN, often with fiberoptic endoscopy. Imaging included CT, MRI, and/or PET/CT routinely performed on a 3–6 month schedule. The follow-up interval was calculated from the last date of RT. Response was characterized using the RECIST criteria [22]: complete response (CR) if all tumor disappeared on follow-up evaluation, partial response (PR) if tumor exhibited at least >30% decrease in sum of diameters, stable disease (SD) if there was no change in tumor volume, and progression of disease (PD) if there was any increase in tumor size >20% and >5 mm relative to pre-RT tumor volume. In certain cases progression was determined by the treating physician using primarily clinical examination.

Statistical analysis

We calculated in-field progression rate, locoregional progression-free rate (LRPF), overall survival (OS), and toxicity. All events were indexed to the final date of RT treatment. In-field progression was defined as failure within the treatment field, and locoregional progression was defined as progression either in the treatment field or in a regional lymph node group or neighboring site. OS was calculated from the date of completion of the initial course of HFRT, to the date of death. Patients without events were censored at last follow-up. Complications were scored per the Common Terminology Criteria for Adverse Events, version 4 (CTCAEv.4) [23,24]. The Kaplan-Meier method was used for the generation of survival curves, and differences in survival curves were compared statistically with the log-rank test. Univariate and multivariate analyses of potential prognostic factors were performed using the Cox proportional hazards model. The chi-square test was used to compare rates between subgroups of patients. All provided p values are two-sided with an α-level of 0.05 considered significant. All statistical analysis was accomplished with the SPSS software package, version 22 (IBM, Armonk, NY).