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Original article

A nomogram to predict loco-regional control after re-irradiation for head and neck cancer ☆

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ABSTRACT

Background and purpose: Loco-regionally recurrent head and neck cancer (HNC) in the setting of prior radiotherapy carries significant morbidity and mortality. The role of re-irradiation (re-RT) remains unclear due to toxicity. We determined prognostic factors for loco-regional control (LRC) and formulated a nomogram to help clinicians select re-RT candidates.

Material and methods: From July 1996 to April 2011, 257 patients with recurrent HNC underwent fractionated re-RT. Median prior dose was 65 Gy and median time between RT was 32.4 months. One hundred fifteen patients (44%) had salvage surgery and 172 (67%) received concurrent chemotherapy. Median re-RT dose was 59.4 Gy and 201 (78%) patients received IMRT. Multivariate Cox proportional hazards were used to identify independent predictors of LRC and a nomogram for 2-year LRC was constructed.

Results: Median follow-up was 32.6 months. Two-year LRC and overall survival (OS) were 47% and 43%, respectively. Recurrent stage ($P = 0.005$), non-oral cavity subsite ($P < 0.001$), absent organ dysfunction ($P < 0.001$), salvage surgery ($P < 0.001$), and dose >50 Gy ($P = 0.006$) were independently associated with improved LRC. We generated a nomogram with concordance index of 0.68.

Conclusion: Re-RT can be curative, and our nomogram can help determine a priori which patients may benefit.

Loco-regional recurrent head and neck cancer (HNC) occurs in 8–30% of patients with squamous cell cancer of the head and neck despite aggressive multi-modality definitive treatment consisting of surgery, radiotherapy (RT), and chemotherapy [1–5]. Patients who have previously received RT presenting with unresectable recurrence are offered chemotherapy as standard of care, resulting in median overall survival (OS) of 5–9 months and a 2-year OS of only 10% in patients with solely loco-regionally recurrent disease [6]. In patients with resectable disease, surgery is the standard of care, but patients are still at high risk for loco-regional recurrence [7]. Because uncontrolled loco-regional progression is often the cause of death for these patients, investigators have incorporated re-irradiation (re-RT) in resectable and unresectable recurrent HNC management.

Haraf et al. demonstrated the feasibility of re-RT with concurrent chemotherapy in the recurrent setting, albeit with significant toxicity [8]. Subsequently, two single-arm prospective studies of concurrent chemotherapy and re-RT demonstrated 2-year OS of 15–26%, an improvement from historical cohorts treated with chemotherapy alone [9,10]. A randomized French trial demonstrated improved loco-regional control (LRC) and disease-free survival (DFS) in post-operative patients who received adjuvant re-RT with chemotherapy, though without improvement in OS [7]. In the unresectable setting, two randomized trials failed to accrue due to the technically demanding nature of re-treatment [11]. Given the significant toxicity of re-RT, national guidelines remain ambiguous on its indications in the recurrent setting [12].

In an attempt to identify patients who may benefit most from re-RT, prior studies have investigated different prognostic factors in re-RT [13–17]. Tanvetyanon et al. formulated a nomogram identifying patient characteristics such as comorbid disease, organ

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dysfunction, recurrence beyond the neck, tumor bulk, and time between RT (i.e., time between first course of RT and re-RT) to predict OS for patients receiving re-RT [18]. Although OS is an important endpoint, loco-regional progression is the major cause of death, and prior studies have suggested both OS and distant metastases (DM) are associated with advanced local disease [19–21]. Furthermore, local disease is associated with significant morbidity, including tumor bleeding, intractable pain, and asphyxiation, and has significant effects on quality of life, ranging from organ impairment to tumor odor and visibility [22]. Given that it is predictive of OS and morbidity and that the intent of RT is to control loco-regional disease, LRC is a critical endpoint in evaluating the effectiveness of re-RT.

We thus evaluated our institutional experience and constructed a nomogram to predict the efficacy of curative-intent treatment in providing durable loco-regional control. This tool can be used by physicians in the clinic to detail the benefits and risks of re-RT with patients and facilitate a decision on curative or palliative intent to treatment. Ultimately, patients with negative prognostic factors for LRC may benefit more from palliative intent re-irradiation than intensive 2-month curative-intent radiotherapy and its attendant toxicities.

Methods

Patients

From 7/96 to 4/11, 348 patients with recurrent HNC underwent fractionated re-RT with significant overlapping area with their prior RT. Exclusion criteria included Karnofsky performance status (KPS) <60 ($n = 4$), melanoma or sarcoma histology ($n = 28$), hypofractionated RT, <6 months between courses of RT ($n = 8$), and distant metastases at time of salvage ($n = 51$). After exclusions, 257 patients were eligible for this analysis.

Patients were evaluated by a radiation oncologist, medical oncologist, and head and neck surgeon prior to re-RT. Pretreatment evaluations consisted of history and physical, complete blood count, chemistry, chest X-ray, dental evaluation, and imaging: computed tomography (CT), magnetic resonance imaging (MRI), and/or positron emission tomography (PET) before re-RT. For those receiving chemotherapy, urinalysis, creatinine clearance, electrocardiogram, and audiogram were obtained. The institutional review board issued a waiver of informed consent for this study.

Radiation therapy

RT was delivered as previously described [14]. For IMRT or three-dimensional conformal RT, simulation was performed by 3-mm slice CT with intravenous contrast when indicated. When possible, PET/CT simulation was performed. Beams were generally selected such that 95% of the dose encompassed the target volume, and constraints for critical tissues such as the spinal cord and brain stem were almost always respected. No efforts were made to spare the parotid glands as most patients had baseline xerostomia.

Treatment volumes and techniques have been previously described [14,23]. No attempt was made to encompass the prophylactic subclinical regions at risk in the re-RT IMRT fields. For patients with unresectable disease, gross tumor volume (GTV) was defined as visible disease on physical examination or imaging. For patients whose disease was resected, clinical tumor volume (CTV) was defined as the preoperative GTV and postoperative bed. Volumes and critical structures were defined slice by slice on axial CT. In the first few years, a margin of 1–2 cm was added to the GTV and CTV to define the planning target volume (PTV). However, more recently we have decreased this margin to 0.3 cm. The PTV expansion was reduced in regions near critical structures.

Chemotherapy, surgery, and follow-up

Chemotherapy was given at the medical oncologist's discretion. If the tumor was resectable, the surgeon performed gross total resection. Patients were evaluated weekly during treatment, every 2–3 months in the first 2 years, and every 4–6 months thereafter by a member of the multidisciplinary team. Surveillance imaging with CT, MRI, or PET was done 2–4 months after treatment and then as indicated clinically.

Data collection

Recurrent disease was staged based on the American Joint Committee on Cancer, seventh edition [24]. The National Social Security Death Index was used to verify patient deaths. Acute toxicities and late complications were assessed retrospectively by reviewing patient records according to the Common Toxicity Criteria, version 3.0. [25]. Similarly, comorbid status and organ dysfunction were evaluated through retrospective review using definitions described by Tanvetyanon et al. [18]. Organ dysfunction included patients requiring feeding tube or tracheostomy or with soft tissue defect, fistula, or osteonecrosis. Prophylactic feeding tube placed prior to re-RT was not identified as organ dysfunction. Surgical margins were considered close if tumor was within 1 mm of the margin for larynx or tonsil subsites, or otherwise within 5 mm of the margin. Patient outcomes were calculated with intention to treat.

Statistical methods

Primary endpoints were 2-year actuarial LRC, time for freedom from distant metastasis (FFDM), and OS. Elapsed time was calculated from the first day of re-RT. LRC and FFDM were assessed based on routine physical exam and imaging. LRC was defined as time to local (primary site) or regional (other head and neck) progression or recurrence. Actuarial estimates were calculated with the Kaplan–Meier method and a Cox proportional hazards model was used to determine predictive factors of outcome. Prognostic factors investigated were whether or not patients had surgery, concurrent chemotherapy, high-dose RT or brachytherapy boost, IMRT, radiotherapy site (isolated primary, isolated neck, or both), Charlson comorbidity score, presence of organ dysfunction, histology, oral cavity, nasopharynx or other subsite, number of recurrences prior to re-RT, time elapsed since first course of RT, whether or not disease was a new primary, recurrent stage, sex, and age.

Multivariate models were built with stepwise variable selection. The R software package (version 2.15.1) was used to construct a nomogram based on independent predictors of LRC. As it has been previously used as a definition for successful salvage therapy for recurrent HNC, we used LRC at 2 years as the predictive endpoint. A bootstrap corrected calibration plot with data split into quintiles was generated and the concordance index for the nomogram was computed (see Supplementary data for more details).

Results

The median patient age was 61 years (range, 21–89). Initial sites of disease were larynx ($n = 57$), oral cavity ($n = 52$), oropharynx ($n = 43$), nasopharynx ($n = 38$), paranasal sinus ($n = 23$), or other ($n = 44$). A minority of patients (15.6%) developed a new primary in a previously irradiated field. Sites of recurrence were primary site ($n = 131$), neck ($n = 54$), or both ($n = 72$). The majority of patients (73%) had a KPS of 80 or greater, and 77% had no signs

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