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Re-irradiation for recurrent and second primary cancers of the head and neck

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ABSTRACT

Purpose: To evaluate a single-institutional experience with the use of re-irradiation for recurrent and new primary cancers of the head and neck.
Methods: The medical charts of 80 consecutive patients who underwent re-irradiation for local-regionally recurrent or second primary head and neck cancer between November 1998 and December 2015 were analyzed. Multivariate analysis was performed using Cox proportional hazard and logistic regression to determine predictors of clinical outcomes.
Results: Seventy-six of the 80 patients were evaluable. The median age was 57.5 (range 26.6–84.9); Intensity-modulated radiotherapy (IMRT) was used in 71 (93.4%) patients with a median dose of 60 Gy. Thirty-one patients (40.8%) underwent salvage surgery before re-irradiation and 47 (61.8%) received concurrent systemic therapy. The median time interval between radiation courses was 25.3 months (range 2–322 months). The 2-year estimates of overall survival, progression free survival, locoregional control, and distant control were 51.0%, 31.3%, 36.8% and 68.3%, respectively. Patients who underwent salvage surgery prior to re-irradiation had significantly improved locoregional control, progression free survival, and overall survival ($p < 0.05$, for all). On multivariate analysis, gross tumor volume (GTV) at re-irradiation and interval between radiation courses were associated with improved overall survival. Severe (grade $\geqslant 3$) late complications were observed in 25 patients (32.8%).
Conclusions: Re-irradiation for recurrent or second primary head and neck cancer is feasible and effective in select patients with head and neck cancer. The high observed rate of treatment-related morbidity highlights the continue challenges that accompany this approach.

Introduction

Despite advances in the multi-disciplinary management of head and neck cancer, a significant proportion of patients who present with locally advanced disease subsequently develop recurrences. Locoregional recurrences in previously irradiated fields have historically carried a poor prognosis with a median survival of 6 months with best supportive care [1,2]. As locoregional recurrences after definitive radiation may indicate intrinsic tumor resistance, salvage surgery is the preferred treatment modality for patients whenever possible. For those deemed inoperable, chemotherapy alone is generally considered palliative given response rates ranging from 10% to 40% [3–5].

Although the role of re-irradiation remains controversial due to concerns for high rates of severe chronic toxicity, studies have shown that it is a potentially curative treatment option for patients with locoregionally recurrent tumors [6]. While the efficacy of re-irradiation is often limited by the tolerance of previously-irradiated organs at risk, pre-clinical data suggest that previously irradiated organs at risk like the spinal cord can experience significant dose tolerance recovery, especially when the interval between radiation courses is long. Such data has provided some reassurance that re-irradiation may be safer than historically considered [7,8]. Additionally, the clinical implementation of advanced technologies such as intensity-modulated radiotherapy (IMRT) have made it possible to deliver high effective biological doses to more conformal areas, likely improving the therapeutic ratio. The purpose of this study was to thus evaluate our institutional experience with re-irradiation of the head and neck for recurrent or second primary head and neck cancers.

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Methods and materials

Study design

Between November 1998 and December 2015, eighty consecutive patients with a history of previously irradiated head and neck cancer underwent salvage re-irradiation for recurrent or second primary tumors at our institution. Patients were excluded from the study if they had evidence of distant metastasis at the time of recurrence and/or received salvage brachytherapy. After exclusion of these patients, 76 patients were eligible for analysis. Evaluation prior to re-irradiation therapy included patient history, physical examination, and basic blood work in all patients. Axial imaging with computed tomography (CT) and/or or magnetic resonance imaging (MRI) of the head and neck with intravenous contrast was required in all patients as part of their work-up prior to re-irradiation. Sixty patients had positron emission tomography performed. Histological confirmation of recurrence with a biopsy was performed for 58 patients with the remaining 18 patients having tumors that were deemed inaccessible due to its anatomical location. Re-irradiation was defined as any overlap in dose distributions after careful review of the initial and re-irradiation treatment plans.

Treatment

Treatment was delivered using fractionated IMRT in 71 patients and stereotactic body radiotherapy (SBRT) in 5 patients. Before undergoing re-irradiation, patients were evaluated by a multimodality treatment team consisting of a radiation oncologist, medical oncologist and head and neck surgeon where all imaging was reviewed.

Before re-treatment, patients underwent CT simulation and were immobilized using a thermoplastic mass to ensure reproducibility of treatment setup and positioning during re-irradiation. In the majority of patients who were treated with conventional fractionation, the treatment target was defined at the gross tumor volume (GTV), which was further expanded by 0.1–0.5 cm to create a clinical target volume (CTV), accounting for microscopic disease extension. In some cases where tumor abutted critical structures, the CTV expansion was zero. The CTV was then circumferentially expanded 0.3–0.5 cm to devise a planning target volume (PTV). For patients treated with stereotactic body radiotherapy (SBRT), the PTV was the GTV expanded by a 0.3 cm margin. No elective nodal coverage was performed with either technique. Daily image-guidance was used with real-time digital X-ray images or cone-beam CT images for each patient. Treatment plans were designed using the Eclipse™ treatment planning system (Varian Medical Systems, Palo Alto, CA). Systemic therapy was administered at discretion of the treating medical oncologist considering such factors as patient performance status, preference, and tumor extent.

Follow-up and statistical analysis

The actuarial rates of overall survival, progression-free survival, locoregional control, and distant control were calculated from the final day of re-irradiation, using the Kaplan-Meier method. Locoregional control was defined as absence of locoregional failure within the re-irradiated volume, all other recurrences were classified as distant. Evidence of tumor recurrence was evaluated by imaging with either CT or MRI and confirmed by tissue biopsy whenever possible. Progression-free survival was defined as survival without evidence of either distant disease and/or locoregional failure. Acute and late toxicity were respectively defined as those occurring within 90 days from treatment completion, and graded according to RTOG/EORTC Radiation Morbidity Scoring Schema.

Predictors of clinical outcomes were determined using a univariate and multivariate Cox Proportional Hazard models. The parameters included in the models were: location of recurrence (neck vs. primary), re-irradiation dose, use of concurrent systemic therapy, time interval between radiation courses (as a continuous variable), histology (squamous vs. non-squamous), and Karnofsky performance status (KPS). These variables were also evaluated as predictors for severe late toxicity (grade 3+) using the Logistic Regression model. Log-rank statistical analyses were performed for comparison between patient subgroups. Analyses were performed using SAS version 9.4 (SAS Institute, NC), with a statistical significance level of a two-tailed p-value < 0.05.

Results

Patients and treatment characteristics

Patient and treatment characteristics are detailed in Table 1. The most common primary site of initial disease presentation

Table 1
Patient and treatment characteristics.

Characteristics	N	Percent or range
Median age, years	57.5	26.6–84.9
Gender		
Female	31	40.8
Male	45	59.2
Primary tumor site		
Nasopharynx	10	13.2
Neck	4	5.3
Paranasal sinus	6	7.9
Oropharynx	14	18.4
Larynx	7	9.2
Hypopharynx	2	2.6
Oral cavity	20	26.3
Nasal cavity	3	3.9
Thyroid	1	1.3
Parotid	2	2.6
Other salivary glands	2	2.6
Skin	4	5.3
Unknown primary	1	1.3
Site of recurrence		
Neck	43	56.6
Primary tumor site	33	43.4
KPS on recurrence		
<80	16	21.1
⩾80	59	77.6
Histology		
SCC	60	78.9
Non-SCC	16	21.1
Salvage surgery for recurrence		
Yes	31	40.8
No	45	59.2
Concurrent systemic therapy		
Yes	47	61.8
No	29	38.2
Type of re-irradiation		
IMRT	71	93.4
SBRT	3	3.9
3DCRT	2	2.6
Median dose of first RT, Gy	68.4	18.2–136
Median dose of RRT, Gy	60	18–70
Median GTV, cc	56	0.7–220

Abbreviations: KPS: Karnofsky Performance Scale, SCC: Squamous Cell Carcinoma, IMRT: Intensity Modulated Radiotherapy, SBRT: Stereotactic Body Radiotherapy, 3DCRT: 3D Conformal Radiotherapy RT: Radiation Therapy, RRT: Re-irradiation treatment, GTV: Gross Tumor Volume.