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Patterns of failure after reirradiation with intensity-modulated radiation therapy and the competing risk of out-of-field recurrences

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ABSTRACT

Purpose: To describe patterns of failure (POF) after reirradiation (reRT) with intensity modulated radiation therapy (IMRT) for recurrent/second primary squamous cell carcinoma of the head and neck.
Methods: From 08/2004-02/2013, 75 consecutive patients received reRT with IMRT. Gross tumor was generally treated with a 5 mm planning target volume (PTV) margin. For postoperative cases, a 5 mm PTV was added to the clinical target volume which included the postoperative bed. Elective neck coverage was not standard. POF were characterized by correlating the recurrent tumor location on CT-imaging with the reRT IMRT plan.
Results: Patients received definitive reRT (55%) or postoperative reRT (45%) to a median 60 Gy (range, 59.4–70 Gy). Most patients (88%) received concurrent chemotherapy including induction (16%). The median overall survival was 1.8 years. Isolated local-regional recurrence (LRR) was the most common failure-type (2-year cumulative incidence [CI] 22.5% [95% C.I. 13.6–32.7%]), but concurrent LRR and distant-failure occurred frequently (2-year CI LRR + distant-failure 19.6% [95% C.I. 11.3–29.5%]); isolated distant-failure was rare (2-year CI 5.7% [95% C.I. 1.8–12.8%]). The 2-year in-field control was 65% (95% C.I. 52–81%) reflecting encouraging control within the irradiated target. Patients with gross disease were more likely to recur in-field ($p = 0.02$), whereas postoperative patients were more likely to recur out-of-field/marginally than in-field ($p = 0.02$).
Conclusions: POF after reRT differ when treating gross disease or postoperatively and should be considered when delineating reRT targets. Aggressive local therapy resulted in favorable in-field control, yet there remains a high competing risk of regional and distant micrometastatic disease. Better systemic agents are needed to control clinically occult local-regional and distant disease.

Introduction

Re-irradiation (reRT) is a treatment option for select patients with unresectable recurrent squamous cell carcinoma of the head and neck (SCCHN) or postoperatively for recurrent, operable patients with high-risk features such as positive margins or extracapsular extension. While a single randomized trial did not show an overall survival (OS) benefit with the addition of postoperative chemo-reRT to surgery, local-regional control (LRC) was improved [1]. However, the LRC benefit with reRT frequently comes at the expense of significant treatment-related toxicity [2–5].

In order to minimize the toxicity of reRT and improve LRC, technical advances in radiation therapy including IMRT and stereotactic body radiation (SBRT) are increasingly utilized. Also, in contrast to the upfront treatment setting, the volumes treated in reRT are typically more limited. For example, when treating gross disease, the clinical target volumes to treat subclinical disease are generally smaller, if present at all, and prophylactic neck treatment is usually avoided.

Few studies have analyzed the detailed patterns of failure (POF) after reRT using these smaller treatment volumes after IMRT for both definitive and postoperative reRT cases. A prior POF analysis

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of patients with unresectable head and neck cancers, including both three-dimensional conformal and IMRT treatments, showed that most recurrences occur in-field in the high-dose region [6]. We aimed to characterize the POF after reRT with IMRT and concurrent chemotherapy and compare/contrast the POF based on whether the reRT was definitive or postoperative. Furthermore, we aimed to identify the relationship between local regional recurrences and technique-related factors such as CTV or PTV margins or elective neck-coverage.

In addition to studying the POF in relation to radiation target-volumes, we assessed the relative frequency of distant failure as a competing risk. As in the upfront setting for most cases of mucosal SCCHN, local-regional failure is still the most common site of failure after reRT [1,7]. This serves as rationale for intensifying local treatment with modalities such as stereotactic body radiation therapy (SBRT), yet the competing risk of distant metastases is not well-characterized. We sought to determine the competing risk of distant failure in this population treated with aggressive local therapy. Such information may inform future trial-design related to radiation technique and treatment volumes as well as the relative importance of incorporating systemically-active drugs into reRT studies.

Materials and methods

Patients and treatment

We reviewed the records of seventy-five consecutive patients that received re-irradiation with IMRT for R/SP SCCHN from 08/2004 (when IMRT was introduced to the clinic) to 02/2013 at the Dana-Farber Cancer Institute. All patients received a prior course of definitive or postoperative RT either at our institution or at an outside institution. Patients were considered to have a second primary tumor if the tumor was diagnosed >5 years after the initial cancer and/or occurred in an anatomically-distinct region. Definitive re-irradiation was offered to select patients after multidisciplinary evaluation by the radiation oncologist, head and neck surgeon, and medical oncologist. Patients with resectable disease were offered salvage surgery. Post-operative reRT was offered in select cases with high-risk features such as close or positive margins and extracapsular spread. Patients were offered definitive reRT without surgical salvage if they had unresectable disease or refused surgery. Two patients were excluded from the analysis because they stopped reRT due to local tumor progression (received 8 Gy) and transitioned to hospice (received 20 Gy); neither patient had treatment-related side effects at the time of discontinuation.

For patients who had an initial course of radiation at an outside institution, the graphic plan or simulation films were obtained where possible to confirm dose to the target volumes and normal tissues. In general, patients who completed radiation within 6 months of recurrence were not candidates for reRT unless, after review of the prior radiation plan, the recurrence was considered to be a 'marginal miss' and predominantly out of the high-dose area suggesting that the recurrence did not necessarily represent radioresistant disease.

Radiation therapy was delivered with IMRT for all patients and planned using Eclipse planning software (Varian Medical Systems, Palo Alto, CA). The radiation target volume included gross disease (GTV) with a 5 mm planning target volume (PTV) margin. Postoperative clinical target volumes (CTV) included the postoperative bed or the area of highest concern after discussion with the surgeon and pathology review, with a 1–1.5 cm margin for subclinical spread and a 5 mm (PTV) expansion. Elective neck irradiation was not routinely used, but was considered when there was a high-risk of subclinical spread to the neck in an area that was not included in the target volume during the initial course of radiation. The primary avoidance structure was the spinal cord with a limit of 10–12 Gy (Gy) at the time of reRT. Similar limitations were used for the brain stem dose. In general, the prescription dose was 60 Gy in 30 fractions (range, 59.4–70 Gy).

Concurrent chemotherapy was given in most cases. Induction chemotherapy was given at the discretion of the treating physicians, but in general was considered for patients with T4 tumors or N3 nodal disease.

Outcome assessment

At the completion of reRT, patients were monitored every 1–2 weeks until resolution or stabilization of acute side effects and every 1–2 months for the first two years. The diagnosis of recurrence after reRT was confirmed with biopsy for most patients (n = 23), radiographic imaging only (n = 10), or clinical examination only (n = 2). In all cases, detailed information regarding the sites of recurrence in relation to the irradiated area was obtained. To characterize the POF, radiographic imaging showing the site of recurrence was available for 32 of the 35 patients. For the 3 patients without radiographic imaging, the clinical description of the tumor location was used to identify the site of failure after reRT. All radiation plans used CT-imaging and were available for review on the treatment planning system to determine the location of the local-regional failure following reRT in relation to the radiation isodose curves. The method previously described by Popovtzer et al. [6] was used to classify recurrences as follows: in-field defined as majority of recurrent tumor within the 95% isodose line; marginal defined as $\leqslant$50% of recurrence within the 95% isodose line; and "outside" if <20% of recurrence was contained within the 95% isodose line. Additionally, patients were scored as having concurrent out-of-field recurrences if there were a separate tumor nidus outside of the treated area. Fig. 1 shows images from two representative cases of recurrences after reRT.

Statistical analysis

The Kaplan-Meier method was used to estimate the OS time which was defined as the time from the re-RT start date to death or last follow-up. Single and multivariable Cox proportional hazard regression models were used to evaluate the association between patient and treatment characteristics with OS and recurrence-free survival (RFS). RFS was defined as first of local recurrence or distant metastasis or death. Local-regional recurrence (LRR) and distant metastasis (DM) were treated as time-varying covariates in the RFS and OS models. The variables with p-value $\leqslant$ 0.10 in a single variable analysis were included in the multivariable model.

The cumulative incidence (CI) of LRR was defined as LRR, including concurrent LRR and distant failure. DM was considered a competing risk if it occurred prior to LRR or regardless of subsequent LRR. The CI of DM was defined as DM, including events of DM and concurrent LRR. LRR was considered a competing risk if it occurred prior to DM or regardless of subsequent DM. For both LRR and DM endpoints, death in the absence of DM or LRR respectively was considered a competing risk. Fine & Gray competing risk analysis was used. Rates of isolated LRR-only, concurrent LRR and DM, and DM-only were also calculated.

The in-field local control rate was defined as the time from re-RT start to the date of LRR where at least one component of failure was in-field, or to last disease follow-up date. The Kaplan Meier method was used to estimate in-field control and patients were censored at the date of last assessment. The one patient with unknown POF was excluded from the analysis.