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The Pattern of Failure after Re-Irradiation of Recurrent Squamous Cell Head and Neck Cancer: Implications for Defining the Targets

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Abstract

Purpose—Re-irradiation (re-RT) of recurrent head and neck cancer (HNC) may achieve long term disease control in some patients, at the expense of high rates of late sequelae. Limiting the re-RT targets to the recurrent gross tumor volume (rGTV) would reduce the volumes of re-irradiated tissues, however, its effect on tumor recurrence pattern is unknown.

Methods—Retrospective review of 66 patients who underwent curative-intent re-RT for non-resectable recurrent or second primary mucosal squamous cell HNC. Treatment was delivered with 3-dimensional conformal (3D) RT or intensity modulated RT (IMRT). The targets in all patients consisted of the rGTVs with tight (0.5 cm) margins, with no intent to treat prophylactically lymph nodes or sub-clinical disease in the vicinity of the rGTVs. The sites of local-regional failures (LRFs) were determined using imaging at the time of failure, and were compared to the rGTVs.

Results—Median re-RT dose was 68 Gy. 47 patients (71%) received concomitant chemotherapy and 31 (47%) received hyperfractionated, accelerated RT. At a median follow up 42 month, 16 (23%) are alive and free of disease. Fifty patients (77%) had a third recurrence or persistent disease, including 47 LRFs. All LRFs occurred within the rGTVs except for two (4%) (95% C.I. 0; 11 %). Nineteen patients (29%) had grade ≥ 3 late complications, mostly dysphagia (12 patients).

Conclusion—Almost all LRFs occurred within the re-irradiated rGTVs despite avoiding prophylactic RT of tissue at risk of subclinical disease. These results support confining the re-RT targets to the rGTVs to reduce re-irradiated tissue volumes.

Keywords

Recurrent head and neck cancer; re-irradiation; IMRT; 3D radiotherapy; Target definition

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Introduction

Following irradiation of advanced head and neck cancer (HNC) the most common patterns of failure are either locoregional (LR) or the development of a second malignancy (1–4). Both are difficult to manage when they occur in a previously irradiated area. In selected cases, surgery may constitute an effective salvage treatment (5–8). Chemotherapy in the setting of non-resectable local or regional recurrence is associated with a median survival of 5–6 months, with no chance of long-term control (9). Lately, many reports have suggested that re-irradiation (re-RT) concomitantly with chemotherapy is feasible in this setting and may achieve long term disease control in some patients, at the expense of a substantial rate of late toxicities (10–20). In contrast to primary HNC RT, where adjuvant RT of draining neck lymph nodes and tissue near the tumor at risk of sub-clinical disease is standard of care, there is no consensus regarding the treatment targets in re-RT. Should the targets include prophylactic neck and mucosa at risk of sub-clinical disease, or focus only on the gross tumors in order to minimize the volume of re-irradiated tissue?

Re-RT studies utilized different re-RT techniques depending on the era of the study, including 2 dimensional RT (15), 3 dimensional conformal RT (16,21), and recently intensity modulated RT (IMRT) (12,13,13b). The definition of the targets varied in these studies, ranging from the recurrent tumor as well as the mucosal surfaces and lymph node areas at risk of sub-clinical disease (14,17,19), to studies limiting the targets to the recurrent tumor with various margins around the tumor (10–13,16). In the typical series, the decision about the targets varied depending on the treating radiation oncologist (13b). Limiting the volume of the re-irradiated tissue by defining the re-RT target as the recurrent gross tumor volume (RGTV) with tight margins around the RGTV, may help reduce late toxicity of re-RT. However, it is necessary to verify that such a strategy does not compromise tumor control by assessing where have local/regional failures (LRF) occurred after re-RT. None of the published re-RT studies have examined the sites of LRF relative to the targets and the delivered doses.

At our institute a uniform policy has been to re-irradiate the RGTV only, with tight margins, using three dimensional RT or IMRT, and avoid prophylactic irradiation of neck or mucosal regions at risk of subclinical disease, in order to minimize the volume of re-irradiated tissue. An earlier analysis (21) described the outcome of some of these patients. In the current study we sought to assess what was the implication of this policy regarding the pattern of LRF and the late toxicity of re-RT.

Patients and Methods

We retrospectively reviewed files, images studies, and treatment plans of all patients who underwent curative-intent re-RT between 1994 and 2007 for mucosal squamous cell HNC at our institute and who had minimal follow-up of 6 months. Patients eligible for analysis had non-skin squamous cell carcinoma with local-regional recurrences, or new primary cancers, occurring in a previously irradiated head-and-neck sites. During that time period, institutional policy has been to surgically resect recurrent cancers previously irradiated. Therefore, only patients with unresectable recurrent tumors, those with residual disease after a trial of resection, or with involved surgical margins following surgery, were re-irradiated and were included in this study. Exclusion criteria included patients treated for palliation, skin cancer or non-squamous cell cancers.

A complete history, physical examination, and computed tomography (CT) scan were completed before re-RT for all patients. Pre-treatment workup generally included an examination under anesthesia and screening for distant metastases with a chest X-ray, thoracic

CT scan, and PET or PET-CT scans in recent years. All available modalities were used to define the RGTV.

66 patients with recurrent HNC were re-irradiated with a curative intent between 1994–2007. Patient and tumor characteristics are detailed in Table 1. In 31(47%) patients the recurrence after the first RT course occurred at a mucosal site, 19 (29%) recurred in the neck, and 16 (24%) had both neck and mucosal recurrences. A total of 44 patients underwent primary re-RT and 22 underwent re-RT after surgery, 18 of whom had incomplete gross resection due to extensive neck disease involving carotid artery or deep muscles (11 patients) or due to skull base involvement (7 patients). Four Patients had complete gross resection and underwent adjuvant re-RT due to microscopically involved margins.

Re-RT in the earlier years of the study was delivered using 3D conformal techniques or multisegment forward-planned IMRT, and in recent years (after 2002), inverse-planned IMRT. Patients had planning CT scans, typically at 3-mm slice spacing and i.v. contrast. The RGTVs were outlined using all available information gained from the pre-therapy examination and imaging. The RGTVs were expanded by 0.5 cm to yield planning target volumes (PTVs). There was no intent to treat adjacent sites or regional lymph nodes at risk of subclinical disease. In four cases treatment was performed adjuvantly following surgery. In these cases the clinical target volume (CTV) was confined to the part of the surgical tumor bed suspected of containing microscopic disease.

Until 2002, multiple fields arrangements and field shapes were designed using Beam's Eye View (BEV) displays to assist in determining beam directions and locations. The average number of fields was 4, range 1–12 (a single electron beam was used for treatment of neck levels with extracapsular lymph node metastases in 3 patients, and two off-cord beams were used for 5 patients with glottic larynx recurrences). In order to improve conformality and achieve target dose homogeneity within $\pm 5\%$ of the prescribed dose, 2–4 segments were typically devised for each field using BEV of isodose surfaces as previously detailed (22). In latter years, treatment consisted of IMRT using an in-house optimization system, and target dose homogeneity ($\pm 5\%$) was achieved using previously detailed methods (23).

In all cases an effort was made to avoid re-RT of critical normal structures such as the spinal cord and brainstem, while achieving minimal PTV of 95% prescribed dose. The cumulative radiation doses to spinal cord and brainstem, which were determined by adding the maximal doses from the first and second RT courses, were limited to 50 Gy and 60 Gy, respectively. If these limits were not feasible, the doses to these organs were limited to $\leq 20\%$ prescribed PTV doses in the re-RT plan. Hyperfractionated radiation was considered for all patients, unless logistical constraints allowed conventional fractionation only (e.g., patients traveling from far distances who could not stay for twice-daily RT). Patients receiving hyperfractionation were treated according to a modification of a regimen published by Brizel et al (24). The modification consisted of avoiding the one week treatment break at mid therapy, accelerating the total treatment time (total 70 Gy at 1.25 Gy/fraction B.I.D. over six weeks), concurrent with chemotherapy, as previously detailed (25).

Re-RT was delivered with concurrent chemotherapy in 47 patients (71%). Chemotherapy regimens contained cisplatin or carboplatin, taxotere, or cetuximab. Patients receiving hyperfractionated RT received concurrent cisplatin and 5FU according to a published regimen (24,25).

For all patients with local-regional recurrences after re-RT, the recurrent tumor volume (V_{recur}) was identified on CT or MRI scans obtained at the time of diagnosis of recurrence. The exact site and extent of each tumor were then compared visually to the pretreatment planning CT datasets, focusing on the 95% isodose lines. The recurrences were categorized

according to previously published criteria as occurring inside or outside the previously irradiated targets, depending on the location of V_{recur} : “in-field,” if the majority of V_{recur} was judged to be within the 95% isodose; “marginal,” if $\leq 50\%$ of V_{recur} was within the 95% isodose; or “outside,” if less than 20% of the V_{recur} was inside the 95% isodose (26).

Acute toxicities and late complications were assessed retrospectively by chart reviews. Toxicity grading was assigned retrospectively according to the Common Terminology Criteria for Adverse Events (CTCAE) v3.0.

Statistical methods

The median potential follow-up was measured from the first day of re-RT to the day of death or the last clinic visit before analysis (December 2007). Actuarial estimates for local/regional progression free survival (LRPFS) and overall survival (OS) were calculated using Kaplan-Meier estimates. Cox proportional hazard model was used to examine the effect of the time period between the first and the second radiation courses on survival and LRPFS.

Results

The Median radiation dose in the initial treatment course was 64 Gy (range 46–76.8 Gy). In the re-RT courses, 35 patients (54%) were treated with conventional fractionated and 31 (46%) with accelerated hyperfractionated radiation. Intracavitary brachytherapy (20–60 Gy, 60 cGy/h) was used as a component of therapy in two patients with recurrent nasopharyngeal cancer. The re-RT course was delivered at a median of 37 months (range, 6–184) after the first course. The median delivered re-RT dose was 68 Gy (range 15–79.6 Gy). Four patients received less than 50 Gy due to acute toxicity requiring early discontinuation of therapy (aspiration pneumonia, cisplatin-induced renal failure) or tumor progression during therapy. Eight patients received 50–60 Gy, 49 received 60–70 Gy and 5 received 70–75 Gy. The median overall treatment time was 41 days. The median cumulative delivered dose in both RT courses was 129.2 Gy (range 79.2–140). Forty-seven patients (71%) received platinum-based concurrent chemotherapy.

At a median follow up of 42 month, 44 (67%) patients died and 22 (33%) are alive, of whom 16 (23%) are free of disease. Actuarial overall survival at two years was 40% and at 5 years 22% (95% confidence interval 10%; 32%) (Fig 1). Seven (11%) patients are alive at minimal 5 years follow up.

Locoregional Control

The 2- and 5- year actuarial locoregional progression free survival was 27% and 19%, respectively (Fig 2). Forty seven patients (71%) had local-regional failure (LRF). In 45 (96%) of these patients the LRFs occurred within the 95% isodose lines (in-field recurrences) (Fig 3). In two patients (4%, 95% C.I. 0; 11%) an isolated LRF was out-of-field. None of the patients had marginal LRF. We evaluated the association between locoregional recurrence and radiation dosage and use of chemotherapy. The median dose among patients who recurred was 68 Gy, which was not different from the median dose in patients who did not recur (69 Gy). Concurrent chemotherapy was not a statistically significant factor associated with LR failures in this retrospective series (74% of 47 patients receiving chemotherapy recurred, compared with 63% failure rate among 19 patients who did not receive chemotherapy).

Of the two patients with out-of-field recurrences, one patient had an initial supraglottic larynx cancer and received re-RT for a base of tongue second primary cancer. This patient experienced LRF in low neck nodes (level IV), which was included in the targets in the initial but not in the re-RT treatment course. The second patient with an out of field recurrence was initially

diagnosed with a left sided buccal mucosa cancer with left neck nodes. Cancer recurred in the right neck which was re-irradiated, and subsequently failed in the left neck, which was included in the targets of the first but not the re-RT course.

Eighteen of the patients (27%) had distant metastases, 15 of whom had both LRF and distant failure. The sites of distant metastases included lung (10 patients), brain (3 patients), skin (3 patients), bone (2 patients) and liver (2 patients)

The time to failure and OS for patients with inter-treatment intervals larger than the median (37 months) were longer compared with those with smaller intervals, however, the differences were not statistically significant: Median time to failure 11 vs. 5.3 months, respectively ($p=0.27$), and median OS 27 vs. 15 months, respectively ($p=0.62$).

Grade ≥ 3 acute complications included aspiration and laryngeal edema in one patient each, one of whom died from aspirations. One patient who received concomitant Cisplatin died from acute renal failure.

Grade ≥ 3 late complications occurred in 19 patients (29%), Including 12 (18%) with longterm feeding tube dependency, two with pharyngeal stenosis requiring repeated dilatations, two with laryngeal chondronecrosis following cumulative laryngeal doses of 130 and 140 Gy (one of whom also had severe neck fibrosis). One patient with recurrent maxillary sinus cancer developed asymptomatic, MRI evident, temporal- lobe necrosis 30 months after re-RT in an area of the brain adjacent to the previous tumor which had received a cumulative RT dose of 115 Gy. Three patients were tracheostomy-dependent as a result of therapy, including two patients who underwent total laryngectomy for chondronecrosis, and a patient who discontinued treatment due to laryngeal edema.

Two patients had carotid artery blow-out necessitating salvage surgery. Each of these patients had non-resectable neck nodal metastases and received a cumulative RT dose of 140 Gy to the carotid artery. One of these patients died within a year from advanced neck disease. In the second case, carotid blow-out occurred following post-re-RT trial of salvage neck dissection performed due to persistent disease. This patient eventually died from extensive neck disease.

There were no statistically significant associations between late complications and the radiation doses or concurrent chemotherapy.

Discussion

The main findings in this series are that almost all LRFs (96%) occurred in-field, inside the RGTV, despite omitting prophylactic re-RT of lymph nodes at risk or the vicinity of the gross tumor at risk of subclinical disease, apart for small (0.5 cm) margins around the RGTV. The other important finding was that the rate of these in-field failures was very high (68%), despite a high local re-RT dose (median 68 Gy), and despite altered fractionation and/or concurrent chemoradiation in most patients.

In the two patients with LRF outside the irradiated targets, the failures occurred in non-first-echelon nodes, which would not have been considered to be at highest risk for recurrence at the time of re-RT. An unpredictable pattern of recurrence has been reported in patients with previously dissected neck, due to altered lymphatic pathways developing over time after neck dissection (27–28). This phenomenon may also apply to the previously irradiated neck. These considerations would complicate prophylactic lymph node re-irradiation had a decision been made to include them in the targets.

The high rate of both distant metastases and LRF found in our series are similar to those reported in other series of re-RT (10–20). These series used various margins around the tumors to define the targets. Some series used narrow margins, similar to our definition of the targets, while the majority used much wider margins (10–20) (Table 2). For example, RTOG multi-institutional study of re-RT defined the targets as a minimum of 2 cm around the recurrent tumor, and no details of the actual margins used by the participating institutions were provided (16). None of the previous published series detailed the sites of failures of re-RT relative to the irradiated targets.

The high rate of in-field recurrences in our series may be explained by several factors. The simplest explanation is patient selection: all patients were either deemed non-resectable, or a trial of surgical resection failed to completely excise the tumor. These selection factors have likely been similar in many other re-RT series. Another possible explanation is a higher radioresistance of tumor clonogens surviving and recurring in previously irradiated areas, especially in cancers recurring soon after the first course of RT.

We observed a very low rate of out-of-field LRF after re-RT despite avoiding prophylactic treatment of neck regions at risk or large margins around the tumor. This does not imply that the risk of subclinical disease remote from the tumor is lower at re-RT compared to primary RT for HNC. The low rates of regional or mucosal out-of field/marginal failures can be explained by the very high competing rates of in-field and distant failures. These competing events reduce markedly the potential therapeutic gain expected from treatment of regions at risk of sub-clinical disease in the re-RT course compared with primary RT of HNC, in which the rates of the competing events are lower. If in the future a strategy will be found that reduces the rate of in-field failures, it will likely increase the potential gain of treatment of subclinical disease in the re-RT setting. Various strategies to improve LR tumor control rates achieved by chemo-RT are currently being tested; this topic is beyond the scope of this paper.

Despite limiting the re-RT targets to the gross disease, we observed a substantial rate of late complications. While this rate is in the range reported in other series (Table 2), it is impossible to make any direct comparisons due to the extreme heterogeneity in re-RT series regarding doses, tumor sites and sizes, and intervals between the courses of RT. The use of IMRT in recent years resulted in improvements in dose conformity around the targets compared with the 3D RT techniques used in the earlier years in this series. Whether this higher conformity resulted in lower complication rate is an issue which cannot be addressed due to the heterogeneity of the patient population cited above and the shorter follow-up in the patients who received IMRT. This issue is not likely to be resolved in single institutional series containing limited patient numbers.

In conclusion, re-RT with a curative intent for non-resectable, recurrent HNC is curable in a minority of patients at the expense of a high rate of sequelae. Almost all LRR were in-field despite restricting re-irradiation to the RGTV and avoiding prophylactic RT of tissue at risk of subclinical disease. These results suggest that reirradiation may be confined to the RGTV in an effort to minimize re-irradiated tissue volumes. If a substantial improvement in local tumor control will be achieved in the future, it is likely that the potential gain from prophylactic treatment of high risk subclinical disease will be higher.

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Fig1.
1 Overall survival.

Fig 2.
Local regional Progression free survival

Fig: 3.

A case of local failure following re-RT of a patient with recurrent tonsillar carcinoma. The tumor at the time of re-RT involved the tonsil and spread to the parapharyngeal space and base of skull.

- A. Re -RT planning; MRI registered into the planning system. PTV=GTV+0.5 cm
- B. 95% isodose line (arrow) and PTV (arrowhead).
- C. In-field local failure (arrows) on CT scan 18 month after re-RT.

Characteristics	No.	Percent
Gender		
Male	49	74
Female	17	26
Age: Median (range)	57 (13–84)	
Primary tumor site		
Oral Cavity	18	27
Oropharynx	16	24
Larynx	15	23
Nasopharynx	6	9
Unknown primary	5	8
Para nasal Sinuses	5	7
Hypopharynx	1	2
Primary stage		
Stage I	6	9
Stage II	18	27
Stage III	29	44
Stage IV	13	20
Recurrent tumor/Second Primary	59 / 7	89 / 11

Table 2

Summary of Previous Curative Series

Series	No. of Patients	Targets + Margins (cm)	Median Re-TT Dose (Gy)	(%) Late Severe Toxicity Rates	(%) 2-Year Survival Rates
Spencer (16)	79	GTV+minimum 2	60	23	15
Salama (14)	114	GTV+1+nodes	64	18	22 (3 yr)
Lee (12)	105	GTV+(1-2)	59.4	11	37
Biagoli (13)	42	GTV+(1-2)	59	12	48
Crevoisier (15)	169	GTV+(1.5-2)	65	50	21
Langer (17)	99	GTV+2+nodes	65	38	25
Schaefer (18)	32	GTV+2	40-50	15	10
Hehr (10)	27	GTV+1	40	N/A	18
Kramer (20)	38	GTV+2	50-60	38	35
Goldstein (19)	28	GTV+1+nodes	61	57	28
Current Series	66	GTV+0.5	68	29	40