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ORIGINAL ARTICLE

Reirradiation for recurrent head and neck carcinoma

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Summary

Purpose: *To present the outcome and toxicity profile of reirradiation (re-RT) in patients with recurrent head and neck cancer (HNC).*

Methods: *From 1995 to 2009, 35 patients underwent re-RT at our institution. Twenty-seven (77%) patients were initially diagnosed with stage III/IV disease. The median total doses of irradiation –first and second courses– were 66.0 Gy (range 54.0-70.0) and 55.8 Gy (range 32.5-66.6), respectively. The median time from the first course of irradiation to re-RT was 25.2 months (range 8-136). Six (17%) patients underwent salvage surgery before reirradiation. Concurrent chemotherapy was administered to 18 (51%) patients.*

Results: *With a median follow-up of 12.9 months (range 2.5-109.6), the 1- and 2-year locoregional control (LRC) rates were 41 and 9%, respectively. The 1- and 2-year disease free survival (DFS) rates were 30 and 7%, respectively. The 1- and 2-year overall survival (OS) rates were 42.9 and 7.9%, respectively. Grade 3 acute toxicity was reported in 7 (20%) patients while grade 3-4 late radiation-induced complications were seen in 8 (23%) patients. In univariate analysis, an improvement in OS was observed in patients with initial N0/N1 stage vs. those with N2/N3 stage (p=0.004). Prior neoadjuvant chemotherapy was associated with significantly inferior OS (p=0.028), while neoadjuvant chemotherapy in recurrence was predictive of improved LRC (p=0.041).*

Conclusion: *re-RT in HN cancer is associated with poor prognosis, especially in patients with inoperable disease. Complications due to treatment are not infrequent. Nonetheless, our outcomes remain encouraging and applicable to a carefully selected patient population.*

Key words: 3DCRT, head and neck cancer, recurrence, re-irradiation,

Introduction

Despite significant improvements in the treatment of locoregionally advanced HNC, locoregional recurrence remains a serious problem, occurring at a rate of 20-30% [1-5]. Recurrences developing in a previously irradiated area pose a great challenge, since treatment options are limited, and the prognosis is poor.

Surgical salvage is the preferred treatment approach, but only few patients are candidates for radical surgery because of tumor extent and medical comorbidities [6]. Alternative nonsurgical treatments, ranging from chemotherapy alone to re-RT with or without chemotherapy have been recommended by single and multi-institutional clinical trials [7].

With modern radiotherapy techniques (IMRT, IGRT) the total irradiation dose can be raised. This approach in combination with new chemotherapeutic agents could give better results in the future.

The aim of this retrospective study was to present our experience and analyse the effectiveness of 3D conformal techniques of re-RT in patients with recurrent HNC regarding toxicity, LRC, and OS, using 3-dimensional (3D) treatment planning techniques (3D-TPS).

Methods

Patient and disease characteristics

From April 1996 to October 2009, 35 patients with recurrent HNC received re-RT with curative intent at the University of Ioannina. Eligible patients were those with histologically proven locoregional recurrence occurring in a previously irradiated head-and-neck location. Exclusion criteria were: limited data about previous RT,

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Karnofsky performance status <60, absence of significant comorbidities or presence of metastatic disease.

All patients underwent pretreatment work-up with complete medical history, physical examination, endoscopy under general anesthesia, computed tomography (CT) scan, and/or magnetic resonance (MR) imaging. Assessment of distant metastases included chest CT scan, liver ultrasound, and bone scintigraphy, depending on symptoms. Laboratory tests were performed to evaluate hematologic, renal, and hepatic function.

Treatment characteristics

A) Radiation

Patients were immobilized from head to shoulders with commercially available thermoplastic masks in supine position. CT images (5 mm slice thickness) were acquired from the top of the vertex to the level of the carina without contrast agent infusion.

The sites and volumes of re-RT were assessed retrospectively by reviewing radiation charts. All patients were re-irradiated with curative intent. The majority of patients were re-irradiated using 3D conformal techniques, with 6 MV photons. All target volumes and adjacent critical normal structures were outlined on axial CT slices. Beam arrangements and field shapes were designed using 3D beam's-eyeview (BEV) displays of targets and normal structures, to avoid re-RT of critical normal structures such as the spinal cord and brainstem. The cumulative RT dose of the first treatment (including the calculated sublethal repair) and the retreatment were kept below 50 Gy for the spinal cord and 60 Gy for the brainstem. No major efforts were made to spare the parotid glands, because patients already complained of xerostomia before re-RT.

B) Radiation target volumes/Total dose

The Gross Tumor Volumes (GTV) for both the primary tumor and the lymph nodes encompassed the clinically and radiologically detectable recurrent disease with 1- to 2-cm margins to form Planning Target Volumes (PTVs). In general, there was no intention to treat other subclinical disease, except in selected cases, where regions considered to be at risk for microscopic disease were included in the PTV.

The median total re-RT dose was 55.8 Gy (range 32.5-66.6). The daily dose was 1.8 Gy. In general, beams were chosen to ensure that at least 95% of the dose encompassed the target volume. Every effort was made to avoid re-RT of critical normal tissues such as the spinal cord and brainstem.

C) Chemotherapy

Chemotherapy was administered concurrently with RT (CRT) to 19 (54%) patients (cisplatin 40 mg/m^2 i.v. weekly). One to 3 cycles of neoadjuvant cisplatin-based chemotherapy were given to 8 (23%) patients. Two patients had also received additional chemotherapy, as an adjuvant.

D) Surgery

Six (17%) patients who had resectable tumors underwent salvage surgery. Postoperative RT was given according to the histopathological data of the resected specimens (tumor size, invasion, positive margins) to reduce the possibility of local recurrences.

Toxicity assessment

Normal tissue side effects due to RT were graded according to the Radiation Therapy Oncology Group (RTOG)/ European Organization for Research and Treatment of Cancer (EORTC) radiation morbidity scoring criteria [8].

Follow-up

During irradiation all patients were clinically assessed at weekly intervals, and 2 months after treatment completion. Institutional standards for patient assessment included physical examination with additional flexible fiberoptic endoscopy approximately every 2 months in the first year of follow-up, every 3 months in the second and third year and every 6 months in the fourth and fifth year. Posttreatment imaging was indicated in the first year of follow-up and thereafter only based on signs and/or symptoms.

Statistical analysis

Descriptive statistics were used for patient and tumor characteristics, treatment features, and toxicities. Potential prognostic factors for locoregional control and overall survival were examined by univariate analysis. Statistical calculations of Kaplan-Meier curves were performed using StatView® program (Abacus Concepts Inc., Berkeley, CA). A p-value of ≤ 0.05 was considered statistically significant.

Results

Patients/Treatment

The mean age of the cohort was 71 years (range 52-89). Median follow-up from re-RT was 12.9 months (range 2.5-109.6). Twenty-seven (77%) patients had locally advanced disease (stage III/IV) at first diagnosis. Patient, tumor and treatment characteristics of the study cohort at the time of reirradiation are outlined in Table 1.

Six (17%) patients underwent salvage surgery before re-RT. The median time from the first course of RT to re-RT was 25.2 months (range 8-136). The median dose of the first treatment was 66 Gy (range 54.0-70.0) and the median re-RT dose was 55.8 Gy (range 32.5-66.6), resulting in a median total cumulative RT dose of 117.0 Gy (range 73.8-133.2). The mean total treatment time was 45 days (range 8-60). Two (6%) patients refused to complete their prescribed total dose of re-RT because of subjective acute toxicity complaints.

Toxicity

No severe acute toxicity during the first course of RT was observed. During re-RT, grade 3 acute toxicity was observed in 7 (20%) patients: tongue swelling (n=1), skin (n=3), and mucositis (n=3). In one (3%) patient, percutaneous endoscopic gastrostomy feeding tube (PEG) was placed during treatment. A median weight loss of 5 kg (range 0-16) was registered during treatment.

Grade 3-4 late treatment complications were seen in 8 (23%) patients. In total, 14 events of severe late

Table 1. Patient, disease and treatment characteristics

Characteristics	*N*	*%*
Patients		
Gender		
Male	31	89
Female	4	11
Age, years, mean (range)	70.5 (52-89)	
Tumor		
Primary tumor site		
Oropharynx	10	29
Larynx	8	23
Oral cavity	6	17
Nasal cavity/sinuses	5	14
Nasopharynx	5	14
Parotid gland	1	3
Primary stage III/IV	27	77
Histology		
Squamous	30	85
Adenoid cystic	2	6
Non-keratinizing NPC (WHO type 2/3)	2	6
Melanoma	1	3
Recurrent tumor		
Primary site only	19	54
Neck only	12	34
Both primary and neck	4	11
Treatment		
Reirradiation setting		
Primary/definitive	29	83
Postoperative	6	17
Chemotherapy		
Concurrent	19	54
Neoadjuvant	8	23
Neoadjuvant and concurrent	8	23

toxicity were observed. Neck fibrosis was reported in 4 (11%) patients; however, the majority of these patients had already moderate subcutaneous fibrosis attributable to their first course of RT. There was one episode of neck cutaneous fistula. One patient complained of chronic neck pain, requiring opioids. Seven (20%) patients presented with chronic dysphagia –3 of them due to strictures– requiring feeding tube for some or all of their nutrition. One patient presented with cranial neuropathy (ophthalmoplegia) at the 12th month of follow-up. No cases of RT-associated myelopathy or brainstem damage were reported.

Treatment response and disease outcomes

At the time of analysis, 32 (11%) patients had progressive disease; 28 (80%) patients had locoregional disease progression, while in 2 (6%) distant metastases were diagnosed. The remaining 2 (6%) patients had both locoregional failure and distant metastasis.

With a median follow-up from re-RT of 12.9 months (range 2.5-109.6), the actuarial 1- and 2-year LRC rates were 41 and 9%, respectively (Figure 1A). The 1- and 2-year PFS rates were 30 and 7%, respectively (Figure 1B). The median OS was 10.8 months (range 3.0-107.6). The median survival of patients with resectable disease (n=6) and unresectable disease was 13.5 months and 9.5 months, respectively. The actuarial 1- and 2-year OS rates were 42.9 and 7.9%, respectively (Figure 1C).

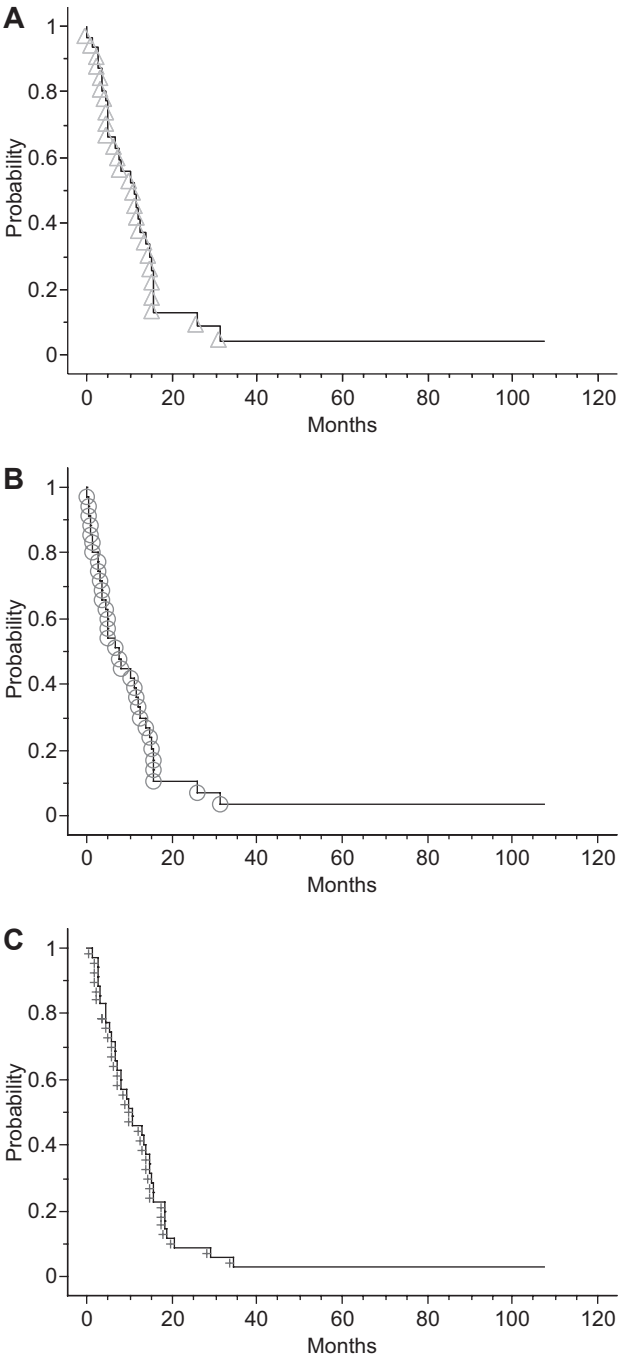

Figure 1. Kaplan-Meier estimates of treated patients: **(A):** Locoregional control, **(B):** Progression free survival, and **(C):** Overall survival.

Potential prognostic factors

Univariate analysis was performed to examine the impact of various prognostic factors on LRC and OS.

No statistically significant results were observed regarding LRC and OS in relation to performance status, gender, age, primary tumor site, histology, time interval between first course of RT and re-RT, surgical resection before re-RT, total initial RT dose, total re-RT dose, cumulative RT dose and concurrent chemotherapy.

Regarding tumor stage, initial N status (N0/N1 vs. N2/N3) correlated significantly with OS (p=0.004) (Figure 2A), favoring those patients with N0/N1 disease. Prior neoadjuvant chemotherapy was associated significantly with inferior OS (p=0.028) (Figure 2B), while neoadjuvant chemotherapy given at the time of recurrence was predictive of improved LRC (p=0.041) (Figure 2C).

Discussion

Several studies have demonstrated that re-RT with or without chemotherapy is feasible and provides a chance of cure in a subset of patients with recurrent HNC [9,10]. However, toxicity is substantial, with a relatively high incidence of treatment-related deaths [11]. When possible, salvage surgery preceding re-RT/± chemotherapy offers the best chance of LRC and possibility of cure when compared with re-RT/± chemotherapy alone [12,13].

The current study represents a single-center data analysis of cases with re-RT either alone or in combination with chemotherapy with or without surgery in patients with recurrent HNC. The major concern with chemotherapy/re-RT is the risk of irreparable damage that can influence the quality of life or even survival. In our cohort, the rate of grade 3/4 long term toxicity was 23%, considerably better than that observed in other conformal radiotherapy studies and comparable to IMRT studies [14]. It is also important to note that the majority of our patients had inoperable disease, indicating larger radiation fields and larger field overlaps. No treatment-related death was encountered among patients of the study.

According to our results, the 2-year LRC was comparable to other studies [9,10,15]. The median survival of patients with resectable (n=6) and unresectable (n=29) disease was 13.5 and 9.5 months, respectively. Although the figures seem to be poor, other curative options seem to lack, as chemotherapy alone in the recurrent setting achieves median survival rates of only 5-9 months [5].

It has to be kept in mind that patients with recurrent HNC have mainly locally advanced and inoperable disease with a low chance of cure and therefore the advantages of this treatment modality have to be weighed against the high risk of severe toxicity due to chemotherapy.

Many studies have focused on proposing pretreatment prognostic factors, such as tumor volume, resect-

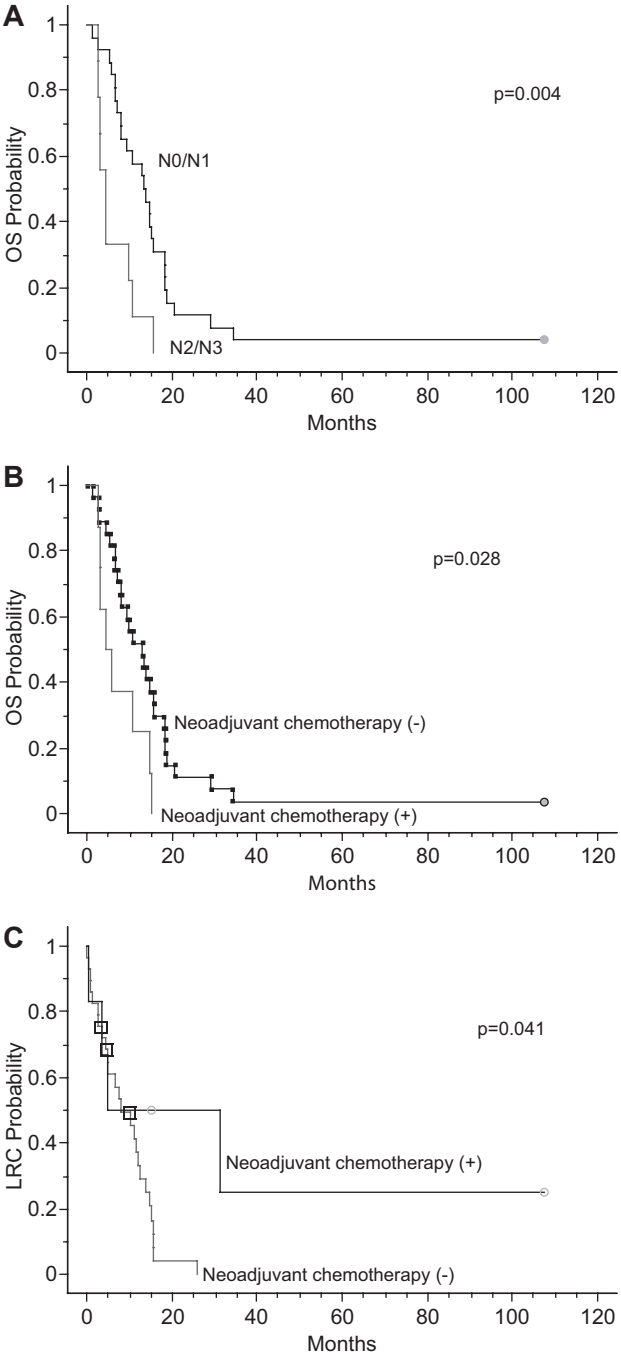

Figure 2. Univariate analysis of the interaction of tumor stage and chemotherapy on patient outcome. Kaplan-Meier curves are shown with p-values determined by log-rank test. **(A):** Correlation between initial N0/N1 status and overall survival (OS). **(B):** Correlation between prior neoadjuvant chemotherapy and OS and **(C):** Correlation between neoadjuvant chemotherapy in recurrence and locoregional control (LRC).

ability, RT interval, and the presence of comorbidities, which may help select optimal patients for chemotherapy/re-RT [15-18].

In the present study, we propose previous treatment approach with neoadjuvant chemotherapy as a potential prognostic factor regarding OS. Choe et al. [19] reported that prior chemotherapy/RT adversely impacts the outcome of recurrent HNC treated with concurrent chemotherapy/re-RT. Similar to those results, we demonstrated that survival after chemotherapy/re-RT was significantly reduced if the patients had received prior neoadjuvant chemotherapy. So, although it is believed that adding chemotherapy prior to RT provides sensitization, intensifying the effect of RT [20], tumor recurrence may lead to acquired therapeutic resistance and subsequent treatments may not be as effective as expected. However, there may be confounding variables, like the initial stage of disease, that could play a role to this result.

Our study showed that neoadjuvant chemotherapy given in recurrence was predictive of improved LRC without influencing OS [20,21]. The reduction in tumor volume could have improved oxygenation of the residual tumor and thus led to improvement of radiation effectiveness.

The results of this study are subject to limitations owing to its retrospective nature and must be interpreted with caution, given also that the number of patients was small. The study population was heterogeneous. Especially with respect to treatment, selection bias was present, since patients with inoperable disease were obviously not candidates for surgical salvage and were therefore treated with definitive chemotherapy/re-RT. Nevertheless, patients were treated relatively consistently and data were collected with meticulous follow-up.

Regarding future directions, the use of advanced RT delivery techniques, such as intensity-modulated RT or image-guided RT, has demonstrated feasibility and efficacy in the setting of HN re-RT [14,22]. The use of these techniques may lead to further improvement in quality of life outcomes. Novel strategies, such as integration of molecularly targeted agents and hypoxic cell sensitizers may be necessary to mitigate the observed therapeutic resistance [23-25]. Treatment within the context of clinical trials remains warranted to establish evidence-based treatment policies.

Conclusion

In conclusion, re-RT in patients with recurrent HNC is associated with poor survival rates, especially in patients with inoperable disease who are given definitive chemotherapy/re-RT. According to our results, neoadjuvant chemotherapy in recurrence was predictive of improved LRC. Patient number and selection potentially served to bias the clinical outcomes; nonetheless, our outcomes remain encouraging and applicable to a carefully selected patient population. In our opinion, concurrent chemotherapy/re-RT±neoadjuvant chemotherapy to patients with inoperable HNC is an acceptable treatment approach, assuming that all its limitations are discussed openly. Novel treatment strategies to improve outcome and minimize late complications in patients with HNC requiring re-RT are warranted.

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