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Curative high-dose reirradiation for patients with recurrent head and neck squamous cell carcinoma using IMRT or proton therapy: Outcomes and analysis of patterns of failure

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Abstract

Purpose: To analyze outcomes of patients treated with curative reirradiation (reRT), with intensity-modulated radiation therapy (IMRT) or proton therapy (PT) for recurrent head and neck squamous cell carcinoma (HNSCC).

Materials: Among the 55 patients reirradiated for head and neck cancer from 30/08/2012 to 08/04/2019, 23 had HNSCC and received IMRT (52.2%) or PT (47.8%) at a median maximum dose to the CTV of 66Gy.

Results: After a median follow-up of 41.3 months, 18 patients developed a locoregional recurrence (LR), of which eight (44.4%) occurred within the previously reirradiated volume. Two-year locoregional failure-free survival and overall survival were 18.3%[95%CI:7.1%–47.1%] and 42.5%[95%CI:26.2%–69.1%], respectively. Disease-free survival was significantly longer in the PT group ($p = 0.031$). Main late grade ≥ 2 toxicities were dysphagia and trismus.

Conclusion: Curative reRT in HNSCC is possible for selected cases, but the LR rate in the irradiated field and the risk of toxicity grade ≥ 2 remain high.

Keywords: Reirradiation; head and neck carcinoma; IMRT; proton therapy; toxicity.

Introduction

Radiation therapy (RT), either definitive or after surgery, is a cornerstone of local treatment of head and neck cancer (HNC), with rates ranging from 77% to 91%, depending on the location of the tumor.¹ Several long-term clinical trials have shown that local and/or regional recurrence (LR) rates can be as high as 30%.^{2,3} Surgery is the treatment modality used for this type of recurrence when possible.⁴⁻⁷ According to a meta-analysis of 32 studies with a total of 1080 patients, a survival rate of 39% can be expected at 5 years after salvage surgery.⁸ Post-operative reirradiation (reRT) allowed significant improvements in locoregional failure-free survival (LFFS) and disease-free survival (DFS).⁹ Exclusive reRT with palliative or curative intent is also a possible option, particularly when the patient is inoperable or the tumor cannot be removed.^{10,11} Nevertheless, the local relapse rate, especially in the irradiated field, remains high.^{12,13} Moreover, several important trials have shown that reRT for HNC can result in up to 8% treatment-related deaths.^{11,14} In other more recent studies, up to 35% of patients reirradiated with intensity-modulated radiation therapy (IMRT) developed grade 3 toxicities.^{13,15} Several techniques, including proton therapy (PT),¹⁶ stereotactic RT,¹⁷ and brachytherapy¹⁸ could be useful to decrease this risk of frequent and severe toxicities. Our objectives were to analyze management, outcomes and toxicities, including patterns of failure, in patients treated with curative reRT (either by intensity-modulated radiation therapy [IMRT], or by proton therapy [PT]) for recurrent head and neck squamous cell carcinoma (HNSCC).

Material and Methods

Patient population

Among the 55 patients reirradiated with IMRT or PT for recurrent HNC at Institut Curie, 23 suffered from HNSCC. The reRT was delivered after surgery when complete resection was not obtained or without surgery when lesions appeared to be unresectable. The 11 patients in the present series reirradiated with PT had been referred from seven separate institutions and practices to our proton therapy center, most often because additional photon therapy was not deemed feasible. For the patients evaluated at our academic center, the selection of PT as the reRT modality was decided when the dosimetric gains of PT were believed advantageous because photon-based reRT could not adequately cover the reRT target without exceeding the critical normal tissue constraints, or would result in an excessive risk of toxicity. This was most often related to the location of the recurrent disease with the disease adjacent to or involving the skull base. The diagnosis of local relapse had been proven by biopsy or surgical specimen. The initial staging evaluation included clinical examination and magnetic resonance imaging (MRI) or contrast-computed tomography (CT) of the neck, and positron emission tomography (PET) for distant disease assessment. The treatment of each patient was discussed by a multidisciplinary team. This study was approved by the Ethics Committee of the Institut Curie on 7 July 2020 (DATA200213).

Radiation Therapy

All patients underwent simulation for radiation treatment planning purposes, which consisted of the fabrication of a customized thermoplastic mask and a thermoformed mattress for immobilization in the supine position, followed by CT imaging without and with contrast enhancement. The target volume and normal tissue structures were delineated on each axial CT slice, supplemented with fused diagnostic MRI, and/or PET-CT scans. TomoTherapy Hi-Art Treatment System (Accuray, Sunnyvale, CA) or the Eclipse photon therapy treatment planning system (Varian, Palo Alto, CA) was used for the IMRT plans, and the ISOgray (Dosisoft, Cachant, France) or Eclipse proton treatment planning system (Varian, Palo Alto, CA) for PT plans. For patients without upfront salvage surgery, the high-risk CTV (HR-CTV) included the GTV of recurrence with an isocentric margin of 5 mm. For patients irradiated after salvage surgery, the HR-CTV included the tumor bed and involved nodal stations, while the low-risk CTV (LR-CTV) included the nodal stations above and below the involved nodal areas. The dose to the HR-CTV was 59.4–70.2 Gy (1.8-2 Gy/fraction), and the dose to the LR-CTV was 56–59.4 Gy (1.8 Gy/fraction). Patients in the IMRT group received helicoidal IMRT (Tomotherapy), using a simultaneous integrated boost (SIB). For patients treated with PT, the target volumes were treated with 201 MeV proton beams using the passive scattered proton therapy (PSPT) technique (Double Scattering Beam). The RBE used for PT was 1.1. Figure 1 illustrates the plan for IMRT and PSPT reirradiation.

Follow-up

Each follow-up visit included a clinical physical examination. An MRI, CT, and/or PET-CT of the neck was conducted every 6 months during the first 5 years, and every 12 months thereafter or until death. Locoregional failure (LRF) was detected within the head and neck by either clinical examination, imaging, and/or biopsy. The Common Terminology Criteria for Adverse Events, Version 5.0 (CTCAE v5.0), formerly called the Common Toxicity Criteria (CTC or NCI-CTC), were used to assess the late toxicities of RT at each patient visit. For patients with evidence of local-regional recurrence or distant metastasis, additional clinical or imaging examinations were performed to confirm or rule out disease progression at the discretion of the treating physician.

Patterns of failure study

For this section, we used the same approach already applied in three previously published studies.^{12, 19, 20} For all patients with locoregional relapse or second primary HNSCC after reRT, the recurrent tumor volume (Vrecur) was identified on MRI and/or PET scans obtained at the time of diagnosis of recurrence. The contours of this volume were validated for each patient by at least a nuclear physician (LC) and/or a radiologist (CAE) expert in this pathology. 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: the Vrecur was deemed “in-field,” if the majority of Vrecur was within the 95% isodose; “marginal,” if ≤50% of Vrecur was within the 95% isodose; or “outside,” if <20% of the Vrecur was inside the 95% isodose (Figure 2).

Statistical Analysis

Follow-up was calculated from the date of the end of reRT to the last clinical follow-up. The median follow-up was estimated by the inverted Kaplan Meier method. Baseline characteristics were summarized as numbers and percentages for qualitative data, and as means and standard deviations or medians with the minimum and maximum (or inter-quartile range) for continuous variables. The Chi 2 test or Fisher's exact test was used for the analysis of the contingency tables. Overall survival (OS) was defined as the time between the date of the end of reRT and the date of death for deceased patients. Patients still alive were censored at the date of their last news. Locoregional failure-free survival (LFFS), including local and nodal progression, was calculated from the date of the end of reRT until the date of LRF. Disease-free survival (DFS) was calculated as the time between the date of the end of reirradiation and the first event: locoregional or distant relapse or death. In the absence of any event, patients were censored at the date of their last news. Survival distributions were estimated by the Kaplan–Meier method and compared using the log-rank test. Univariate Cox regression models were used to assess the relative influence of prognostic factors. The added value of each variable to the Cox model was determined using a likelihood ratio test. As death is a competing risk for locoregional recurrence, the risk of locoregional recurrence based on the survival analysis was assessed according to methodological recommendations within the framework of competing risks, using cumulative incidence functions and models for the sub-distribution hazards ratio (SHR). A Fine–Gray model was implemented to illustrate the regression models of SHRs. A p value <0.05 was considered statistically significant. Analyses were carried out using software R 3.6.3.21

Results

Patient characteristics

The 23 patients analyzed in this study had HNSCC, including 11 (47.8%) with the undifferentiated carcinoma of nasopharyngeal type (UCNT, World Health Organization type III). Baseline characteristics are summarized in Table 1. The median age of the cohort was 47.1 years old. The main initial disease sites were nasopharynx (N = 14). The main sites of recurrence were the nasopharynx (N = 7), lymph nodes (N = 5) and the oropharynx (N = 5). Recurrences were essentially locoregional and staged III-IVa (N = 16). Nine patients underwent surgery prior to reRT, seven had neoadjuvant chemotherapy (most often combining cisplatin and docetaxel), and six had concomitant chemoradiotherapy (most often cetuximab or cisplatin, Table 2).

Reirradiation treatment details

Reirradiation treatment details are summarized in Table 2. The median time between the two irradiations was 29.3 months (IQR: 15.3–37.2 months). The median maximum dose prescribed to the GTV was 66 Gy (IQR: 60.5–66.6 Gy), median overall treatment time: 54 days (IQR: 48.5–56.5 days), median CTV and PTV volumes: 49.8 cc (IQR: 32.4–88.8 cc) and 124.3 cc (IQR: 76.9–208.6 cc), respectively. Half of the patients received PT (especially recurrent UCNT patients) and the other half received IMRT (Supplementary Table 1). The cumulative dose to the organs at risk (OAR) greatly exceeded the dose usually tolerated for a first irradiation (Table 2). The OAR dose

constraints for reRT were chosen by assuming an empirical “forgetting factor” of 5% per year for nerve structures.²² For other structures, the rule was as low as possible.

Disease Control and Survival Outcomes

After a median follow-up of 41.3 months (range, 19.3–71.4 months), a total of 18 patients (78.3%) had developed a locoregional recurrence. For the whole cohort, 1- and 2-year LFFS were 34.1% [95% CI: 18.8%–61.9%] and 18.3% [7.1%–47.1%], respectively (Figure 3A). There was no difference in LFFS between patients who did undergo surgery before reRT and those who did not (Figure 4A). For the IMRT group, 1- and 2-year LFFS was 12.1% [95% CI: 2.0%–75.0%] and 12.1% [2.0%–75.0%], respectively. For the PT group, 1- and 2-year LFFS was 50.0% [95% CI: 28.4%–88.0%] and 22.2% [0.7%–68.9%], respectively (Figure 5A). Among these 18 patients with locoregional failures (LRF), the LRFs occurred within the 95% isodose lines (in-field recurrences) for eight patients (44.4%) and was out-of-field for seven patients (38.8%) (Figure 2). One patient had marginal LRF and for two patients, LRF was detected by clinical examination only (without imaging before death). There were no differences between the two groups for the proportions of “in field” or “marginal” recurrences.

In the whole cohort, over the follow-up period, 17 patients (73.9%) died. For the whole cohort, 1- and 2-year OS was 60.9% [95% CI: 43.9%–84.5%] and 42.5% [26.2%–69.1%], respectively (Figure 3B). There was no difference in OS between patients who did undergo surgery before reRT and those who did not (Figure 4B). For the IMRT group, 1- and 2-year OS was 27.3% [95% CI: 10.4%–71.6%] and 27.3% [10.4%–71.6%], respectively. For the PT group, 1- and 2-year OS was 91.7% [95% CI: 77.3%–100%] and 55.6% [32.5%–95.0%], respectively (Figure 5B). For the whole cohort, 1- and 2-year DFS was 30.4% [95% CI: 16.4%–56.5%] and 16.3% [6.2%–24.3%], respectively (Figure 3C). For the IMRT group, 1- and 2-year DFS was 9.1% [95% CI: 1.4%–58.9%] and 9.1% [1.4%–58.9%], respectively. For the PT group, 1- and 2-year DFS was 50% [95% CI: 28.4%–88.1%] and 22.2% [7.2%–68.9%], respectively (Figure 5C). DFS was significantly longer in the PT group ($p = 0.031$).

In univariate analysis, the location of the 1st relapse (before reRT), histology, surgery before reRT, chemotherapy before reRT, time between the initial RT and reRT, radiation dose, or radiation volume were not significantly associated with locoregional control and overall survival (Supplementary Table 2). LFFS and OS were higher in the PT group, although the difference was not statistically significant ($p = 0.16$ and $p = 0.17$, respectively).

Acute toxicities

Dysphagia, dysgeusia, dermatitis, mucositis, and hearing loss were the most frequent acute toxicities observed in our cohort. Five patients (21.7%) experienced grade 3 acute toxicity (dysphagia, dermatitis, and mucositis) (Supplementary Table 3). The comparison between patients in the IMRT and PT groups revealed that severe dysphagia (grade >2) was significantly more frequent in the IMRT group ($p = 0.006$). Severe dermatitis was also more frequent in the IMRT group than in the PT group, although the difference was not statistically significant ($p = 0.093$). In contrast, hearing loss was significantly more frequent in the PT group than in IMRT group ($p = 0.004$). This result could be explained by the slightly different locations of the tumors treated with PT (skull base) and those treated with IMRT (see Section 4).

Late toxicities

Fibrosis, dysphagia, xerostomia and trismus were the most frequent late toxicities observed in our cohort (Supplementary Table 4). Ten patients (43.5%) experienced grade 3 late toxicity. Among the 23 patients, three (13%) experienced carotid dissection, one in the IMRT group and two in the PT group. Two were truly radiation induced carotid blowouts, whereas the third was rather related to progression of a tumor that completely encompassed the vessel. These three patients died of cataclysmic hemorrhage. Besides this, two patients had grade 1 (asymptomatic) temporal radionecrosis and three patients had symptomatic temporal radionecrosis (vertigo, headaches). Two patients had asymptomatic osteoradionecrosis and two patients had symptomatic osteoradionecrosis. Two patients from the PT group developed grade 1 permanent facial paralysis. Three patients, from the PT group, developed grade 1 visual impairment.

Late toxicities in the IMRT and PT groups are not comparable from a statistical point of view because the follow-up times after reirradiation were different. A representation of these data as Kaplan Meier curves showed no statistically significant difference between the two groups (Supplementary Figure 1).

Discussion

In the present study, we have reported the outcomes and toxicity of a cohort of patients all reirradiated at curative intent for a large local recurrence of HNSCC.

A recent meta-analysis, which included 17 trials and evaluated reRT with IMRT for HNC, showed that LFFS and OS ranged from 36% to 65%, and from 32% to 59%, respectively.²³ This is consistent to the results obtained in several previously reported studies (Table 3).^{13, 15, 20, 24-36} In the whole cohort of our study, 24-month LFFS and OS were 18.3% and 42.5%, respectively. The difference observed in our series for LFFS could be due to the strict selection of patients with only HNSCC and locally advanced disease (73.9% stage III-IV), with a median reRT CTV and PTV of 49.8 and 124.3 cc, respectively. Indeed, Takiar et al.¹³ showed that local control was more difficult to achieve with HNSCC than with any other histology. Moreover, in a prospective study including 21 patients reirradiated for a recurrence of HNC, Chen et al. showed that the only identified parameter predictive of local recurrence was the planning target volume.²⁷ Patients with a tumor volume >27cm³ had a worse prognosis. Besides this, in the recent MIRI collaborative group's study, surgery, interval between the two courses of irradiation, and organ dysfunction (tumor-related trach or feeding tube dependence) appeared to be prognostic factors for OS.³⁶ From recursive partitioning analysis, the patients with >2 years from the first treatment with resected tumors regardless of final margin status, and without severe dysphagia had the best prognosis. Actually, in the Riaz et al. study,³⁰ surgical resection significantly improved overall survival ($p < 0.001$ in multivariate analysis) and in the Phan et al. study,²⁵ this interval was an independent factor of recurrence. Probably due to the small number of patients included in our study, the salvage surgery and the median time between initial irradiation and reRT were not significantly associated with locoregional control and overall survival. Nevertheless, when we applied the MIRI classes in our population (Supplementary Figure 2), the two patients corresponding to RPA MIRI class III had a significantly shorter 2-years OS than the patients of the two other classes ($p < 0.001$). The 2-years OS of patients in class I and II were not significantly different: 0.5 [95% CI: 18%–100%] and 0.45 [26%–78%]. The number of patients included in our series was probably too small to draw

conclusions about the prognostic difference between class I and II (4 patients in class I). Nevertheless, the OS of patients in class II (17/23) was similar to that observed in the MIRI study (0.40 [CI: 33.9%–47.2%]). It is interesting to note that the 11 patients of our cohorts re-irradiated with proton belonged to this MIRI RPA class II. Although not statistically significant, the 2-years OS of patients in this class II re-irradiated with proton was better than that of patients in this class II re-irradiated with photon: 0.53 [95% CI:0.30–0.94] and 0.33 [0.15–0.74], respectively (Supplementary Figure 3).

In our cohort, fibrosis, dysphagia (26.1% grade \geq 3), xerostomia and trismus were the most frequent late toxicities, and three patients experienced carotid dissection. Whatever the indication for reRT, acute and especially late toxicities were much more frequent and more severe than after the first irradiation. For instance, in the RTOG 9911 trial reporting the outcomes of 105 patients who received IMRT for a recurrent HNC, the incidence of grade 3/4 late adverse effects was 33.8%, and the incidence of treatment-related deaths was 8%.¹⁴ In the Takiar et al. study,¹³ 5-year \geq grade 3 toxicities were about 50%, and three patients experienced grade 5 toxicity (death). The most common grade 3 toxicities were dysphagia, odynophagia requiring feeding tube placement, osteoradionecrosis, and esophageal stricture. In the meta-analysis of Lee et al.,³⁶ grade \geq 3 late toxicities ranged from 14.2% to 57.1%, whereas grade 5 late toxicities ranged from 1.3% to 7.4%. The most common cause of grade 5 complications was carotid rupture, followed by soft tissue necrosis. Furthermore, Romesser et al.³⁷ have recently shown that PT is a safe alternative to IMRT as it reduces the risk of late toxicity. In our cohort, dysphagia was more frequent in the IMRT group, whereas hearing loss and temporal radionecrosis were more common in the PT group. This can easily be explained by the location of the reirradiated recurrence: the tumors treated with PT were more frequently in the skull base, whereas the tumors treated with IMRT were often close to the pharyngeal muscles.

To our knowledge, there are currently no dose constraints specific to the context of reirradiation for curative purposes for HNC. In the Takiar et al. study,¹³ dose constraints are often at the discretion of the clinician (except for the parotid: Mean dose <26Gy). In our cohort, cumulative doses to OAR often far exceed the recommended dose constraints for initial irradiation. For example, the average dose received by the parotid glands was 64Gy [range: 23–120] while the dose usually recognized as causing severe xerostomia is 26Gy.³⁸ In a recent study, Embring et al. showed an association between the cumulative dose to (OAR) and the risk of developing osteoradionecrosis and carotid blowout. Their results supported the existing dose constraint for the carotid arteries and bones of 120Gy.³⁹ Furthermore, in our study, the OAR dose constraints for reRT were chosen by assuming an empirical “forgetting factor” of 5% per year for nerve structures.²² This is in agreement with the approach used by Takiar et al. that applied a dose tolerance recovery of 50% for a retreatment interval \geq 12 months.¹³ Besides this, it should be noted that in our study, at least for hearing loss, the majority of patients had hearing loss before the start of reRT, and the dosimetric study confirmed that the dose to the inner ear was very low during reRT. From these results, it seems important to take into account the doses received during the first irradiation when planning the re-irradiation.

Moreover, in our study, among the 18 patients with locoregional failures (LRF), the LRFs occurred within the 95% isodose lines (in-field recurrences) for eight patients (44.4%) and was out-of-field for seven patients (38.8%). These results are consistent with the recent pattern-of-failure study of Margalit et al who reported that

approximately half of these second local recurrences occurred within the re-irradiated GTV, while the other half occurred outside the field (34%) or at the margin (14%) of the isodose line of prescription.²⁰In this particular context of reRT, the target volumes were chosen to be as small as possible in order to limit the dose to OAR as much as possible. In most cases, CTVs include the GTV/ tumor bed with no margin or with a narrow margin (≤ 0.5 cm) of normal-appearing surrounding tissue.¹² Moreover, multimodal imaging and radiomics could be very useful to help define target volumes with respect to potential sites of recurrence. For instance, Akram et al.⁴⁰ compared on MRI the recurrent and the non-recurrent regions of 14 NPC patients with histologically proven “in field” recurrence following curative intent IMRT. Seven features were significantly different between recurrent and non-recurrent regions, suggesting that these features may help to better define the target volume before irradiation. Thus, to reduce the risk of second recurrences, especially marginal recurrences, it seems very useful to define this target volume with the help of a radiologist and, in the postoperative setting, with the surgeon.

The main limitations of our series are that it is retrospective, single-center and included a small number of patients. This small number of patients is explained by the rigorous selection procedure: all included patients had to have been treated for an HNSCC with curative intent, and to have a minimum follow-up of 4 months. In addition, more than half of the patients were treated with proton therapy for advanced recurrence of skull base disease. Finally, we studied clinical features, such as disease control and toxicity, and conducted a detailed search for patterns of failure as well as a dosimetric study to understand the toxicity observed.

As a conclusion, curative reRT in HNC is possible for selected cases, but the local recurrence rate in the irradiated field and the risk of toxicity grade ≥ 2 remain high. Improved selection criteria and more precisely defined target volumes may improve the outcomes of these patients. Proton therapy, essentially for skull base tumors, seems to procure improved locoregional control and overall survival compared to IMRT. These results require confirmation in a prospective randomized study.

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Table 1: Characteristics of the 23 reirradiated patients

Characteristics	Nb	%
Age (mean, range)	47.1 (19.1 – 78.5)	
Gender		
Male	17	73.9
Female	6	26.1
ECOG		
2	1	4.3
1	2	8.7
0	20	87
Histology		
Squamous cell carcinoma	12	52.2
Undifferentiated carcinoma (UCNT)	11	47.8
Initial disease site		
Nasopharynx	14	61
Oropharynx	3	13
Nasal cavity and paranasal sinus	3	13
Larynx	2	8.7
Skin	1	4.3
Surgery before first irradiation	6	26.1
Time elapsed since previous irradiation (months, [median, IQR])	29.3 (15.3 – 37.2)	
Previous treatment course technique		
3D-CRT	6	26.1
IMRT	4	17.4
Tomo/VMAT	13	56.5
Previous treatment course RT total dose (Gy, [median, range])	70 (60 – 70)	
Retreatment disease site		
Nasopharynx	7	30.6
Nodes (upper jugular group, retropharyngeal, retrostyloid)	5	21.7
Oropharynx	5	21.7
Skull base	3	13
Nasal cavity and paranasal sinus	3	13
rTNM (stage)		
I	2	8.7
II	4	17.4
III	6	26.1
IVA	10	43.5
IVB	1	4.3
Chemotherapy regimen		
Induction	7	30.4
Induction. concomitant	1	4.3
Concomitant	6	26.1
No chemotherapy	11	47.8
Surgery before reirradiation	9	39.1

rT stage: T status at the time of reirradiation, rTNM (stage): TNM status at the time of reirradiation

Table 2: Reirradiation treatment details.

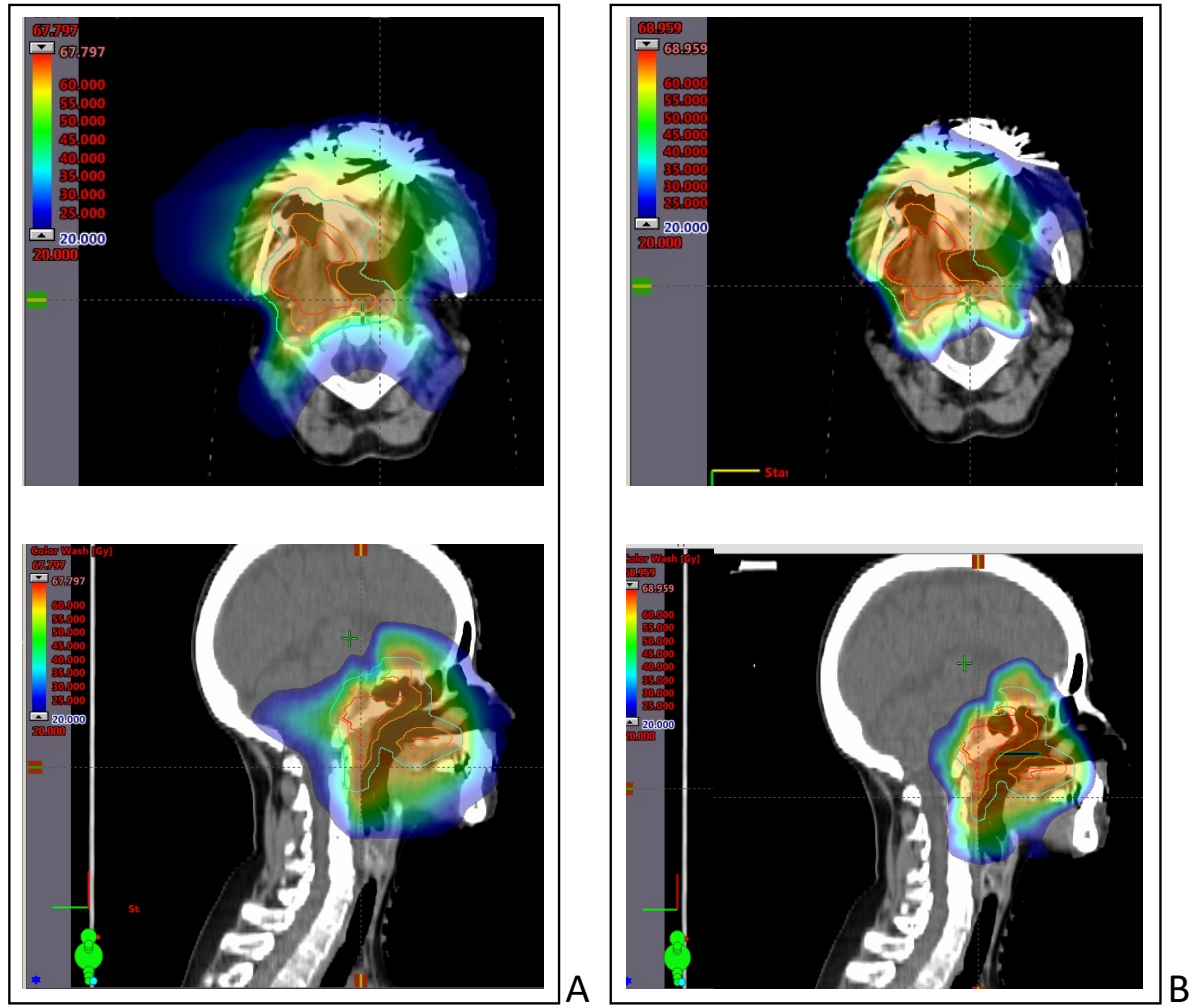
Characteristics	Nb	%
reRT Volumes		
CTV (cc, [median, IQR])	49.8 (32.4 – 88.8)	
PTV (cc, [median, IQR])	124.3 (76.9 – 208.6)	
reRT techniques		
Photon	11	47.8
IMRT	2	18.2
Tomotherapy	9	81.8
Proton (PSPT)	12	52.2
reRT total dose (Gy, [median, IQR])	66 (60.5 – 66.6)	
Overall treatment time during reRT (days, [median, IQR])	54 (48.5 – 56.5)	
Dose in target volumes		
D _{95%} CTV (Gy, [median, IQR])	60.5 (56.2 – 65.6)	
D _{95%} PTV (Gy, [median, IQR])	55.5 (51.3 – 60.4)	
Dose in organ at risks (Gy, [median, IQR])*		
Maximum cumulative chiasm (D _{2%})	47.7 (10.6 – 52.3)	
Maximum cumulative ipsilateral optic nerve (D _{2%})	53.4 (17.8 – 62)	
Maximum cumulative contralateral optic nerve (D _{2%})	50.0 (22.5 – 62.5)	
Maximum cumulative ipsilateral temporo-mandibular joint (D _{2%})	77.6 (68.1 – 77.6)	
Maximum cumulative contralateral temporo-mandibular joint (D _{2%})	61.4 (53.1 – 67.4)	
Avg cumulative ipsilateral inner ear	49.0 (36.2 – 66.8)	
Avg cumulative contralateral inner ear	38.6 (29.5 – 48)	
Maximum cumulative ipsilateral inner ear (D _{2%})	60.1 (45.1 – 79.6)	
Maximum cumulative contralateral inner ear (D _{2%})	45.9 (38.6 – 53.6)	
Avg cumulative ipsilateral temporal lobe	19.1 (8.5 – 29.8)	
Avg cumulative contralateral temporal lobe	16.1 (8 – 25.4)	
Maximum cumulative ipsilateral temporal lobe (D _{2%})	89.2 (59.3 – 126.6)	
Maximum cumulative contralateral temporal lobe (D _{2%})	85.0 (68.5 – 102.9)	
Maximum cumulative brainstem (D _{2%})	63.6 (54.3 – 69.0)	
Maximum cumulative spinal cord (D _{2%})	48.0 (37.9 – 54.1)	
Avg cumulative ipsilateral parotid	64.7 (39.9 – 74.2)	
Avg cumulative contralateral parotid	36.2 (28.8 – 58.8)	
Avg cumulative oral cavity	63.6 (54.3 – 69.0)	
Maximum cumulative mandibula (D _{2%})	120 (103.6 – 126)	
Avg cumulative ipsilateral carotid	74.7 (61.9 – 84)	
Avg cumulative contralateral carotid	62.1 (56.1 – 72.9)	
Avg cumulative pharyngeal constrictor muscles	75.4 (57.4 – 93)	
Maximum cumulative ipsilateral brachial nerve plexus (D _{2%})	61.5 (58.3 – 73.3)	
Maximum cumulative contralateral brachial nerve plexus (D _{2%})	59.0 (55.2 – 65.5)	

Abbreviations: reRT: reirradiation, 3D-RT: three-dimensional RT, IMRT: intensity-modulated RT, PSPT: passive scattered proton therapy, avg: average. D_v: the absorbed dose that covers a specified fractional volume V. For instance, D_{95%} CTV is the minimum absorbed dose that covers 95% of the volume of the CTV. * physical doses without using the “forgetting factor”.

Table 3: Prognostic factors related to locoregional control and overall survival

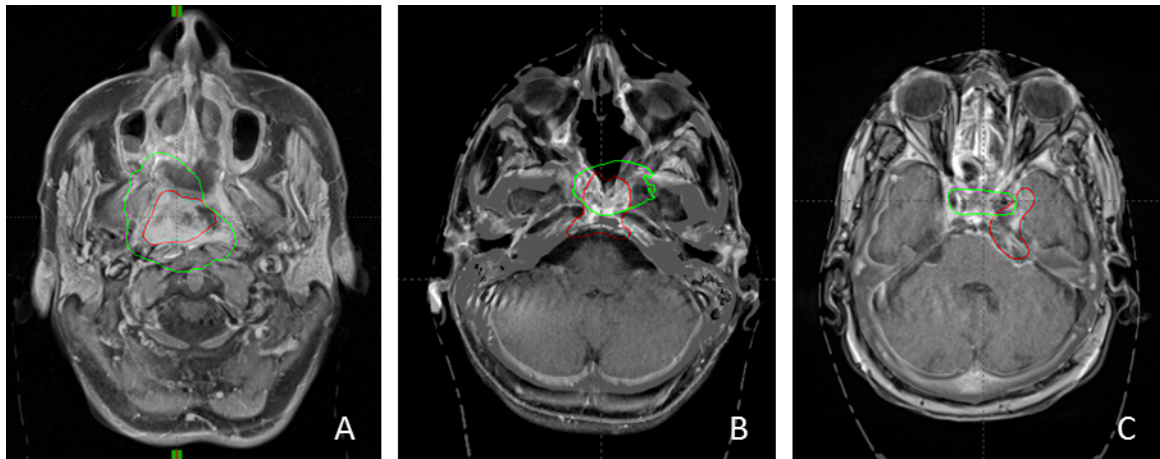
Variable	Locoregional control				Overall survival			
	n	HR	CI95% (HR)	p value	n	HR	CI95% (HR)	p value
<i>Location of 1st relapse (before reRT)</i>								
Nasopharynx/skull base	10	1		0.376	10	1		0.414
Nodes	5	1.56	[0.46 - 5.24]		5	0.83	[0.23 - 3.01]	
Oropharynx	5	2.11	[0.58 - 7.69]		5	0.86	[0.17 - 4.32]	
Other	3	0.52	[0.1 - 2.64]		3	2.22	[0.66 - 7.48]	
<i>Histology</i>								
SCC	12	1		0.418	12	1		0.361
UCNT	11	0.68	[0.27 - 1.74]		11	0.64	[0.24 - 1.68]	
<i>Surgery before reRT</i>								
No	14	1		0.284	14	1		0.242
Yes	9	1.68	[0.64 - 4.42]		9	1.78	[0.67 - 4.74]	
<i>Chemotherapy before reRT</i>								
No	16	1		0.703	16	1		0.542
Yes	7	0.82	[0.31 - 2.22]		7	0.72	[0.25 - 2.08]	
<i>Intervals between initial RT and reRT</i>	23	1	[1 - 1.01]	0.86	23	1	[0.99 - 1]	0.632
<i>ReRT technique</i>								
Protons	12	1		0.16	12	1		0.173
Photons	11	2.24	[0.86 - 5.83]		11	1.95	[0.74 - 5.16]	
<i>Cumulative dose (1st RT et reRT)</i>	23	0.94	[0.84 - 1.05]	0.256	23	0.95	[0.84 - 1.08]	0.451
<i>Volumes (reRT)</i>								
CTV	23	1.01	[1 - 1.01]	0.002	23	1.01	[1 - 1.01]	0.006
PTV	23	1	[1 - 1.01]	0.198	23	1	[1 - 1]	0.9
Target volume coverage: V95% CTV	23	0.19	[0.01 - 4.21]	0.284	23	0.37	[0.01 - 9.55]	0.545
Target volume coverage: V95% PTV	23	0.44	[0.02 - 11.46]	0.618	23	0.22	[0.01 - 6.15]	0.366

Figure 1



Dosimetric comparison between IMRT and proton-therapy. This figure shows a comparison between IMRT (A) and proton-therapy (B) for the same patient. The warm and cold colors represent the highest and lowest doses, respectively.

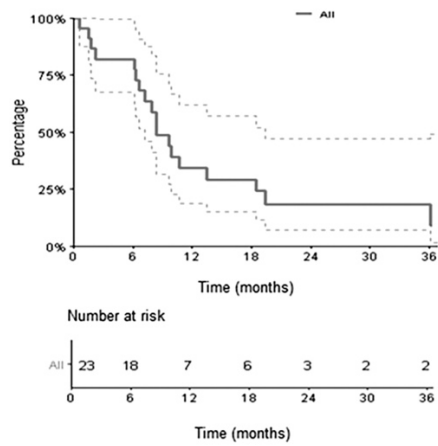
Figure 2



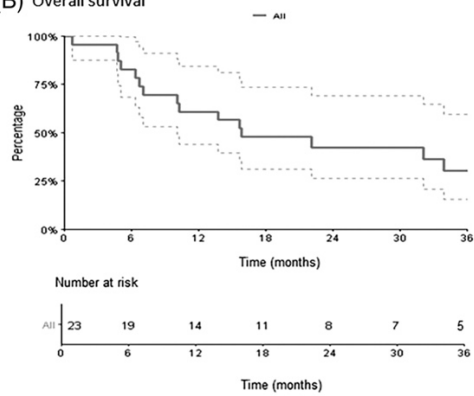
Pattern of failure study. The locations of the second recurrences (red line) were compared to the 95% isodose of the reirradiated GTV (green line) and classified as “in-field” (A), “marginal” (B), or “outside” (C).

Figure 3

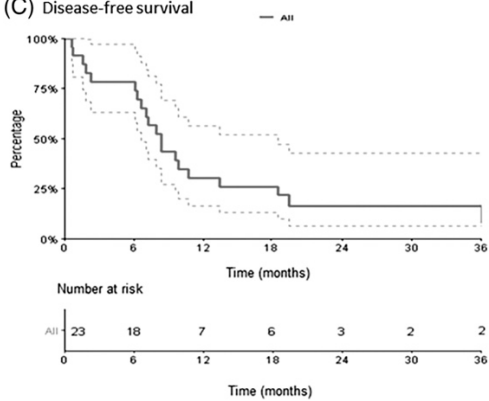
(A) Locoregional failure-free survival



(B) Overall survival



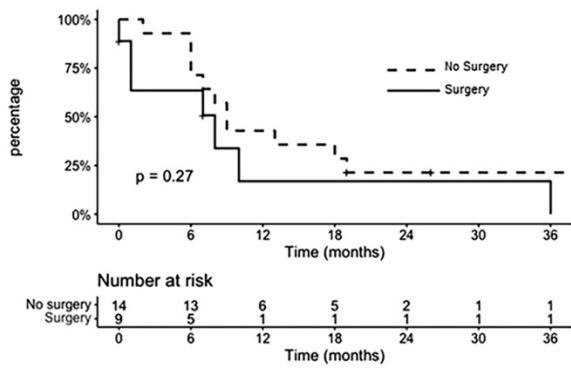
(C) Disease-free survival



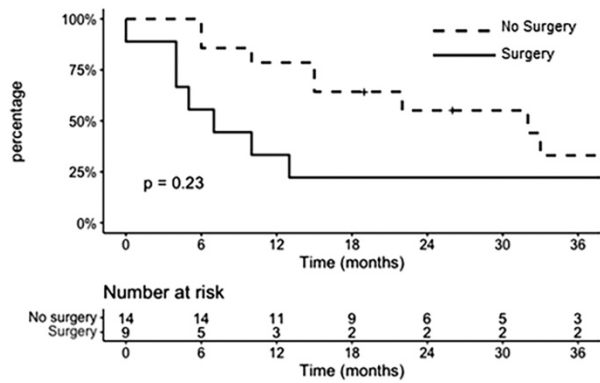
Kaplan-Meier curves in the whole cohort. (A) Locoregional failure-free survival; (B) overall survival; and (C) disease-free survival.

Figure 4

(A) Locoregional failure-free survival



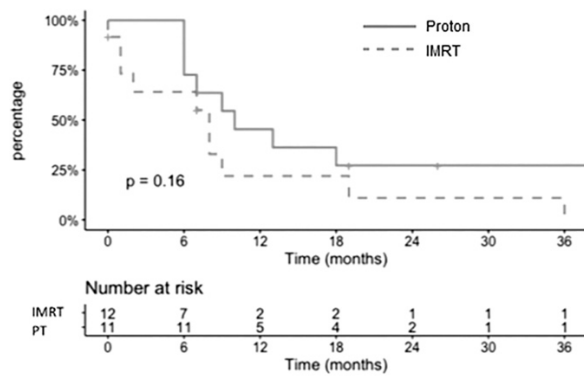
(B) Overall survival



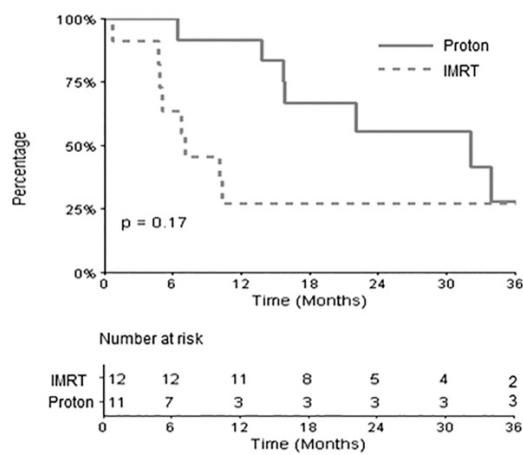
Kaplan-Meier curves comparing operated with nonoperated groups. (A) Local failure-free survival and (B) overall survival.

Figure 5

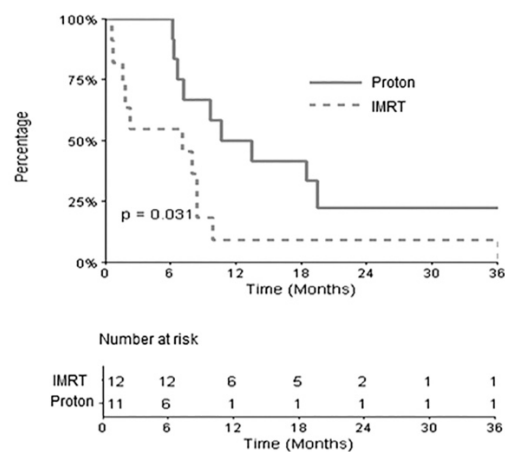
(A) Locoregional failure-free survival



(B) Overall Survival



(C) Disease-free survival



Kaplan-Meier curves comparing IMRT with PT groups. (A) Locoregional failure-free survival; (B) overall survival; and (C) disease-free survival.