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Curative high-dose reirradiation for patients with recurrent head and neck adenoid cystic carcinomas: outcomes and analysis of patterns of failure

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Abstract

Background: To investigate the outcomes of patients who underwent curative reirradiation (reRT), with intensity-modulated radiation therapy (IMRT) or proton therapy (PT) for unresectable recurrent or second primary head and neck adenoid cystic carcinoma (HNACC).

Methods: Ten patients, mostly KPS 90%, were reirradiated (3/10 with IMRT and 7/10 with PT) at a median maximum dose to the CTV of 64.2Gy from July 2011 to November 2021. Locations at the time of reRT were mainly the sinus (4/10) and the salivary glands (including the parotid and submandibular gland, 3/10). CTCAEv5 was used to assess acute and late toxicities. Follow-up was the time between the end of reRT and the date of last news.

Results: The median time between the two irradiations was 53.5months (IQR: 18–84). After a median follow-up of 26months (range, 12.5–51.8months), six patients had developed a locoregional recurrence (LR), of which four occurred within the previously irradiated volume. Two and three-year locoregional failure-free survival (LFFS) and overall survival (OS) were 55.6% [95%CI: 31–99.7%], and 41% [18.5–94%] and 66.7% [42–100%] and 44.4% [21.4–92.3%], respectively. LFFS and OS were significantly better in the subgroup of sinus tumors ($p=.013$) and the subgroup of patients re-irradiated more than two years after the first course of irradiation ($p=.01$). Seven patients had impairments before the start of reRT, including hearing impairment (3/10) and facial nerve impairment (3/10). The most severe late toxicities were brain necrosis (2/10), osteoradionecrosis (1/10) and vision decreased (1/10).

Conclusion: Curative reRT for HNACC is possible for selected cases, but the LR rate in the irradiated field and the risk of severe toxicity remain high. Improved selection criteria and more carefully defined target volumes may improve outcome in these patients. A further study including larger cohort of patients would be useful to confirm these results.

1. Introduction

Adenoid cystic carcinoma (ACC) is a rare tumor, representing 1% of all head and neck cancers, and is usually located in the salivary gland (Ellington et al. 2012; Lorini et al. 2021). Local recurrence (LR) of head and neck adenoid cystic carcinomas (HNACC) after initial curative radiation therapy (RT) are frequent. Patients treated for the first episode of HNACC have 40% risk of locoregional recurrence and 60% risk of metastatic recurrence (Lorini et al. 2021). Therefore, postoperative RT is often indicated for patients with HNACC, especially in incomplete surgical resection, invaded close margins, and presence of perineural invasion (Garden et al. 1997). In a recent study, Sulaiman et al. have reported a 5-year local control rate after surgery and RT with carbon of 68%. In this complex situation of recurrent HNACC, salvage surgery is often complex because of skull base invasion and proximity to neurological structures, such as the brain stem or cranial nerves. Furthermore, systemic therapies in this recurrent setting have not achieved objective response rates above 30% (Dreyfuss et al. 1987). Curative re-irradiation (reRT) for patients with recurrent HNACC is also challenging given the high dose received during the first irradiation (>70Gy) (Garden et al. 1997) and, therefore, a high risk of severe acute and late toxicities. Nevertheless, new RT techniques, including stereotactic body radiation therapy (SBRT) (Yamazaki et al. 2022), carbon ion therapy (Jensen et al. 2015) and proton therapy (PT), have improved the sparing of organs at risk (OAR) compared to intensitymodulated radiation therapy (IMRT, Figure 1). Furthermore, reRT with PT seems to be a safe and effective strategy for the management of recurrent head and neck squamous cell carcinoma (HNSCC) at curative intend (Phan et al. 2016; Romesser et al. 2016; Beddok et al. 2022). Recent European (Andratschke et al. 2022) and international (Ward et al. 2022) guidelines proposed some recommendations for the reRT of head and neck cancer (HNC), but the management of the specific ACC histology remains unclear. The objective of this study was to analyze the outcomes, including patterns of failure and toxicity of curative high doses reRT for a homogeneous series of patients with recurrent HNACC.

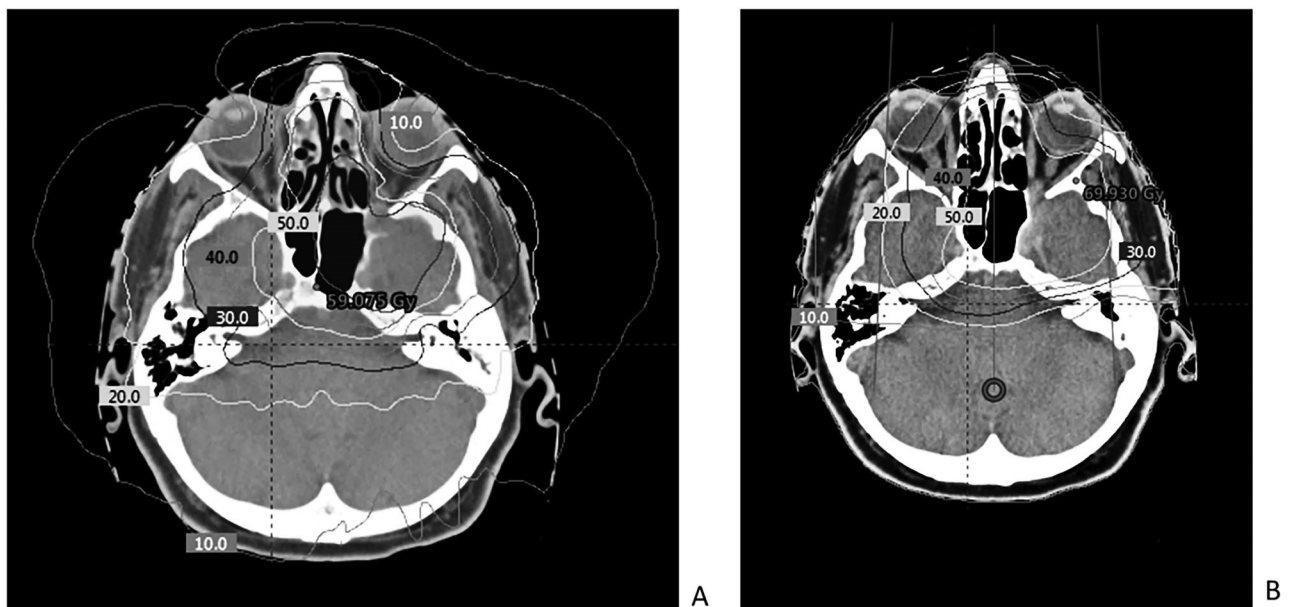


Figure 1. Comparison of TomoTherapy and proton therapy plans for reRT of recurrent HNACC. The image on the left (A) shows the reRT plan of a patient treated with TomoTherapy for recurrent HNACC of the ethmoidal sinus. The right image (B) indicates the reRT plane of a patient treated with proton therapy for recurrent

ethmoidal sinus CCA. The isodose lines shown (10, 20, 30 Gy) illustrate the better preservation of healthy tissue with proton therapy than TomoTherapy, particularly for the cerebellum and temporal lobes, which may reduce the risk of brain necrosis.

2. Materials and methods

2.1. Patients

All patients reirradiated at curative doses for a recurrent HNACC at the Institut Curie between 2011 and 2022 were eligible for the study. Among the 55 patients reirradiated with IMRT or PT for recurrent head and neck cancer at Institut Curie in this period, 15 had HNACC, but five of them were excluded of the study because of palliative doses at reRT. Therefore, ten patients treated with curative doses were analyzed. ReRT with curative intent was defined as previously (Ward et al. 2018) as having a primary treatment of 60 Gy and a second treatment with an overlapping volume of 40 Gy, resulting in a volume with a cumulative dose of 100 Gy. All first recurrences were diagnosed before reRT with biopsy or any histological confirmation. Initial staging assessment, prior to reRT, included a clinical examination and magnetic resonance imaging (MRI) or contrast tomography (CT) of the neck, and positron emission tomography (PET) for evaluation of distant disease. The reRT was delivered after incomplete resection or was definitive if unresectable disease. Some patients had received a first course of irradiation in another hospital and were referred to the proton center, based on the proximity of the recurrence and the cranial pairs or the skull base. For each patient, treatment strategy was discussed during multidisciplinary meeting. This study was approved by the Ethics Committee of the Institut Curie on 7 July 2020 (DATA200213). Patients who had not indicated their nonopposition to the use of data concerning them were excluded.

2.2. Radiotherapy

Each patient underwent simulation for RT planning purposes, which consisted of the fabrication of a customized thermoplastic mask and a thermoformed mattress for prone immobilization, followed by non- and contrast-enhanced CT imaging. The target volume and normal tissue structures were delineated on planning CT after fusion with MRI. TomoTherapyVR Hi-ArtVR Treatment System (Accuray, Sunnyvale, California, USA) or the EclipseVR photon therapy treatment planning system (Varian, Palo Alto, California, USA) was used for the IMRT plans, and the ISOgrayVR (Dosisoft, Cachan, France) for PT plans. For patients without upfront salvage surgery, the Clinical Target Volume (CTV) included the Gross Tumor Volume (GTV) of recurrence, with a margin of 5 mm in soft tissue and 3 mm in the skull base. For patients undergoing reRT post-salvage surgery, the CTV was designed to encompass the tumor bed and, in cases of macroscopic nodal involvement, the involved nodal regions. An isocentric margin of 3 mm around the CTV was added to construct the Planning Target Volume (PTV). Patients in the IMRT group received helicoidal IMRT (TomoTherapy) using simultaneous integrated boost (SIB). For patients treated with PT, the target volumes were treated with 201 MeV proton beams using passive scattered proton therapy (PSPT) (Double Scattering Beam). The Relative biological effectiveness (RBE) used for PT was 1.1. Currently, dose constraints for OAR in this specific context of reRT have not yet been established (Ward et al. 2022). Therefore, for each patient, the electronic dosimetric data of the first irradiation was collected and summation with the reRT plan was performed to determine the cumulative doses to organs at risk (OAR). For nerve structures, a ‘forgetting factor’ of 5% per year was applied (Noël and Antoni 2022).

2.3. Pattern of failure study

For this section, we used the same approach already applied in three previously published studies (Popovtzer et al. 2009; Margalit et al. 2016; Beddok et al. 2022). For all patients with

a second locoregional recurrence or second primary HNACC after reRT, the recurrent tumor volume (Vrecur) was identified on MRI and/or PET scans obtained at the time of diagnosis of the recurrence. The contours of this volume were validated for each patient by at least one nuclear physician (LC) and/or radiologist (CAE) expert in this pathology. The exact site and extent of each tumor was then visually compared to the pretreatment planning CT datasets, focusing on the 95% isodose lines. The second recurrences were classified according to previously published criteria as occurring within or outside of previously irradiated targets: the Vrecur was deemed 'in-field' if >50% of the Vrecur was within the 95% isodose; 'marginal' if 50% of the Vrecur was within the 95% isodose; or 'outside' if less than 20% of the Vrecur was within the 95% isodose.

2.4. Follow-up

Each follow-up visit included a clinical physical examination. MRI, CT scan, and/or PET-CT of the neck were performed every 6 months for the first 4 years. Locoregional failure (LRF) was detected in the head and neck by clinical examination, imaging, and/or biopsy. Common Terminology Criteria for Adverse Events, Version 5.0 (CTCAE v5.0) were used to assess late RT toxicities at each patient visit. For patients with evidence of second locoregional recurrence or distant metastases, additional clinical or imaging studies were performed to confirm disease progression at the discretion of the treating physician.

2.5. Statistical analysis

Follow-up was calculated from the date of the end of reRT to the last clinical follow-up. 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. To compare the means between groups, Wilcoxon rank-sum tests was applied. For analyzing contingency tables, the Chi-square test was used. 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. Progression-free survival (PFS) was calculated as the time between the date of the end of reRT 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. A p value less than 0.05 was considered statistically significant. Analyses were carried out using software R 3.6.3. (R Core Team 2020).

3. Results

3.1. Population characteristics

Baseline characteristics of the 10 included patients are summarized in Table 1. The median age was 52. The main initial disease sites were the oral cavity (N¼ 3) and the salivary glands (including two in the parotid and one in the submandibular gland). Initial staging was mostly T3–T4 (N¼ 6) and N0 (N¼ 9). Most of the patients had high-grade HNACC (70%). The main sites of first recurrence were the sinus (N¼ 4) and the salivary glands (including 2 parotid and 1 submandibular gland). Four patients underwent surgery prior to reRT, all with positive microscopic margin status (R1 resection), and two patients had neoadjuvant chemotherapy.

3.2. Treatment details

ReRT treatment details are summarized in Table 2. Median time between the two irradiations was 53.5 months (IQR: 18 – 84 months). The median maximum dose prescribed to the GTV was 72 Gy (IQR: 62.6–73.8 Gy), median overall treatment time: 58.5 days (IQR: 51.7–61.7 days), median CTV and PTV, volumes: 85.9 cc (IQR: 18.1 – 145 cc) and 162.9 cc (IQR: 56.3–235.7 cc), respectively. The median CTV of patients who had surgery prior to re-irradiation was 69.6 cc (Interquartile Range (IQR): 21.7–190.8), while for those who did not have surgery, it was 85.9 cc (IQR: 68.9–100.7). This difference was not statistically significant ($p \geq 1$, Wilcoxon test). Most patients (N¼ 7) were reirradiated with proton (PSPT). The OAR dose constraints for reRT were chosen by assuming an empirical ‘forgetting factor’ of 5% per year for nerve structures [13]. For other structures. The rule was as low as possible. A summary of cumulative dose to OAR was reported in Table 2, and details for the first and second recourse irradiation in the Supplementary Data 1.

3.3. Disease control and survival outcomes

After a median follow-up of 26 months (range, 12.5–51.8 months), a total of six patients (60%) had developed a locoregional recurrence. The 1-, 2-, and 3-year LFFS were 66.7% [95% CI: 42–100%], 55.6% [31–99.7%], and 41% [18.5–94%], respectively (Supplementary Data 2(A)). Among these six patients with locoregional failures (LRF), the LRFs occurred within the 95% isodose lines (in-field recurrences) for four patients (66.6%) and was out-of-field for two patients (33.4%). The majority (5/6) of these LRF were treated with chemotherapy. The risk of local recurrence did not significantly differ based on whether the tumor was of high or low grade ($v^2 \geq 0.14$, $p \geq 0.7$). Moreover, over the follow-up period, 8 patients (80%) died. The 1-, 2-, and 3-year OS were 77.8% [95% CI: 54.9–100%], 66.7% [42–100%], and 44.4% [21.4–92.3%], respectively (Supplementary Data 2(B)). Over the follow-up period, 5/10 patients developed distant metastasis. The 1-, 2-, and 3-year PFS were 57.1% [95% CI: 32.6–100%], 45.7% [22.4–93.2%], and 30.5% [10.4–89%], respectively (Supplementary Data 2(C)). In univariate analysis, surgery before reRT, radiation dose, or radiation volume were not significantly associated with locoregional control and overall survival. LFFS were significantly better in the subgroup of patients reirradiated for sinus tumors ($p \geq 0.013$) and the subgroup of patients reirradiated more than two years after the first course of irradiation ($p \geq .03$, Supplementary Data 3).

3.4. Toxicity

Most acute toxicities were grade 1 dysgeusia (40%), grade 1 dysphagia (20%), grade 1 mucositis (40%) and grade 1 dermatitis (40%) (Supplementary Data 1). None treatment interruption was observed. One patient had a grade 2 acute hearing impairment. No patient needed nutritional support during the treatment and no significant loss of weight (>5%) was noticed.

Late toxicities were mostly grade 1 xerostomia (20%) and grade 2 neck fibrosis (20%, Table 3). Three patients (30%) had late facial paralysis (grade 3) or late paralysis of other nerves (20%), however, all of these were postoperative complications prior to the start of reRT (called impairments before the reirradiation in Table 3). One patient developed grade 4 obituary osteoradionecrosis associated with a grade 3 brain necrosis. This patient received two courses of PT for an adenoid cystic carcinoma of the lachrymal gland and each RT was postoperative. One patient treated for an adenoid cystic carcinoma of the parotid gland and reirradiated in the parotid loge also developed a grade 3 brain necrosis. A grade 3 trismus was observed in a case of patient treated for a maxillary sinus carcinoma and reirradiated for a palatine relapse but this patient had a grade 2 trismus before the start of the reRT. This study did not find any death for treatment complications; every death was the consequence of the progression of the disease, except for one patient who died from COVID-19.

4. Discussion

The present study reported the outcomes and toxicity of ten patients all reirradiated at curative intent for a recurrent HNACC. Most of them were reirradiated with proton therapy. To date, four studies have evaluated the outcomes and toxicity of patients re-irradiated for recurrent head and neck cancer, including a majority of HNACC (100% HNACC in Jensen et al.'s study), all with carbon ion radiation therapy (CIRT) (Jensen et al. 2015; Hayashi et al. 2019; Held et al. 2019; Vischioni et al. 2020) (Table 4). In these four studies, the median dose for the reRT was lower than the dose used in the present study: 51 – 63 vs. 72Gy RBE, respectively. Patient's characteristics of Jensen et al.'s study were similar to the patients included in the present study regarding the median age (55years old) and the tumors stages (most locally advanced tumors) (Jensen et al. 2015). However, some differences were identified between Jensen et al.'s study and the present study for the number of operated patients: 93.5 vs. 50%, the most frequent reirradiated location: paranasal sinuses vs. oral cavity, the volume of the PTV (median, IQR): 93cc (9 – 618) vs. 162.9cc (56.3 235.7), and the median reRT total dose: 63Gy vs. 72Gy, respectively.

In the present study, the 1-year LFFS and OS were found to be 66.7 and 77.8%, respectively. Most of the locoregional recurrences observed in the present study were 'in-field'. which is consistent with the findings of the four CIRT studies. Moreover, in the present study, LFFS and OS were significantly better in the subgroup of patients reirradiated for sinus tumors ($p = .013$). This is consistent with the study of Jensen et al. that included a majority of paranasal sinus tumors and observed a 1-year LFFS and OS were 70.3 and 81.8%, respectively. Besides this, patients re-irradiated more than two years after the first irradiation were found to have a better prognosis than patients re-irradiated less than two years after the first irradiation. This is consistent with the four CIRT studies in which a short interval between the two courses of RT was associated with less favorable outcomes. Indeed, Held et al. have reported in a multivariate analysis that an interval > 12 months between the two courses of irradiation was a significant prognostic factor for improved LFFS and OS: HR $\frac{1}{4}$ 0.284 [95% CI:0.116–0.697], ($p < .006$) and HR $\frac{1}{4}$ 0.326 [95% CI: 0.169–0.626], ($p < .001$), respectively (Held et al. 2019). In Hayashi et al.'s study, the 2-year PFS and OS rates of an interval <24 months versus > 24 months were 20.8 versus 38.3%, and 37.5 versus 82.7%, respectively (Hayashi et al. 2019). Furthermore, Ward et al. identified prognostic subgroups for the reRT of HNSCC (Ward et al. 2018) and identified three prognostic subgroups with distinct OS: Class I included patients >2 years after the first RT associated with resection, class II patients >2 years with unresected tumors or those 2 years and without a feeding tube or tracheostomy dependence and class III for other patients. Consequently, whatever the histology, a short interval between the two irradiations seems to be a factor of poor prognosis. Recent European recommendations advise avoiding reRT of patients for whom local recurrence occurs less than six months after the first course of RT [10].

In the present study, despite the high cumulative dose to OAR (Table 2), the number of patients who developed severe late toxicity was relatively low and consistent with previously reported data (Dionisi et al. 2019). The main > grade 2 late toxicity were: brain necrosis (2), optic nerve disorder (1), facial nerve paralysis (1), hearing loss (1), osteonecrosis (1), and trismus (1). This is consistent with the toxicity observed in the four CIRT studies (Table 4). The relatively small number of patients who developed severe dysphagia with weight loss in our series compared to series with HNSCC (Phan et al. 2016) can be explained by the location of the re-irradiated tumors: the tumors were more often close to the skull base, and thus

reirradiation resulted in a lower dose to the pharyngeal constrictor muscles. Moreover, several dosimetry and clinical studies have demonstrated the value of proton therapy compared to IMRT in reducing the risk of severe dysphagia (Blanchard et al. 2018). It should also be noted that the majority of severe late toxicities were present as an impairment before the start of the reirradiation (Table 3). It should be noted that the estimates of toxicity in the present study may be lower than the actual risk, as the observed high mortality rate in the study (80% over the follow-up period) poses a competing risk. This potentially results in an underestimation of late toxicity rates and should be considered when interpreting the results.

The main limitations of the present series are that it is a retrospective study, performed in a single center and included a small number of patients. This small number of patients analyzed can be explained by the rare histological type and the extremely rare cases of reRT at curative doses.

5. Conclusion

This study demonstrated the feasibility of curative re-irradiation for recurrent HNACC. The results seem to be better for patients with a long interval between the two irradiations. Despite the use of modern techniques such as proton therapy, the risk of severe toxicity remains high. It would be useful to develop new tools to better select patients who will really benefit from this treatment.

Ethical approval

This study was approved by the Ethics Committee of the Institut Curie on 7 July 2020 (DATA200213).

Disclosure statement

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Table 1 : Population details

	Number	%
Gender		
Male	5	50
Female	5	50
Age (median, range)	52 (29-77)	
Initial disease site (before the first irradiation)		
Oral cavity	3	30
Salivary gland (including parotid and submandibular gland)	3	30
Sinus	2	20
Lachrymal gland	2	20
Grade		
High grade	7	70
Low grade	3	30
Initial staging (before the first irradiation)		
T1	4	40
T3	3	30
T4	3	30
N0	9	90
N1	1	10
Surgery before the first irradiation	8	80
Time elapsed since previous irradiation (months, [median, IQR])	53.5 (18 – 84)	
Previous treatment course		
IMRT	5	50
3D - RT	3	30
Proton	2	20
Previous treatment course RT total dose (Gy, [median, IQR])	63.5 (57 – 65.5)	
Karnofsky performance status (KPS) before the reirradiation		
90%	9	90
80%	1	10
Retreatment disease site (before the second irradiation)		
Sinus	4	40
Salivary gland (including parotid and submandibular gland)	3	20
Oral cavity	1	10
Skull base	1	10
Orbital	1	10
Staging before the reirradiation		
rT3	3	30
rT4	7	70
rN0	9	90
rN2	1	10
Surgery before reRT	4	40

Abbreviations: IMRT: intensity-modulated radiation therapy; reRT: reirradiation.

Table 2: Reirradiation details

Table 2. Reirradiation details.

	Number
reRT volumes	
CTV (cc, [median, IQR])	85.9 (18.1–145)
PTV (cc, [median, IQR])	162.9 (56.3 – 235.7)
reRT techniques	
Photon (IMRT)	3
Proton (PSPT)	7
reRT total dose (Gy, [median, IQR])	72 (62.6 – 73.8)
Overall treatment time during reRT (days, [median, IQR])	58.5 (51.7 – 61.7)
Dose in target volumes	
D _{95%} CTV (Gy, [median, IQR])	64.2 (59 – 70.1)
D _{95%} PTV (Gy, [median, IQR])	60.93 (56.2 – 62.9)
Dose in organ at risks (Gy, [median, IQR])*	
Maximum cumulative chiasm (D _{2%})	45.6 (38.2–52.4)
Maximum cumulative ipsilateral optic nerve (D _{2%})	70.6 (56.1–85.3)
Maximum cumulative contralateral optic nerve (D _{2%})	47.5 (37.8–75.2)
Maximum cumulative ipsilateral temporo-mandibular joint (D _{2%})	80.6 (68.9–105)
Maximum cumulative contralateral temporo-mandibular joint (D _{2%})	35.2 (26.3–69.7)
Avg cumulative ipsilateral cochlea	45.2 (35.5–82.3)
Avg cumulative contralateral cochlea	30.2 (22–58.8)
Maximum cumulative brainstem (D _{2%})	50.7 (50.4–64)
Maximum cumulative spinal cord (D _{2%})	26.5 (17–36.7)
Avg cumulative ipsilateral parotid	44.2 (39.6–50.9)
Avg cumulative contralateral parotid	14.5 (11.6–39.9)
Maximum cumulative mandibula (D _{2%})	105.6 (51.4–133.6)
Maximum cumulative ipsilateral temporal lobe (D _{2%})	124.3 (105.3–130.6)
Maximum cumulative contralateral temporal lobe (D _{2%})	69.9 (54.1–106.6)

Abbreviations: reRT: reirradiation; 3D-RT: three-dimensional RT; IMRT: intensity-modulated RT; PSPT: passive scattered proton therapy;

*physical doses without using the 'forgetting factor'; avg: average; DV: 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.

Table 3: Late toxicities

	Impairments before the reirradiation		Late toxicities	
	Grade	Number (%)	Grade	Number (%)
Fibrosis	0	10 (100%)	0	7 (70%)
			1	1 (10%)
			2	2 (20%)
Hearing impairment	0	7 (70%)	0	7 (70%)
	1	1 (10%)	1	1 (10%)
	2	1 (10%)	2	1 (10%)
	3	1 (10%)	3	1 (10%)
Xerostomia	0	10 (100%)	0	7 (70%)
			1	2 (20%)
			2	1 (10%)
Brain necrosis	0	10 (100%)	0	8 (80%)
			3	1 (10%)
			4	1 (10%)
Osteoradionecrosis	0	10 (100%)	0	9 (90%)
			4	1 (10%)
Trismus	0	9 (90%)	0	8 (80%)
	1	0	1	1 (10%)
	2	1 (10%)	2	0
	3	0	3	1 (10%)
Facial nerve impairment	0	7 (70%)	0	7 (70%)
	3	3 (30%)	3	3 (30%)
Other nerve impairment	0	8 (80%)	0	8 (80%)
	1	1 (10%)	1	1 (10%)
	3	1 (10%)	3	1 (10%)
Endocrine deficit	0	10 (100%)	0	9 (90%)
			1	1 (10%)
Vision decreased	0	8 (80%)	0	8 (80%)
	2	1 (10%)	2	1 (10%)
	4	1 (10%)	4	1 (10%)