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# Predictors of toxicity after curative reirradiation with intensity modulated radiotherapy or proton therapy for recurrent head and neck carcinoma: new dose constraints for pharyngeal constrictors muscles and oral cavity

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# **PREDICTORS OF TOXICITY AFTER CURATIVE REIRRADIATION WITH INTENSITY MODULATED RADIOTHERAPY OR PROTON THERAPY FOR RECURRENT HEAD AND NECK CARCINOMA: NEW DOSE CONSTRAINTS FOR PHARYNGEAL CONSTRICTORS MUSCLES AND ORAL CAVITY.**

Beddok A, Maynadier X, Krhili S, Ala Eddine C, Champion L, Chilles A, Goudjil F, Zefkili S, Amessis M, Choussy O, Le Tourneau C, Buvat I, Créhange G, Carton M, Calugaru V.

## **1. Introduction**

Despite the numerous innovations in radiation therapy (RT) in the last few years, the risk of local recurrence after a first irradiation for head and neck cancer (HNC) remains high (5,6). The therapeutic modality most frequently used for the management of these local recurrences is surgery whenever possible (129–131). Nevertheless, in some cases, surgery is not possible, either because the tumor infiltrates adjacent structures, especially bone, and becomes unresectable, or because the patient is not operable due to his or her comorbidities. In this case, the indication of a reirradiation (reRT), with or without chemotherapy, is increasingly discussed in multidisciplinary staff meeting. In this context of reRT, patient selection is essential because the risk of severe toxicity after a second irradiation is necessarily higher than after a first irradiation, with up to 35% of patients with grade 3 toxicity after intensity-modulated radiation therapy (IMRT) (153,259). These toxicities include very serious and often described side effects such as carotid blowout (107), brain necrosis (27) and osteoradionecrosis (260) but also less described toxicities that may alter patients' quality-of-life such as dysphagia, xerostomia or trismus (160). In a recent study, Ward *et al.* proposed some recommendations regarding both the selection of patients eligible for reRT, and the dose constraints to organs at risk (OAR) that should be respected in this context (239). It should be noted that the protection of vital OAR such as the carotid arteries or the brain were often prioritized to the detriment of OAR that may nevertheless have a strong impact on patients' quality-of-life, for some of whom the post-reirradiation life expectancy will be relatively short (2). Among the multiple parameters that must be considered for the selection of these patients (25), the size of the target volumes, the time between the two courses of irradiation, and the dose to the OAR at the time of the first and second irradiation may be three decisive criteria (2). Based on data from a cohort of patients undergoing curative reRT for recurrent HNC, either with IMRT or with proton therapy (PT), the aim of the present study was to determine whether a relationship existed these three parameters and the risk of moderate to severe radiation-induced toxicity, including those that could induce quality-of-life impairment.

## **2. Material and Methods**

### **2.1. Patients and treatment characteristics**

Among the 55 patients re-irradiated with IMRT or PT at curative intent between 09/2007 and 09/2019 at *Institut Curie* for advanced HNC, 23 patients had dosimetric data from the first and second

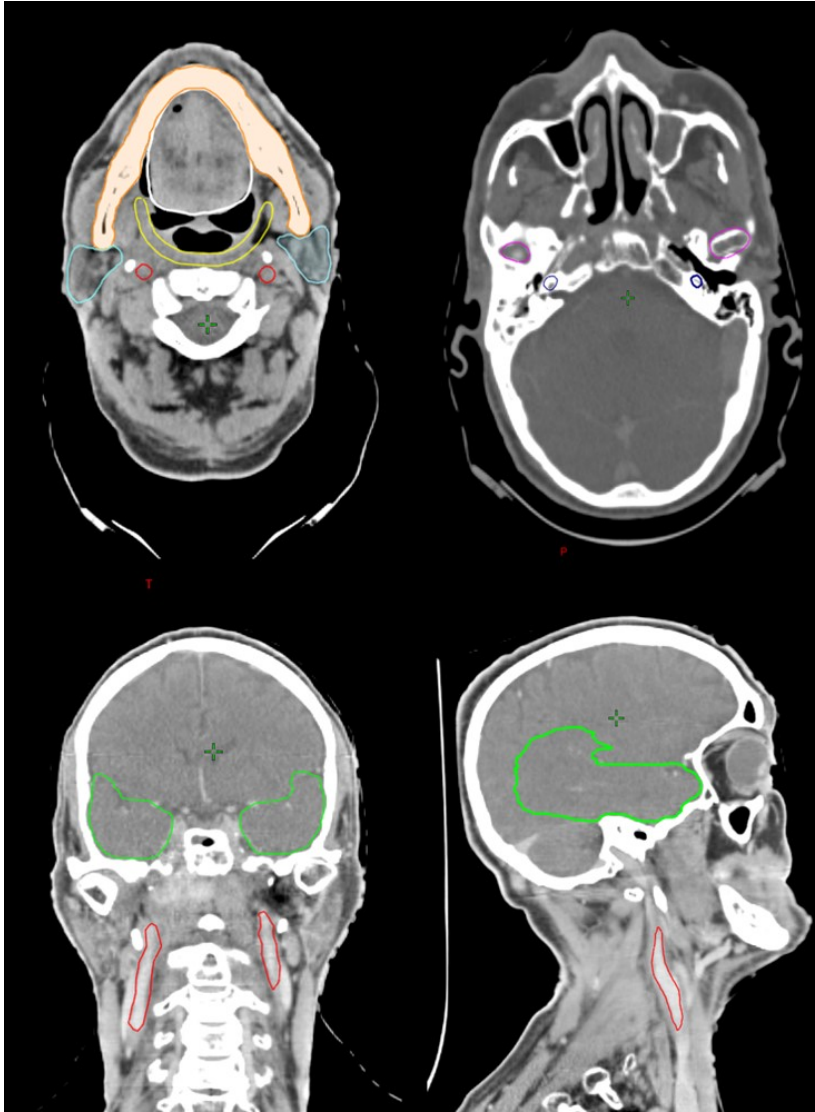
irradiation available and were retrospectively analyzed. ReRT with curative intent was defined as previously (3) as having a primary treatment of  $\geq 60$  Gy and a second treatment with an overlapping volume of  $\geq 40$  Gy, resulting in a volume with a cumulative dose of  $\geq 100$  Gy. This study was approved by the Ethics Committee of the Institut Curie on 07/07/20. Target volumes definition and dose prescription were reported in a previous study (261).

## **2.2.Toxicity**

Data of toxicity were collected from a local quality registry which included information on all patients treated with reRT for HNC in our Institute. In this registry, information on acute (dysphagia, dysgeusia, dermatitis, and mucositis) and late (cervical fibrosis, xerostomia, dysphagia, dysgeusia, hearing loss, vision changes, brain radionecrosis, osteoradionecrosis, trismus, and carotid blowout) toxicity was gathered and graded accordingly. These data were collected prospectively when patients came for routine follow-up visits every three months the first two years after treatment, and then every six months for another three years. Toxicity data were also supplemented with a review of medical records when needed. The Common Terminology Criteria for Adverse Events, Version 5.0 (CTCAE v5.0) was used to assess the acute and late toxicities. Toxicity was considered moderate to severe for grade  $\geq 2$  (262). Toxicities presented after 90 days were labelled as late toxicities. Carotid blowout syndrome was defined as major bleeding from the pharynx in the absence of local recurrence.

## **2.3.Organs at risks delineation**

The OAR investigated were the parotids for the risk of xerostomia, pharyngeal constrictor muscles (PCM) for the risk of dysphagia, the oral cavity (including tongue) for the risk of dysgeusia, the cochleas for the risk of hearing loss, the optic ways (including optic nerves and chiasm) for the risk of vision changes, the temporal lobes for the risk of brain necrosis, the mandible for the risk of osteoradionecrosis, the temporomandibular joints for the risk of trismus and the carotid arteries for the risk of carotid blowouts. The contours of all these OAR were reviewed and corrected in accordance with the International Contouring Atlas of Organs at Risk for this location (263). For some patients, PCM and carotid arteries were *a posteriori* delineated. The doses reported for the paired organs (i.e., parotids, cochleas, temporal lobes, temporomandibular joints, carotid arteries) were the doses from the side that received the highest cumulative doses (i.e., only right or left). Examples of the delineation of the OAR are shown in **Figure 1**.



**Figure 1: Delineation of organs at risk:** parotids (light blue), pharyngeal muscle constrictors (yellow), oral cavity (white), the cochlea (dark blue), temporal lobe (green), mandible (orange) temporomandibular joint (purple), carotid arteries (red).

#### **2.4. Dose summation**

The three-dimensional dose distribution was collected from each course of treatment. For each patient, the different treatment planning images were registered to the planning scan at time of reirradiation, which served as a reference image. An automatic registration was performed in Eclipse<sup>®</sup> using the re-irradiated target volume as the region of interest. For each OAR studied, the doses during the first irradiation, the reRT and the cumulative dose from both irradiations were collected. The OAR dose constraints for reRT were chosen by assuming an empirical “forgetting factor” of 5% per year for nerve structures (145). For other structures, the rule was “as low as possible”.

#### **2.5. Statistical analysis**

Discrete variables were described using percentages whereas continuous variables were described with median and interquartile range. Confidence intervals were presented with a 95% limit. Comparison

between variables were performed using non-parametric tests, Wilcoxon Mann Whitney test for continuous variables and exact Fisher test for discrete variables. Overall survival (OS) was defined as the time from start of reRT to the date of death for any cause; patients still alive were censored at the date of 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. In the absence of any event, patients were censored at the date of their last news. The Reverse Kaplan-Meier method was used to determine the median follow-up (264). Curves for OS were obtained using the Kaplan-Meier method and curve comparisons were performed using the log-rank test. Statistical significance was considered at a 5 % alpha level. All analyses were performed in R. version 4.1.2 (144). The pROC package was used to compute AUC and 95% CI were estimated by 2000 bootstraps (243). Youden Index (optimal value = 1) was used to determine the optimal cutoff value.

### **3. Results**

#### **3.1. Patient and Treatment Characteristics**

The population and treatment characteristics of the 23 included patients are summarized in **Sup. Table 1**. Most of the included patients had a good performance status (ECOG 0–1) at the start of reRT. Definitive reRT (61%) was more common compared to post-operative reRT (39%). Half of the patients received PT (especially recurrent UCNT patients) and the other half received IMRT. The most common tumor site was the nasopharynx (30.6%).

#### **3.2. Outcomes and toxicity**

The median follow-up time after reRT was 41.3 months (range, 19.3–71.4 months). Patients outcomes were detailed in a previous study (261). In brief, the 1-year and 2-year OS were 60.9% [95% CI: 43.9%-84.5%] and 42.5% [26.2%-69.1%], respectively. The 1-year and 2-year LFFS were 34.1% [8.8%-61.9%] and 18.3% [7.1%-47.1%], respectively.

The overall rate of any event of moderate to severe (grade  $\geq 2$ ) acute and late toxicity was 52% and 65%, respectively (**Table 1**). Among the six patients with grade 2 late xerostomia after reRT, two patients had xerostomia before the start of the reRT. Among the eight patients with moderate to severe late dysphagia after reRT, one patient had dysphagia before the start of the reRT. Among the two patients with moderate to severe late dysphagia after reRT, one had dysphagia before the start of the reRT. Among the seven patients with grade 2 trismus after reRT, two patients had trismus before the start of the reRT. The **Sup Table 2** summarize the pre-reRT impairments in relation to the final late toxicities.

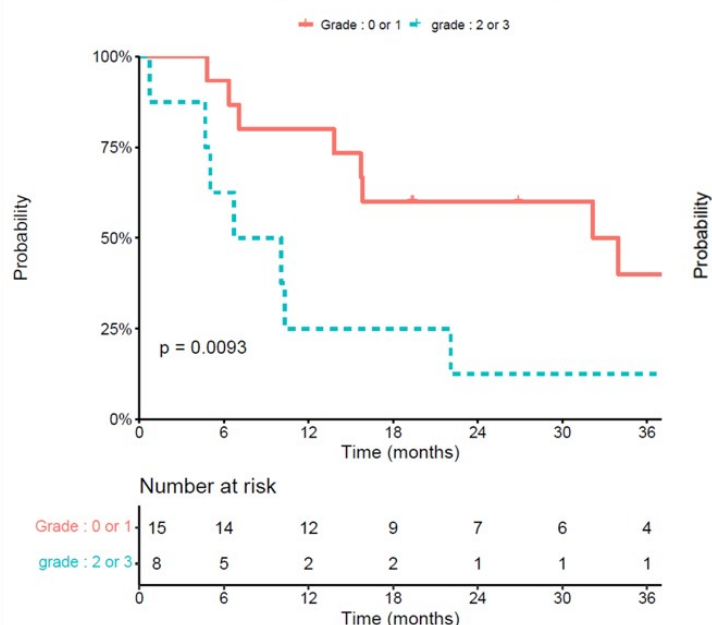
<b>Table 1: Incidence of major toxicities for the 23 patients</b>				
<b>Toxicities</b>	<b>Number of patients by toxicity grade (%)</b>			
	Grade 0	Grade 1	Grade 2	Grade 3
<b>Acute</b>				
Dysphagia	6 (26%)	11 (48%)	1 (4%)	5 (22%)*
Dysgeusia	14 (61%)	6 (26%)	3 (13%)	0
Dermatitis	0	20 (88%)	2 (8%)	1 (4%)
Mucositis	2 (8%)	11 (48%)	9 (40%)	1 (4%)
Hearing loss	15 (65%)	8 (35%)	0	0
<b>Late</b>				
Fibrosis	12 (52%)	9 (40%)	1 (4%)	1 (4%)
Xerostomia	0	17 (74%)	6 (26%)	0
Dysphagia	10 (44%)	5 (22%)	2 (8%)	6 (26%)
Dysgeusia	13 (59%)	4 (15%)	0	6 (26%)
Hearing loss	16 (70%)	5 (22%)	2 (8%) **	0
Vision changes	20 (86%)	3 (14%)	0	0
Brain radionecrosis***	19 (84%)	2 (8%)	2 (8%)	0
Osteoradionecrosis***	18 (78%)	2 (8%)	0	3 (14%)
Trismus	9 (40%)	7 (30%)	7 (30%)	0
* These five patients required the insertion of a feeding tube for the majority of their treatment.				
** Audiogram assessment				
*** Imaging (MR and /or PET) assessment				

There were two cases of moderate and severe late fibrosis and these events occurred 8 and 11 months after reRT, respectively. The median time to develop moderate late xerostomia (6 patients) was 27 months. The median time to develop moderate (2 patients) to severe (6 patients) late dysphagia was 10.6 months. The median time to develop severe late dysgeusia (6 patients) was 8.9 months. There were two cases of moderate late hearing loss and these events occurred 8 and 28 months after reRT, respectively. There were two cases of moderate brain radionecrosis and these events occurred each 21 months after reRT, respectively. There were three cases of severe ORN, and these events occurred 8, 28, and 32 months after reRT, respectively. The median time to develop moderate late trismus (7 patients) was 19.6 months. There were three cases of fatal carotid blowout and these events occurred 13, 15, and 36 months after reRT, respectively.

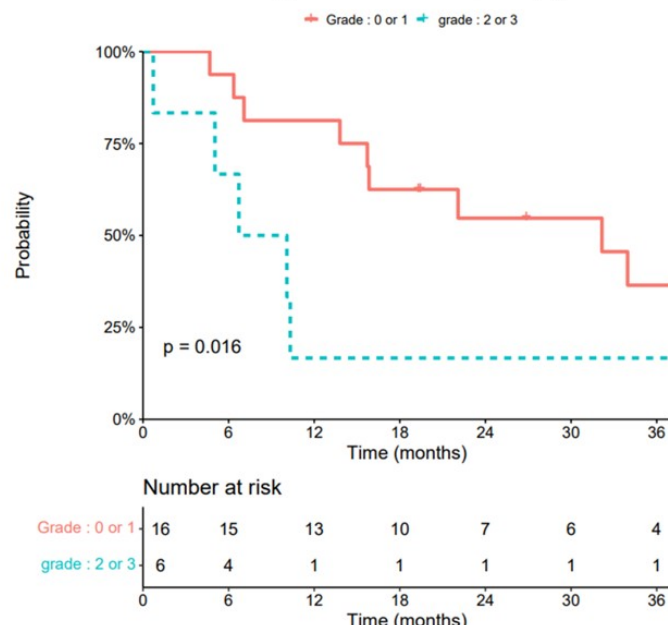
At closure of the database (20/08/2021), six out of 23 patients (26%) were alive without disease. Two years after reRT, 26.1% (13.1 – 51.9%) of the 23 patients had experienced no severe late side effects. OS was significantly shorter in patients with grade  $\geq 2$  dysphagia and dysgeusia,  $p = 0.009$  and  $p = 0.016$ , respectively (**Figure 2**). OS was not associated with the grade of late fibrosis ( $p=0.19$ ),

xerostomia (p=0.27), hearing loss (p=0.63), brain radionecrosis (p=0.2), ORN (p=0.12), trismus (p=0.94).

2A: Overall survival in regard to the severity of dysphagia



2B: Overall survival in regard to the severity of dysgeusia



**Figure 2: Kaplan Meier Curve for Overall Survival as a function of the presence of severe dysphagia (A) and dysgeusia (B):** 2A: Overall survival as a function of the severity of dysphagia; 2B: Overall survival as a function of the presence of severity of dysgeusia.

### 3.3. Predictors of toxicity

#### 3.3.1. Non dosimetric parameters

The median interval time between irradiations was 29.3 months (IQR, 15.3 – 37.2). For each acute and chronic toxicity, the time between the two irradiations was compared for patients with no toxicity (i.e., grade 0 or 1) and those with moderate or severe toxicity (i.e., grade 2 or 3). Our analysis did not show any statistically significant association between the time between the two courses of irradiation and the occurrence of acute or late toxicity (**Sup. Table 3**). Nevertheless, we observed that the three carotid blowouts, the two grade 2 brain necrosis, and the seven grade 2 trismus occurred for relatively short median interval times: 13.2 months, 15.6 months, and 18 months, respectively. Besides this, the median volume of PTV was 124.3 cc (IQR, 76.9 – 208.6). For each chronic toxicity, the volume of PTV was compared for patients with no toxicity (i.e., grade 0 or 1) and those with moderate or severe toxicity (i.e., grade 2 or 3). Our analysis did not show any statistically significant association between the volume of PTV and the occurrence of acute or late toxicity (**Sup. Table 4**).

#### 3.3.2. Dose – response study

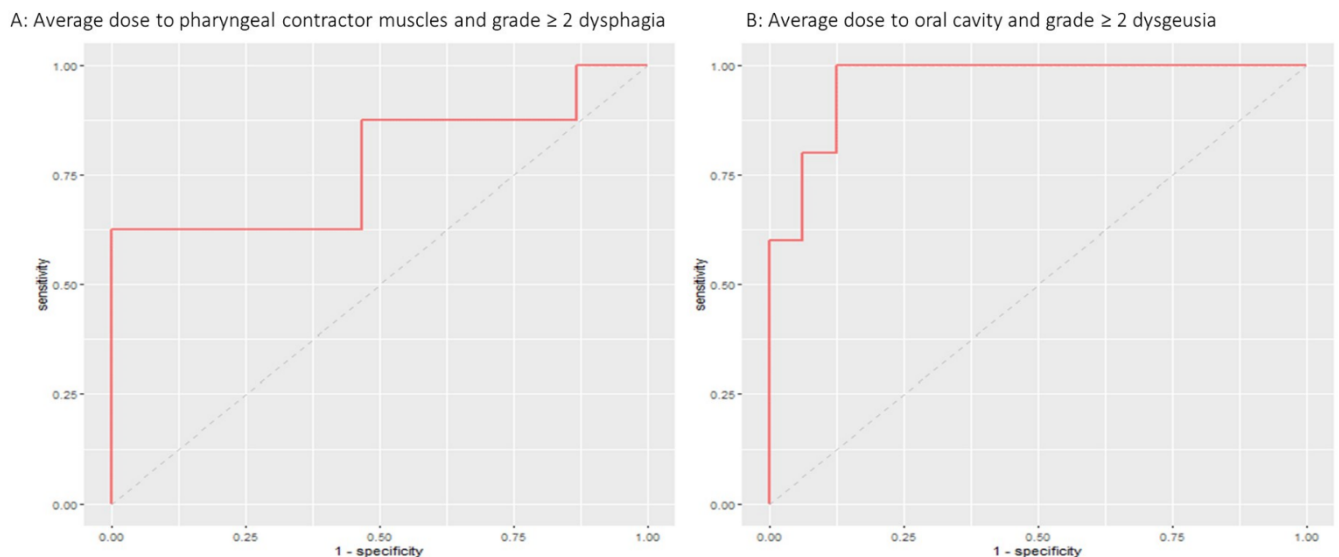
For each acute and chronic toxicity, the doses received by OAR at the first irradiation, the reRT, and the cumulative dose were compared for patients with no toxicity (i.e., grade 0 or 1) and those with moderate



or severe toxicity (i.e., grade 2 or 3) (**Table 2**). Our analysis showed that patients with grade  $\geq 2$  dysphagia received a significantly higher cumulative average dose to the PCM than patients with grade 0 - 1 dysphagia: 96 Gy (86.5 – 104.4) vs 74.8 Gy (53.6 – 82), respectively ( $p = 0.01$ ). The average dose to PCM at the first irradiation was not different between both groups. The average dose to PCM at the time of reRT was significantly higher for the patients with grade  $\geq 2$  dysphagia than patients with grade 0 - 1 dysphagia: 45.3 Gy (22.3 – 54.6) vs. 8.9 Gy (4.2 – 24.4), respectively ( $p = 0.036$ ). ROC curve for a logistic model of grade  $\geq 2$  dysphagia vs. average dose to the PCM showed AUC = 0.78 (95% CI:0.531 - 1) and a cut-off value of 36.7 Gy (sensitivity 62%/specificity 100%) (**Figure 3A**). Similarly, the patients with grade  $\geq 2$  dysgeusia received a significantly higher cumulative average dose to oral cavity than patients with grade 0 - 1 dysgeusia: 78.9 Gy (68.8 – 79) vs. 49.5 Gy (39 – 66.3), respectively ( $p = 0.006$ ). The average dose to oral cavity at the first irradiation was not different between both groups. The average dose to oral cavity at the time of reRT was higher for patients with grade  $\geq 2$  dysgeusia than patients with grade 0 - 1 dysgeusia: 51.5 Gy (35 – 52.3) vs. 10.8 Gy (5.4 – 18), respectively ( $p < 0.001$ ). ROC curve for a logistic model of grade  $\geq 2$  dysgeusia vs. average dose to the oral cavity showed AUC = 0.96 (0.89 - 1) and a cut-off value of 20.5 Gy (sensitivity 100%/specificity 88%) (**Figure 3B**). The patients with grade  $\geq 2$  trismus received a significantly higher cumulative maximal dose at the temporomandibular joint than patients with grade 0 - 1 trismus but this higher dose was more due to a significantly higher maximal dose at the temporomandibular joint during the first irradiation: 69.5 Gy (59.4 – 69.8) vs. 54.1 Gy (45 – 58.3), respectively ( $p = 0.035$ ). For the other studied toxicities, we did not find any association between dose and severity of toxicities (**Table 2**).

**Table 2:** Dose in OAR and risk of late toxicity

<b>Table 2: Dose in OAR and risk of late toxicity</b>										
Organ at risk (dosimetric parameter)	Toxicity	First irradiation - Dose (Gy, [median, IQR])			Reirradiation - Dose (Gy, [median, IQR])			Dose accumulation - Dose (Gy, [median, IQR])		
		Grade 0 - 1	Grade 2 - 3	<i>p-value</i>	Grade 0 - 1	Grade 2 - 3	<i>p-value</i>	Grade 0 - 1	Grade 2 - 3	<i>p-value</i>
Parotid (Dmean)	Xerostomia	41.2 (29 – 60)	32.4 (26.5 – 39.8)	0.20	17.4 (6.6 – 34.2)	23.5 (6.4 – 36)	0.91	68 (43.2 – 76.3)	58.5 (32.5 – 65.7)	0.28
PCM (Dmean)	Dysphagia	54.8 (49.5 – 57.5)	50.6 (46.2 – 55.6)	0.88	8.9 (4.2 – 24.4)	45.3 (22.3 – 54.6)	<b>0.036</b>	74.8 (53.6 – 82)	96 (86.5 – 104.4)	<b>0.01</b>
Oral cavity (Dmean)	Dysgeusia	38.4 (31.8 – 47.1)	27 (25.8 – 45.3)	0.65	10.8 (5.4 – 18)	51.5 (35 – 52.3)	<b>&lt; 0.001</b>	49.5 (39 – 66.3)	78.9 (68.8 – 79)	<b>0.006</b>
Cochlea (Dmean)	Hearing loss	32.9 (22.9 – 48.3)	54.3 (47.6 – 61)	0.13	14.9 (1.1 – 30.7)	3.2 (2 – 5.7)	0.23	49 (33.5 – 64.6)	57.8 (52.1 – 63.4)	0.74
Temporal lobe (Dmean)	Brain necrosis	9.6 (4.3 – 25)	14.1 (12.6 – 15.5)	0.96	3.5 (0.5 – 10.6)	4.1 (3.7 – 4.6)	1	19.1 (8.5 – 29.8)	18.2 (17.1 – 19.4)	0.77
Temporal lobe (Dmax)	Brain necrosis	65.1 (35.3 – 68.8)	57.8 (53.9 – 61.6)	0.91	41.9 (24.8 – 64.3)	64.1 (61.4 – 66.8)	0.39	89.2 (59.3 – 126.6)	127.7 ( 124.6 – 130.8)	0.17
Mandible (Dmax)	Osteoradionecrosis	68.9 (65.8 – 76.1)	67.4 (61.4 – 69.7))	0.24	49.2 (45 – 58.6)	58.5 (46.5 – 67.6)	0.81	103.7 (101.1 – 118.6)	120.8 (103.7 – 125.5)	0.55
Temporomandibular joint (Dmax)	Trismus	54.1 (45 – 58.3)	69.5 (59.4 – 69.8)	<b>0.035</b>	34.8 (18.4 – 56.7)	56.9 (30.2 – 62.7)	0.29	74.8 (67.2 – 91.1)	99.7 (87.8 – 123.8)	<b>0.035</b>
Carotid artery (Dmax)	Carotid blowout	66.6 (59.1 – 69.8)	72.4 (71.2 – 75.3)	0.03	46.5 (18.2 – 61.8)	44.9 (30.1 – 55.5)	0.9	112.7 (75.6 – 128.6)	113 ( 101.5 – 122.4)	0.83



**Figure 3: Receiver-operator characteristics (ROC) curve for logistic models:** A: Average dose to pharyngeal contractor muscles for predicting grade  $\geq 2$  dysphagia: AUC 0.78 (95% CI: 0.531 - 1) with a cut-off value of 36.7 Gy (sensitivity 62%/specificity 100%). B: Average dose to oral cavity for predicting grade  $\geq 2$  dysgeusia: AUC = 0.96 (95% CI: 0.89 - 1) with a cut-off value of 20.5 Gy (sensitivity 100%/specificity 88%).

#### 4. Discussion

The selection of patients with recurrent HNC who would really benefit from re-irradiation is complex, especially because re-irradiation potentially induces more severe late radiation-induced toxicities than a first course of irradiation. In the present study, we investigated the predictive criteria for late side effects based on a retrospective cohort of patients who were all re-irradiated for curative purpose.

In our study, the most severe late toxicity developed within 1.5 to 2 years after retreatment and the median time to develop any severe late side effect was 15.36 (8.3 – 28.1) months. This is consistent with the findings in Ward et al.'s study (265). In that large multi-institutional study including 505 patients, severe late side effects presented at a median of 9.2 months and the majority of all late side effects presented within two years (74 of 85 events). In 2019, Dionisi *et al.* have analyzed the data of 39 studies included 3766 patients who were re-irradiated within the head and neck region (25). The authors of this meta-analysis observed a very high degree of heterogeneity regarding the severe toxicities reported in the 39 included studies ( $I^2=195.4$ ,  $P < 0.001$ ). In a recent study, Margalit et al. have reported the outcomes of 75 consecutive patients reirradiated with IMRT for recurrent HNSCC. Overall, 39 (52%) patients had at least one serious toxicity as listed, with a median time to serious toxicity of 1.1 years (237). This is consistent with our studies in which, 52% of the patients have developed at least one grade 3 toxicity or was dead after a follow-up of 18 months. The main frequent and severe (grade 3) toxicity was dysphagia with the need of feeding tube in both studies. Moreover,

in our series, most patients had tumors located close to the skull base, including nasopharyngeal and sinus tumors (**Sup. Table 1**). In a recent study, Chan *et al.* have reported the outcomes of 38 patients reirradiated with IMRT for rT3 or rT4 nasopharyngeal carcinoma: a total of 73.7% patients experienced at least one grade 3 late toxicities and 3 patients died of massive epistaxis (266). Moreover, as previously reported (261), late toxicities in the IMRT and PT groups were not comparable from a statistical point of view in our study, because the follow-up times after reirradiation were different between both groups. Nevertheless, a representation of these data as Kaplan Meier curves did not find any difference between the two groups (**Sup Figure 1**).

In contrast to previously published data, our analysis did not show any statistically significant association between the interval time between the two courses of irradiation and the occurrence of severe late toxicity. In Lee *et al's* study, shorter time (<20 months) between the two courses was an independent predictor of developing severe late side toxicity (267). While not significant, in our cohort, patients with carotid rupture, brain radionecrosis, and severe trismus appeared to occur in patients with slightly shorter inter-irradiation times than those without such toxicities: 1.1 vs 2.8 years, 1.3 vs. 2.7 years, and 1.5 vs 2.8 years, respectively. This suggests that there may be a forgetting factor (268): tissues that have been irradiated a long time ago may have healed and may have received a higher cumulative dose than that prescribed for the first irradiation. This mechanism has been implemented for the moment only for nervous structures (34) but could be widespread to other structures.

Besides this, in several studies the size of the reirradiated volume appeared to be a strong predictor of late toxicity (25). In 2016, Phan *et al.* reported the outcomes of 60 patients undergoing retreatment with PT for recurrent HNC and have showed that a CTV > 50 cc was significantly associated with both acute and late grade  $\geq 3$  toxicities (148). Similarly, Lee *et al.* [39] analyzed the outcomes of 66 patients undergoing reRT with modern IMRT and have showed that a PTV > 100 cc was significantly associated with the risk of severe toxicities at 2 years (36% vs. 14%) (267). In the present study, the size of the PTV was not significantly associated with the risk of moderate to severe toxicity. This is consistent with the results reported by Margalit *et al.*, in which the total irradiated volume was not a significant predictor of toxicity (237).

The most common moderate to severe late toxicities after reRT for recurrent HNC were radionecrosis, dysphagia requiring feeding tube placement, and trismus (25). For such events, several studies have proposed specific suggestions regarding OARs tolerance and re-irradiation recommendations (239). Several authors have mentioned that a maximum cumulative dose to the mandible greater than 114 Gy (269) or 119 Gy (162) (RBE) could be predictive of ORN. In our series, we did not observe significant differences between the presence or the absence of ORN, regarding the maximum cumulative dose to the mandible. Nevertheless, the median of the maximum cumulative dose to the mandible of the three patients who developed grade 3 ORN was slightly higher than the median of the maximum cumulative

dose to the mandible of the other patients: 120.8 Gy vs. 103.7 Gy (RBE), respectively. Conversely to Garg *et al.* who did not find any clear relationship between composite dose to the pharyngeal constrictor muscles (PCM) and the risk of severe dysphagia requiring a feeding tube (270), in the present study, we observed a significant association between the risk of moderate to severe dysphagia and the cumulative average dose to PCM. ROC curve for a logistic model allowed to determine a cut-off value of 36.7 Gy (sensitivity 62%/specificity 100%) for the reRT course. Similarly, we observed a significant association between the risk of moderate to severe dysgeusia and the cumulative average dose to oral cavity. ROC curve for a logistic model allowed to determine a cut-off value of 20.5 Gy (sensitivity 100%/specificity 88%) for the reRT course. It is interesting to note that in the present study, moderate to severe dysphagia and dysgeusia were significantly associated with overall survival. The respect of these new dose constraints would allow both to improve the quality of life of patients re-irradiated for a recurrence of head and neck cancer and would also allow to improve the overall survival. This model would be particularly applicable for patients for whom the PCM and the oral cavity could be spared at the time of reRT, especially the patients with recurrent UNCT or skull base tumors, who were most of the patients included in the present study. Besides this, we have found a significant association between the risk of moderate to severe trismus and the cumulative maximum dose in temporomandibular joint, but this was in fact rather related to the dose received during the first irradiation.

## **5. Conclusion**

Although based on a small retrospective cohort, we performed a detailed analysis of the main risk factors for severe toxicity reported in the literature after reRT for recurrence HNC. It should be noted that in the present study, in most of cases, the PCM were delineated *a posteriori* as one structure for this dosimetric analysis. However, there is some evidence that the tolerance of the superior, inferior and middle constrictor muscles to RT dose could vary (271). Therefore, it would have been better to distinguish between the three parts of the PCM. Nevertheless, we have illustrated in the present study for the first time a significant association between the risk of moderate to severe dysphagia and dysgeusia and the dose received at the time of reirradiation in the PCM and oral cavity, respectively. It is an important finding because these OAR are not always delineated in reRT cases where the focus is more often on the carotid arteries, mandible, and temporal lobes. With the development of new RT technologies, such as IMRT and PT, which have allowed better sparing of organs at risk (161), the delineation of all these OARs and structures, at the time of the first irradiation, appears here as even more essential. In addition, a significant association has been found between the presence of grade  $\geq 2$  dysphagia and OS on the one hand and grade  $\geq 2$  dysgeusia and OS, on the other hand, further supporting the need for limiting the doses to the PCM and the oral cavity in reRT treatment planning.