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Outcomes and patterns of radiation associated brain image changes after proton therapy for head and neck skull base cancers

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Abstract

Background and purpose: To characterize patterns and outcomes of brain MR image changes after proton therapy (PT) for skull base head and neck cancer (HNC).

Material and methods: Post-treatment MRIs 6 months were reviewed for radiation-associated image changes (RAIC) in 127 patients. All patients had received at least a point dose of 40 Gy(RBE) to the brain. The MRIs were rigidly registered to planning CTs and RAIC lesions were contoured both on T1 weighted (post-contrast) and T2 weighted sequences, and dose–volume parameters extracted. Probability of RAIC was calculated using multistate survival analysis. Univariate/multivariate analyses were performed using Cox Regression. Recursive partitioning analysis was used to investigate dose–volume correlates of RAIC development.

Results: 17.3% developed RAIC. All RAIC events were asymptomatic and occurred in the temporal lobe (14), frontal lobe (6) and cerebellum (2). The median volume of the contrast enhanced RAIC lesion was 0.5 cc at their maximum size. The RAIC resolved or improved in 45.5% of the patients and were stable or progressed in 36.4%. The 3-year actuarial rate of developing RAIC was 14.3%. RAIC was observed in 63% of patients when V_{67} Gy(RBE) of the brain 0.17 cc.

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Conflict of Interest
None.

Appendix A. Supplementary data
Supplementary data to this article can be found online at <https://doi.org/10.1016/j.radonc.2020.07.008>.

Conclusion: Small RAIC lesions after PT occurred in 17.3% of the patients; the majority in nasopharyngeal or sinonasal cancer. The estimated dose–volume correlations confirm the importance of minimizing focal high doses to brain when achievable.

Radiation therapy for head neck cancers (HNCs) at the skull base can result in high doses of radiation delivered to the brain, potentially leading to radiation-associated image changes (RAIC) [1]. Often the diagnosis of RAIC is based solely on radiographic findings on post-treatment MRIs obtained for routine cancer surveillance purposes. For HNCs, information on RAIC stems largely from studies in patients with nasopharyngeal cancers (NPC) treated with Intensity Modulated Radiation Therapy (IMRT), with reported incidences of temporal lobe RAIC ranging between 2% and 14% [2–12]. From patients treated proton therapy (PT) a few mixed cohort studies including selected HNCs report incidences of brain RAIC of 11–31% [13–16]. In studies evaluating the dose–response relationship for RAIC development, constraints have been suggested for several dose–volume parameters as well as for the Equivalent Uniform Dose (EUD) (Table 1), whereas the recently published international consensus guideline for NPC radiotherapy recommend to aim for a temporal lobe $D_{0.03cc}$ 65 Gy and $D_{0.03cc}$ 70 Gy for T1–T2 and T3–T4 tumors, respectively [17].

Owing to the proximity to Central Nervous System (CNS) critical structures, HNCs with tumor at the skull base or with intracranial extension are often selected for treatment with PT to improve or maintain target volume coverage while respecting normal tissues tolerance and reducing the toxicities and symptoms associated with the greater integral dose with IMRT. However, studies on the development of RAIC after PT for HNCs are limited. Thus, as part of a broader effort to better define the role and value of PT for HNC and to provide PT-specific dose recommendations to guide clinicians and the PT community, the specific aims of this study were to:

- Characterize the incidence and patterns of RAIC after PT for skull base HNCs
- Identify candidate clinical and dose–volume parameters associated with RAIC
- Propose practical dose constraints to minimize the risk of RAIC

Methods and materials

Patient cohort

Adult patients treated with PT for HNC at University of Texas MD Anderson Cancer Center were eligible for participation in two consecutive Institutional Review Board-approved prospective studies ([ClinicalTrials.org](https://clinicaltrials.org) identifiers: [NCT 00991094](#) and [NCT 01627093](#)). Eligibility included: (1) Anatomic tumor location at the base of skull, including primary tumors of the nasopharynx, sinonasal, periorbital, parotid, and skin, (2) A point dose of at least 40 Gy to the brain (relative biological effectiveness = 1.1), and (3) one or more follow-up MRI 6 months after completion of PT. Patients with prior radiation therapy to the region or who had received photon-based treatment as part of therapy were excluded.

Treatment

All PT plans were based on non-contrast CT images and generated in the Eclipse treatment planning system (TPS) (Varian Medical Systems, Palo Alto, CA, USA) using either Intensity Modulated Proton Therapy (IMPT), Passive Scattered Proton Therapy (PSPT) or a combination of IMPT/PSPT. For dose prescription a proton relative biological effectiveness (RBE) value of 1.1 was used as recommended by the ICRU [18]. Dose (prescribed to CTV) and fractionation regimens were generally 60 Gy(RBE) in 30 fractions or 63–66 Gy(RBE) in 30–33 fractions in the postoperative PT setting or 66–70 Gy(RBE) in 33–35 fractions in the definitive PT setting. Induction chemotherapy regimens used were typically 3 cycles with taxane and platinum or taxane, platinum and fluorouracil (TPF), and concurrent chemotherapy was usually platinum-based.

Follow-up and diagnosis of RAIC

Follow-up MRIs took place regularly at 8–12 weeks after therapy completion and then every 3 months in the first year, every 4 months in the second year, every 6 months until 5 years, and annually thereafter. Defined as RAIC were (i) contrast enhanced lesions on T1 weighted (T1w) MRIs located in previously irradiated brain tissue and/or (ii) cysts or white matter lesions manifested as high signal intensity on the T2 weighted (T2w) sequences [19]. All RAICs were initially diagnosed by a radiologist during routine disease surveillance and were, for this analysis, identified through review of all MRI reports, and retrospectively reassessed by two board certified radiation oncologists (GBG and SJF). No additional RAIC to those already diagnosed in the MRI reports was discovered. The clinical grading of RAIC was performed retrospectively by chart review according to CTCAE v4.03 [20].

Extraction of clinical and treatment related data

Patient, tumor and treatment characteristics were retrieved from the patients' medical records (Epic Systems Corporation, Verona, WI) and the TPS. The MRIs were rigid registered to the initial treatment planning CT and qualitatively evaluated through visual inspection and further manually corrected if deemed necessary. To detect the extent of the RAIC, gadolinium contrast enhanced lesions on T1w sequences (T1w lesions) and hyperintensities including visible edema from T2w sequences (T2w lesions) were contoured as individual structures and propagated to the planning CT. dose–volume histograms (DVHs) for all patients were exported using bin size of 0.1 Gy(RBE) from where candidate dose volume parameters for the brain tissue were retrieved, including: the maximum dose ($D_{\max}$), the dose delivered to 0.5cc ($D_{0.5\text{cc}}$) and 1cc ($D_{1\text{cc}}$) to 5cc ($D_{5\text{cc}}$) of the brain in 1cc steps, as well as the volume of brain receiving 40–70 Gy(RBE) in 1 Gy(RBE) steps ($V_{40\text{Gy(RBE)}}$ to $V_{70\text{Gy(RBE)}}$). The selection of candidate variables were based on (a) previously identified dose–volume parameters judged as important in predicting RAIC and (b) applicability to clinical practice and plan optimization and evaluation. In addition, for each patient the T1w and T2w lesion volumes with the corresponding minimum dose ($D_{\min}$), the mean dose (D_{mean}) and the $D_{\max}$ were extracted for the first MRI and the MRI with the largest volume of RAIC (“worst” MRI).

Statistical analysis

The follow-up time was calculated as the time between the last PT fraction and the patient's last follow-up MRI. The RAIC latency time was calculated as the time between the last PT fraction and first MRI with RAIC. Time to resolution from RAIC was calculated from date of the first MRI with RAIC and the date of the first MRI where lesion had resolved.

In a course where the event of interest can transient between different states, multistate analysis can provide better accuracy of events reporting. As RAIC resolution is common in a considerable proportion of patients, multistate analysis was used to estimate the probability of RAIC over time [21]. For the current analysis the event of interest was RAIC, and data were censored if patients were alive and RAIC free at last available follow-up MRI. Bootstrapping ($n = 1000$) was used to estimate the 95% confidence intervals [22,23].

Comparisons between patients with and without RAIC were performed using the Mann Whitney U test, the Chi Square and Fishers exact test. All tests were two-sided with a significance level of 0.05. Correlations between the clinical and dosimetric predictor variables were calculated using Spearman's rank correlation and Pearson's correlation coefficient. Univariate and multivariate analysis of the association between RAIC and candidate predictors were performed using Cox Proportional Hazards Regression Analysis [24,25]. Covariates with p value <0.2 from the univariate analysis were considered for inclusion in the multivariate analysis. However, since DVH parameters are highly correlated, the dose volume variables with the lowest significance level from variables where the correlation coefficient were >0.8 were chosen for the analysis.

To identify important V_D parameters, recursive partitioning analysis (RPA) was applied. The chosen endpoint was RAIC three years post-treatment; dose-volume statistics from patients with three years follow-up time or more were included in the analysis. RPA was performed using bootstrapping ($n = 1000$) with number of observations in the terminal node constrained to 10% of the dataset and splitting of nodes based on the Gini index [26,27]. Statistical analyses were performed in SPSS version 24 (IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp, US) and R version 3.6 (R Foundation for Statistical Computing, Vienna, Austria).

Results

One-hundred and ninety-three patients treated from 12/2010 through 06/2018 met the inclusion criteria. Of these, 66 were excluded due to prior photon treatment to the same region. The remaining 127 patients formed the cohort.

Patient, tumor and treatment characteristics are displayed in Table 2. Eighty-five patients (66.9%) were treated exclusively with IMPT, 15 patients (11.8%) exclusively with PSPT and 27 patients (21.3%) with a combination of PSPT and IMPT. Thirty eight patients (29.9%) had one adaption of the treatment plan and 6 patients (4.7%) had two. Twenty patients (15.7%) received both induction and concurrent chemotherapy.

Median follow-up time was 29 months (range: 6–97). Twenty-two patients (17.3%) developed RAIC with a median latency of 24 months (9–37); all but one RAIC had developed within three years after PT. Median follow-up time after diagnosis of RAIC was 14 months (0–70). All patients with RAIC were asymptomatic at initial diagnoses and subsequent follow-up visits. However, due to progression of the image changes on the follow-up MRIs, two patients were treated with pentoxifylline and vitamin E (one of whom also received dexamethasone), and a third patient was treated with bevacizumab [28]. A decision to initiate treatment suggests that the lesions were considered to be clinically severe enough to warrant medical intervention, therefore, 3 patients were rated to have Grade 3 and 19 patients Grade 1 CNS necrosis according to CTCAE 4.03 (Supplementary material Table 1). At last available MRI the lesions had resolved in six patients, progressed in four, regressed in four, were stable in four and four patients had yet to have a follow-up MRI. A case example of the observed RAIC evolution including overview of evolution timeline can be found in Supplementary Material Figs. 1 and 2. Overall, the estimated probability of RAIC at two, three and five years was 8.7% (95% CI: 3.8%, 13.7%), 14.3% (95% CI: 8.2%, 20.4%), and 12.7% (95% CI: 6.9%, 18.5%), respectively (Supplementary Fig. 3).

Tumor and treatment characteristics for patients with RAIC including dose–volume summary statistics for the contoured lesions are provided in Supplementary Materials (Table 2–4). Of patients diagnosed with RAIC, 68.2% patients had been treated for T4 or unresectable disease, and 63.6% had intracranial tumor extension. RAIC was located in the temporal lobe (14 patients), frontal lobe (six patients) and in the cerebellum (two patients). The majority of RAIC developed in patients with NPC or sinonasal cancers (77.3%); all (eight) RAIC occurred in the temporal lobe for the NPCs and for the patients with sinonasal cancer RAIC was found both in the temporal lobe (four) and the frontal lobe (five) (Supplementary Material Fig. 4). Two of the contrast-enhanced T1w lesions were inside and seven were outside the CTV, the remaining 13 were overlapping with the CTV. At first MRI 92% of the T1w contrast-enhanced lesions were 1cc or less, with a median volume of 0.3cc (punctuate to 1.1cc); on the MRIs where the RAIC was at its largest size, 77% of the T1w lesions were less than 1cc with a median volume of 0.5cc (0.1–3.1cc). The T1w lesion doses were highest in lesions located in the temporal lobe and for lesions inside the CTV (Fig. 1).

Statistical significant differences by RAIC group were only found for prescribed dose and brain dose–volume parameters (Tables 2–3). $V_{40 \text{ Gy(RBE)}} - V_{70 \text{ Gy(RBE)}}$ for the brain were included in the RPA. The result showed that 63.1% of the patients with $V_{67 \text{ Gy(RBE)}} > 0.17\text{cc}$ developed RAIC (Fig. 2/Supplementary Material Table 5). Based on the result from RPA, we included $V_{67 \text{ Gy(RBE)}} > 0.17\text{cc}$ in the univariate cox regression analysis. From this analysis prescribed dose, D_{max} , $D_{1-5\text{cc}}$, $V_{70 \text{ (GyRBE)}}$ and $V_{67 \text{ Gy(RBE)}} > 0.17\text{cc}$ were significantly associated with the development of RAIC. In the multivariate analysis; $V_{67 \text{ Gy(RBE)}} > 0.17\text{cc}$ was the only statistically significant predictive factor (HR: 7.57, 95% CI: 1.48, 38.76, $p = 0.015$) (Table 4).

Discussion

In the current study, we characterized the patterns and clinical outcomes of RAIC after PT in a relatively large and heterogeneous cohort of patients with HNCs at the skull base. The

crude incidence rate of RAIC in our study was 17.3%, but given the transient nature of observed lesions, the estimated probability of RAIC at 2, 3, and 5-years was 9%, 14%, and 13%, respectively.

In contrast to reported elsewhere, the patients in our study were asymptomatic. There are several possible explanations for our findings in contradistinction to other series. Both higher doses and larger RAIC volumes have been suggested to have an impact on the development of clinical symptoms [1,28,29]. In the current study the median T1w and T2w lesion volumes were 0.5cc and 2.9cc at its worst, whereas lesion volumes reported in other studies were considerable larger. Zhou et al. [12] found mean T1w and T2w lesion volumes of 4.2cc and 21.7cc, and 30% clinical symptoms. Su et al. [6] reported mean T1w and T2w lesion volumes of 7.7cc and 21.2cc and 22% clinical symptoms. McDonald et al. [13] found significant difference in the mean and maximum lesion doses between Grade 1 vs. Grade 2 lesions. In the McDonald study the D_{mean} and D_{max} for symptomatic contrast enhancing lesions were 73.0 Gy(RBE) and 82.9 Gy(RBE), respectively, compared to 62.2 Gy(RBE) and 69.0 Gy(RBE) for asymptomatic lesions in the current study. Secondly, asymptomatic RAIC could be considered an early sign of impending symptomatic progression, future development of clinical symptoms in our cohort cannot be ruled out. Thirdly, as no formal assessment of neuro-cognitive function was routinely performed, it is possible that the clinical impact of the lesions and corresponding edema is underestimated.

In RPA all possible combinations of thresholds among the V_D parameters were evaluated and showed that 63% of the patients with $V_{67 \text{ Gy(RBE)}} > 0.17\text{cc}$ developed RAIC; the $V_{67 \text{ Gy(RBE)}}$ therefore provides practical and useful reference to support clinical decision making, particularly in difficult cases where higher dose to the brain is unavoidable and where the risk of developing RAIC is high. Our result is in good agreement with the recently published international consensus guideline for NPC, that recommend avoiding $V_{65 \text{ Gy}} > 0.03\text{cc}$ and $V_{70 \text{ Gy}} > 0.03\text{cc}$ for T1–T2 and T3–T4 tumors, respectively [17]. The result agrees reasonable well with the proposed dose constraint from McDonald et al. [13], who identified of $V_{70 \text{ Gy(RBE)}} < 1.7\text{cc}$ for 15% probability of RAIC using Generalized Estimating Equation modelling of dose response relationship with RAIC in 66 patients treated with PT. Niyazi et al. [14] used DVH reduction methods when developing a mixture NTCP model for patients with intracranial- and extracranial tumors treated with PT. An a-value of 9 fitted their data best, and they estimated an $\text{EUD}_9 = 39.5 \text{ Gy}$ for 50% probability of symptomatic CNS necrosis. It is not possible to directly compare this to our result, however, an a-value of 1 equals the mean dose, while with increasing a-values the high dose area of the DVH curve are more weighted and the calculated EUD gets closer to the near-maximum dose.

An important goal of the current study was to provide a comprehensive overview over the incidence of RAIC in HNC treated with proton therapy. HNC are a heterogeneous patient group with varying dose to the brain, depending on both dose prescription and tumor location; a brain dose threshold as one of the inclusion criteria was therefore considered appropriate. Previous studies have identified $V_{40\text{Gy}}$ as one predictor of RAIC and in order to ensure identification of all RAIC events in the cohort, we selected $D_{\text{max}} > 40 \text{ Gy(RBE)}$ as the minimum cut-off point.

Although all MRI reports and images in the current study were retrospectively reviewed and diagnoses verified, inherent limitations of retrospective review apply. Other limitations in our study exist, including a relatively short follow-up time, as RAIC can develop at a later time point or existing lesions could potentially progress. The MRIs in our study were acquired for standard post treatment surveillance purposes, and T2 flair sequences were not routinely available, thus standard T2w sequences were used for contouring T2w edema signal, which can be less accurate than T2 flair. Differences in scanner types and image acquisition protocols inherently influence image quality, sensitivity and specificity and could influence the interpretation of the images. However, as the MRIs were only used for detection and contouring of the brain image changes the uncertainty should therefore be small with simple sequences as T1w and T2w. Further, since the lesions were very small, accuracy of the calculation of the lesion doses may be influenced by uncertainties in the image registration procedure. Finally, our material included a variety of tumor sites treated with both PSPT and IMPT. PSPT generally has a larger irradiated volume, whereas IMPT is conformal, but more sensitive to uncertainties. Although PT technique was not significantly correlated with RAIC development, we cannot rule out that it may influence our results. In addition, the study could also have limited power to define dose–volume constraints since our cohort was too small to split into a training and a validation set for RPA. Therefore, our results should be externally validated.

We investigated RAIC in a heterogeneous cohort of skull base HNC and found that 17.3% developed RAIC, the majority of these occurred in nasopharyngeal or sinonasal cancers. The lesions were small and asymptomatic, resolved in 27% of the patients and progressed in 18% of the patients. The estimated dose–volume correlations identified in our study were in agreement with previous studies and confirm the importance of minimizing focal high doses to brain when achievable.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1. RAIC lesion doses for all lesions (left column), according to location in the brain (middle column) and location relative to the CTV (right column).

Fig. 2.

Results from RPA: 17 out of 27 patients with $V_{67} \text{ Gy(RBE)} \geq 0.17\text{cc}$ developed RAIC, whereas 4 out of 30 patients with $V_{67} \text{ Gy(RBE)} < 0.17\text{cc}$ developed RAIC.

Table 1

Outcome and dose volume constraints reported in literature.

Author (# pat)	Incidence	Grading/clinical symptoms (% of diagnosed RAIC)	Actuarial rates	Median FU in months (range)	Median latency months (range)	Prescribed dose Gy/Gy (RBE) (# fx)	D-V constraints/features/probabilities
IMRT							
Zeng et al. (351) [10]	8.3% T4; 28.0%	CTCAE V3.0: G1: 58.6%, G2: 31.0%, G3: 3%	3y: 5.6%, 5y: 9.7%	76 (6–100)	33 (12–83)	66 (30)	TD5/5: D _{1cc} : 62.8 Gy TD50/5: D _{1cc} : 77.6 Gy
Kong et al. (132) [4]	12.9%	8 out of 17 symptomatic (47.1%)	5y: 4.7% (T3)	64 (11–106)	43 (19–68)	64–75 (32–34)	TD5/5: D _{1cc} : 62.8 Gy TD50/5: D _{1cc} : 80.9 Gy
Feng et al. (695) [2]	8.5%	Vertigo, headache, memory deterioration, muscle weakness and personality changes	32.8% (T4 tumors only)				TD5/5: D _{max} : 69.0 Gy TD50/5: D _{max} : 82.1 Gy
SU et al. (870) [6]	4.6%	22%: Dizziness, headaches, memory deterioration, muscle weakness, epileptic attack	NR	73 (22–108)	38 (22–55)	66–76 (30–33)	TD5/5: D _{2cc} : 60.3 Gy TD50/5: D _{2cc} : 76.9 Gy
Zhou et al. (1887) [12]	2.3%	Symptomatic : 30.2%	3y : 3.5%, 5y: 7.0%	40 (6–104)	30 (6–56)	68 (30)	2.7% risk 5 years: V _{40Gy} < 11cc
Wang et al (749) [9]	5.1%	100% according to RTOG/EORTC: G1: 84.2%, G2: 5.3%, G3: 10.5%	NR	28 (6–60)	30 (10–54)	60–70.4 (30–32)	Lesion volume < 5 cc: V _{45Gy} < 15.1 cc
Huang et al (506) (stage T4 only) [3]	12.5%	CTCAE: G1: 72.4%, G2: 17.4%, G3: 10.3% Total 46.3%: headache, dizziness, memory impairment, epileptic attacks personality changes, consciousness	Cumulative incidence: 3 y: 5.4%, 5 y: 13.2%	40.1 (6–120.1)	NR	66–70.4(32)	Identified features by LASSO *: D _{0.5cc} D _{10cc}
Takiar et al (66) [8]	14.0%	2 cognitive impairment	NR	35 (1–124)	NR	66–70 (33–35)	5y: 13.2%: D _{1cc} 71.1 Gy, 63.3%: D _{1cc} > 71.1 Gy
Proton							
Pehlivan (62) [16]	11.3%	G1: 5, G3: 2	NR	38 (14–92)	19 (10–38)	68.4–73.5 (4 fx/ week)	NR
McDonald et al. (66) [13]	18.2%	G1: 12.4%, G2: 5.7%	3 y: 12.4%, G2+ at 3 Y: 5.7%, G1: 9, G2: 1, G3: 4, G4: 2	31 (6–96)	21 (8–51)	62.0–79.2 (31–44)	15% risk 3 year: V _{40Gy(RBE)} > 16.55cc V _{50Gy(RBE)} > 55.0cc V _{70Gy(RBE)} > 1.7cc
Niyazi et al. (179) [14] (intracranial and extracranial tumors)	20.7% (only G2 necrosis)	Grade 2 (CTCAE 4.0): total: 20.7%; intracranial: 8.4%, extracranial : 31.3%	2 y: Intracranial: 2.5%, extracranial: 25.5% 5 y: intracranial: 4.5% extracranial: 42.4%.	4.4 years (0–13.0)	1.5 years (0.2–6.9)	Intracranial: 59.4 (NR) Extracranial: 70.0 (NR)	Intracranial: EUD ₅₀ 57.7 Gy(RBE) Extracranial: EUD ₅₀ : 39.5 Gy (RBE)

Author (# pat)	Incidence	Grading/clinical symptoms (% of diagnosed RAIC)	Actuarial rates	Median FU in months (range)	Median latency months (range)	Prescribed dose Gy/Gy (RBE) (# fx)	D-V constraints/features/probabilities
Dagan et al (84) [15]	16.7% **	G2: 11 %, G3: 4% G5: 1.7%	NR	29 (5–86)	NR	74.4 Gy(RBE)	NR

D–V: dose volume, CTCAE: Common terminology Criteria for Adverse Events, FU: follow up, y: year.

* Least Absolute Shrinkage and Selection Operator.

** Only symptomatic patients reported; results not based on MRI findings.

Table 2

Patient, treatment and tumor characteristics for the entire cohort and by RAIC group.

Characteristic	All patients (n = 127)		No RAIC (n = 105)		RAIC (n = 22)		P
	n	%	n	%	n	%	
Sex							0.98
Male	67	52.8	57	54.3	10	45.5	
Female	60	47.2	48	45.7	12	54.3	
Age							0.69
Median (Q1–Q3)	51 (39–64)		50 (37–63)		54 (41–61)		
Anatomic Site							0.16
Base of Skull, NOS	7	6.3	6	5.7	1	4.5	
Nasopharynx	35	26.8	27	25.7	8	36.4	
Simonasal	29	22.8	20	19.0	9	40.9	
Parotid	14	11	14	13.3	-	-	
Orbital	23	18.1	21	20.0	2	9.1	
Skin	10	7.9	9	8.6	1	4.5	
Other	9	7.1	8	7.6	1	4.5	
T-category							0.77
T1–T2	28	22	24	22.9	4	18.2	
T3–T4	53	41.7	41	39	12	54.5	
Recurrent	29	22.8	25	23.8	4	18.2	
Tx	5	3.9	5	4.8	-	-	
No stage	12	9.4	10	9.5	2	9.1	
Surgery							0.23
No	49	38.6	38	36.2	11	50	
Yes	78	61.4	67	63.8	11	50	
Induction chemotherapy							0.76
No	106	83.5	86	81.9	20	90.9	
Yes	21	16.5	19	18.1	2	9.1	
Concurrent chemotherapy							0.04
No	54	42.5	49	46.7	5	22.7	

Characteristic	All patients (n = 127)		No RAIC (n = 105)		RAIC (n = 22)		P
	n	%	n	%	n	%	
Yes	73	57.5	56	53.3	17	77.3	
PT technique							0.72
IMPT	85	69.9	69	65.7	16	72.7	
PSPT	15	11.8	12	11.4	3	13.6	
IMPT/PSPT	27	21.3	24	22.9	3	13.6	
Prescribed dose							
Median (Q1–Q3)	64.0 (60.1–69.7)		64.0 (60.1–68.3)		69.3 (63.1–70.0)		0.04
Brain D_{max} < 60 Gy(RBE)							0.01
No	95	74.8	74	70.5	21	96.9	
Yes	32	25.2	31	29.5	1	3.1	
Brain D_{max} > 70 Gy(RBE)							<0.01
No	89	70.1	81	77.1	8	36.4	
Yes	38	29.9	24	22.9	14	63.6	

Q1: 25 percentile, Q3: 75 percentile. Base of Skull: Adenoid cystic carcinoma, adenocarcinoma, neuro-endocrine carcinoma, chondrosarcoma, ameloblastoma, osteosarcoma. Other: vagus nerve schwannoma, paraganglioma, melanoma inferior turbinate, unknown primary site. IMPT: Intensity Modulated Proton Therapy, PSPT: Passive Scattering Proton Therapy.

Table 3

Dose volume statistics for those with and without RAIC. Median (Q1–Q3) reported.

	No RAIC (<i>n</i> = 105)	RAIC (<i>n</i> = 22)	<i>P</i>
Dose parameters brain	Median Gy[RBE] (Q1–Q3)		
$D_{\max}$	64.3 (58.6–69.6)	73.1 (67.7–75.8)	<.001
$D_{1.0 \text{ cc}}$	59.1 (51.4–64.7)	67.0 (62.8–72.1)	<.001
$D_{2.0 \text{ cc}}$	56.7 (49.8–63.9)	66.2 (58.7–70.5)	<.001
$D_{3.0 \text{ cc}}$	54.3 (48.2–64.4)	64.7 (57.9–69.0)	<.001
$D_{4.0 \text{ cc}}$	51.9 (46.5–61.5)	63.7 (57.4–67.8)	<.001
$D_{5.0 \text{ cc}}$	50.3 (45.3–60.7)	63.0 (56.3–66.7)	<.001
Volume parameters brain	Median cc (Q1–Q3)		
$V_{40 \text{ Gy(RBE)}}$	16.3 (7.7–41.4)	40.4 (25.8–63.9)	0.001
$V_{45 \text{ Gy(RBE)}}$	10.0 (5.2–31.5)	30.2 (17.3–49.9)	0.001
$V_{50 \text{ Gy(RBE)}}$	5.1 (1.8–21.1)	23.7 (10.7–36.2)	<.001
$V_{55 \text{ Gy(RBE)}}$	2.7 (0.11–13.6)	14.3 (6.2–25.1)	<.001
$V_{60 \text{ Gy(RBE)}}$	0.5 (0–6.9)	9.2 (1.5–16.7)	0.001
$V_{65 \text{ Gy(RBE)}}$	0.0 (0.0–0.9)	2.4 (0.4–6.8)	<.001
$V_{70 \text{ Gy(RBE)}}$	0.0 (0.0–0.0)	0.14 (0.0–2.7)	<.001

Table 4

Results from univariate and multivariate cox regression analysis of clinical and dosimetric variables associations with the development of RAIC.

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Age	1.02 (0.99–1.04)	>0.1		
Anatomical site *	2.52 (0.99–6.45)	0.054	1.23 (0.41–4.05)	>0.1
T3–T4 **	1.83 (0.79–4.25)	>0.1	0.44 (0.12–1.66)	>0.1
Surgery	0.56 (0.24–1.30)	>0.1	2.46 (0.41–4.05)	>0.1
Induction chemotherapy	0.67 (0.20–2.28)	>0.1		
Concurrent chemotherapy	2.22 (0.82–6.03)	>0.1	1.99 (0.42–9.33)	>0.1
PT technique ***	1.06 (0.41–2.72)	>0.1		
Prescribed dose	1.11 (1.01–1.23)	0.035	1.03 (0.88–1.20)	>0.1
$D_{\max}$	1.15 (1.07–1.24)	<0.01	1.06 (0.92–1.21)	>0.1
$D1_{cc}$	1.11 (1.05–1.18)	<0.01		
$D2_{cc}$	1.10 (1.04–1.16)	<0.01		
$D3_{cc}$	1.08 (1.03–1.13)	<0.01		
$D4_{cc}$	1.07 (1.02–1.12)	<0.01		
$D5_{cc}$	1.07 (1.02–1.12)	<0.01		
V_{40} GY(RBE)	1.01 (0.998–1.02)	0.061	0.99 (0.98–1.01)	>0.1
V_{50} GY(RBE)	1.01 (0.996–1.03)	0.080		
V_{60} GY(RBE)	1.01 (0.985–1.04)	>0.1		
V_{70} GY(RBE)	1.18 (1.03–1.34)	<0.01	1.06 (0.87–1.29)	>0.1
V_{67} GY(RBE) 0.17 _{cc}	7.72 (2.84–21.0)	<0.01	7.41 (1.48–38.76)	0.015

* Nasopharyngeal carcinoma/sinonasal vs other.

** T3/T4 vs other.

*** IMPT vs other, HR: Hazard Ratio.