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Temporal Lobe Necrosis in Head and Neck Cancer Patients after Proton Therapy to the Skull Base

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Abstract

Purpose: To demonstrate temporal lobe necrosis (TLN) rate and clinical/dose-volume factors associated with TLN in radiation-naïve patients with head and neck cancer treated with proton therapy where the field of radiation involved the skull base.

Materials and Methods: Medical records and dosimetric data for radiation-naïve patients with head and neck cancer receiving proton therapy to the skull base were retrospectively reviewed. Patients with <3 months of follow-up, receiving <45 GyRBE or nonconventional fractionation, and/or no follow-up magnetic resonance imaging (MRI) were excluded. TLN was determined using MRI and graded using Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Clinical (gender, age, comorbidities, concurrent chemotherapy, smoking, radiation techniques) and dose-volume parameters were analyzed for TLN correlation. The receiver operating characteristic curve and area under the curve (AUC) were performed to determine the cutoff points of significant dose-volume parameters.

Results: Between 2013 and 2019, 234 patients were included. The median follow-up time was 22.5 months (range $=$ 3.2–69.3). Overall TLN rates of any grade, $\geq$ grade 2, and $\geq$ grade 3 were 5.6% (N $=$ 13), 2.1%, and 0.9%, respectively. The estimated 2-year TLN rate was 4.6%, and the 2-year rate of any brain necrosis was 6.8%. The median time to TLN was 20.9 months from proton completion. Absolute volume receiving 40, 50, 60, and 70 GyRBE (absolute volume [aV]); mean and maximum dose received by the temporal lobe; and dose to the 0.5, 1, and 2 cm^3 volume receiving the maximum dose

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(D0.5cm^3, D1cm^3, and D2cm^3, respectively) of the temporal lobe were associated with greater TLN risk while clinical parameters showed no correlation. Among volume parameters, aV50 gave maximum AUC (0.921), and D2cm^3 gave the highest AUC (0.935) among dose parameters. The 11-cm^3 cutoff value for aV50 and 62 GyRBE for D2cm^3 showed maximum specificity and sensitivity.

Conclusion: The estimated 2-year TLN rate was 4.6% with a low rate of toxicities ≥grade 3; aV50 ≤11 cm^3, D2cm^3 ≤62 GyRBE and other cutoff values are suggested as constraints in proton therapy planning to minimize the risk of any grade TLN. Patients whose temporal lobe(s) unavoidably receive higher doses than these thresholds should be carefully followed with MRI after proton therapy.

Keywords: temporal lobe necrosis; proton therapy; head and neck cancer; toxicity

Introduction

Proton therapy in patients with head and neck cancer has the benefit of decreasing the total integral dose and the dose to organs at risk (OARs) compared with intensity-modulated radiation therapy (IMRT) [1]. Proton therapy has been shown to improve both clinician-reported and patient-reported toxicities [2]. Furthermore, in select disease sites within the head and neck, proton therapy offers improvement in oncologic outcomes in comparison to historical controls [3–5]. Although proton therapy can decrease the low to medium radiation dose spillage compared with IMRT [6, 7], in the high-dose region, it is similar, if not worse, in terms of tumor conformality. Thus, irradiating to the skull base region poses a substantial concern for toxicities in the adjacent healthy brain and temporal lobes, especially when using non–pencil beam 3-dimensional proton techniques. As a result, radiation-associated temporal lobe necrosis (TLN) can occur and result in devastating outcomes, which can compromise patients' quality of life and cause long-term morbidity. In the photon setting, many clinical factors have been found to be associated with development of TLN, such as age, chemotherapy, diabetes [8–10], total dose, and fractionation size [8, 11]. Multiple studies have suggested dose-volume constraints for the temporal lobes in patients with head and neck cancer receiving IMRT [9, 10, 12–16]. There is a paucity of literature on TLN in patients treated with proton therapy. In this study, we aimed to demonstrate the rate of TLN and identify risk factors and dose-volume parameters associated with TLN in radiation-naïve patients with head and neck cancer treated with proton therapy to the skull base. We report not only the rate of TLN but also the incidence of brain necrosis.

Materials and Methods

Patient Characteristics

This study was an institutional review board–approved (no.16-1648) retrospective analysis of patients with head and neck cancer who were treated with proton therapy to the skull base at our proton facility (Procure, Somerset, New Jersey). Metastatic patients who were irradiated with curative intent and dose to the skull base were eligible. Patients with prior radiation at the head and neck areas, less than 3 months follow-up time, who received less than 45 GyRBE of radiation dose, who received nonconventional fractionation and/or no follow-up magnetic resonance imaging (MRI) were excluded from the study. Primary brain tumors were not included. The electronic medical records and all available dosimetric data for eligible patients were reviewed.

Radiation Therapy

All patients underwent computed tomography (CT) simulation in the supine position with 3-point or 5-point head and neck masks. Positron emission tomography (PET)/CT and magnetic resonance (MR) simulation were co-registered to the CT simulation to facilitate target volume delineation. Gross tumor volume (GTV) was defined as any gross primary or nodal disease detected clinically or radiographically. Clinical target volume (CTV) was defined as GTV plus areas at risk of subclinical microscopic spread in both primary site and neck. In patients who were exclusively treated with proton therapy, CTV was used as a volume for plan evaluation of dose coverage. For those who were irradiated with IMRT followed by proton boost, planning target volume was generated by adding 3 to 5 mm margin to CTV to account for interfraction and intrafraction motion errors. Patients with definitive head and neck cancer received 70 to 76 GyRBE for those with intact tumor while postoperative patients were prescribed 60 to 66 GyRBE to tumor beds depending on pathologic risk factors in keeping with

current standard of care. Subclinical areas at high risk, for example, adjacent sites in general head and neck cancers/whole nasopharyngeal area in the nasopharyngeal cases, were given a median dose of 60 GyRBE, while the areas at lower risk (elective nodal volume and perineural invasion coverage) were treated to 45 to 54 GyRBE. All patients received conventional fractionation defined as 1.8 to 2.12 GyRBE per fraction, once daily, 5 days a week. Most patients were treated with an initial irradiation to 45 to 54 GyRBE to the gross volume/tumor beds and areas at risk followed by a cone-down boost if any. We included metastatic patients who were treated to the skull base with curative intent (median dose 70 GyRBE, range 66-76) as their survival was comparable to that of nonmetastatic patients (87.5% vs 90.4%, *P* value .946), posing them at the same risk of developing TLN. The IMRT and proton dose summation was reported in GyRBE.

Proton Techniques

All patients were treated with proton therapy using Proteus 235 system (Ion Beam Applications, Louvain-la-Neuve, Belgium). Before April 2016, uniform scanning beam (US) using the match field technique was utilized for all patients. Apertures and compensators were custom-made to shape the lateral and distal edges of the target, respectively. After April 2016, patients were treated with either US or pencil beam scanning (PBS), depending on machine availability. The PBS was delivered in 2 ways; single-field uniform dose, with each beam angle delivering a uniform dose covering the whole volume, or multifield optimization, using each beam to collectively cover the volume. Monte Carlo algorithm was used as a PBS calculation model. Setup variations of 3 to 5 mm and range uncertainties of $\pm$3.5% were accounted for in the planning optimization. A relative biological effectiveness (RBE) value of 1.1 was applied in planning and plan evaluation. Daily orthogonal x-ray imaging on a 6 *df* couch was performed for setup verification. Weekly quality assurance (QA) CT scans were implemented to assess any anatomic change. When significant changes were observed, a QA plan was calculated based on weekly QA CT to ensure dose to the target and the OARs. Any unacceptable dose coverage required adaptive radiotherapy planning.

Follow-up

Patients were evaluated weekly during radiation therapy by radiation oncologists and, if applicable, by a multidisciplinary team including medical oncologists, head and neck surgeons, nurses, and advanced practice providers. Patients were followed clinically and radiographically at approximate intervals of 1 to 3 months after treatment completion, every 3 months up to 2 years, and every 6 to 12 months thereafter. In general, MRI of the head and neck was performed 3 months after the end of radiotherapy then every 6 to 12 months or as clinically indicated.

TLN Evaluation

TLN was defined as radiographic evidence of temporal lobe injury on brain MRI. Some patients had pathologic confirmation. Radiographic TLN was defined as new contrast-enhanced lesions on postcontrast T1-weighted images and/or new T2-weighted signal consistent with edema [17–19] in location(s) corresponding with the prior radiation portals. Cerebral radionecrosis typically demonstrates some contrast enhancement on imaging; however, new edema without enhancement is evidence of radiation injury to the brain and can produce the same clinical issues as enhancing lesions. Therefore, for the purposes of our study we included both enhancing lesions with or without edema and non-enhancing edematous changes as radionecrosis. MR perfusion of the brain and/or PET/CT and/or follow-up MRI were subsequently performed after the diagnosis of TLN and to rule out recurrent tumor or new brain primary sites. TLN was graded with Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 [20] by 3 independent radiation oncologists. Any discordance was resolved by consensus. Time to TLN was calculated from the date of proton completion to the date of first TLN radiographic appearance. All other necrosis in non–temporal lobe regions were described but not further analyzed.

Dosimetric Parameters

Right and left temporal lobes were either prospectively or retrospectively contoured in patient's radiation plans. The incidence of brain necrosis and its dose-dependent relationship were well demonstrated in various studies using conventional radiation [8, 21]. However, necrosis can be seen in the brain area receiving a dose as moderate as 50 Gy [21]. For this study, absolute volume (aV) of the temporal lobe receiving 40, 50, 60, 70 GyRBE (aV40, aV50, aV60, aV70, respectively, in cm^3); dose to the 0.5 cm^3, 1 cm^3, and 2 cm^3 volume receiving the maximum dose (D0.5cm^3, D1cm^3, and D2cm^3, respectively, in GyRBE); maximum dose received by the temporal lobe (Dmax in GyRBE); and mean dose received by the temporal lobe (Dmean in

GyRBE) were investigated. When the tumor involved the temporal lobe (N = 1 patient), dose-volume parameters of a virtual organ of the temporal lobe subtracted by GTV was evaluated instead of the actual temporal lobe.

Both $D2cm^3$ and Dmax were comprehensively documented during the planning process in 84.2% of patients. Other dose-volume parameters, not recorded at time points before the study, were subsequently extracted from the treatment planning system after proton therapy was completed. In summary, the data of 197 patients (394 temporal lobes) was available for $D2cm^3$ and Dmax, and the data of 147 patients (294 temporal lobes) was available for other dose-volume parameters.

Statistical Analysis

Patient characteristics between patients with and without TLN were compared using the χ^2 test (or Fisher exact test if indicated) for categorical data. All continuous data were tested for the normality and compared using the Mann-Whitney *U* test for the median(s). Logistic regression analysis was performed to identify predictive clinical parameters for TLN. For dose-volume parameters, right and left temporal lobes in each patient were considered separately. Generalized estimating equation, which adjusted for intrasubject repeated measures (right and left temporal lobes), was used for determining dose-volume variables and TLN correlation in the univariate analysis (UVA). Any factor with a *P* value less than .2 in the UVA was entered into the multivariate analysis (MVA). The receiver operating characteristic (ROC) curve and area under the curve (AUC) were used to identify the predictive performance of any statistically significant dose-volume parameters. Youden's index was performed to determine the cutoff points of each significant dose-volume predictors that gave maximum sensitivity and specificity. Time to events was calculated between the date of proton completion to date of target events. Overall TLN rate was reported in crude rate. The estimated actuarial rate was performed using Kaplan-Meier analysis. All tests were 2-sided. A *P* value less than 0.05 was considered statistically significant. All statistical analysis was performed using IBM SPSS statistics software version 26 (IBM Corporation, New York, USA).

Results

Between September 2013 and August 2019, 270 patients with head and neck cancer were treated with proton therapy to the skull base in the definitive primary setting. After excluding patients with inadequate follow-up time (N = 21), receiving dose <45 GyRBE (N = 8), or receiving nonconventional fractionation (N = 7), 234 patients were included. Twelve patients with metastatic disease who were treated to the skull base with a curative radiation dose (median = 70 GyRBE, range = 66-76) were included. Two-year survival was not statistically different between metastatic and nonmetastatic patients (87.5% vs 90.4%, *P* value .946). There was no statistical difference in overall survival of patients with and without TLN. The median follow-up time was 22.5 months (range = 3.2-69.3).

Patient characteristics are summarized in Table 1. There was no statistically significant difference in hypertension, diabetes, smoking, and concurrent chemotherapy between the 2 groups. Overall, 86.3% of patients received proton therapy exclusively while 13.7% received IMRT with a median dose of 50 Gy followed by proton boost with a median dose of 20 GyRBE. Also, 35% received PBS while 65% received US. Patients with TLN were mostly T3-4 and had adenoid cystic carcinoma (ACC) histology. The most common primary sites for TLN patients were oral cavity (all were hard palate), nasopharynx, and sinonasal primary. Median prescribed doses were higher in patients with TLN than patients without TLN (proton only: 70 vs 66 GyRBE *P* value .001; IMRT+proton: 76 vs 70 GyRBE, *P* value .104), although not reaching statistical significance in the IMRT+proton group. An additional comparison between patients with and without any brain necrosis showed no statistical difference in types of radiation (proton only: 76.5% vs 87.1%; IMRT+proton: 23.5% vs 12.9%; *P* value .263). In patients treated exclusively with proton, the median prescribed dose was significantly higher in patients with any necrosis than in patients without necrosis (70 vs 66 GyRBE, *P* value < .001), similar to findings in the TLN groups. In patients treated with IMRT+proton, no statistical differences in median IMRT dose (50 vs 50 Gy, *P* value .755), proton boost dose (25 vs 20 GyRBE, *P* value .594), and summation dose (75 vs 70 GyRBE, *P* value .405) were found between patients with and without any brain necrosis.

Overall, there were 21 sites of brain necrosis (13 in the temporal lobes and 8 in other brain parts) in 17 patients. Of the 13 patients who developed TLN, 1 patient had synchronous grade 2 cerebellar necrosis. Radiographic findings of TLN showed new contrast-enhanced lesions in 12 patients and non-enhancing edema in 1 grade 1 patient. The other 4 patients developed frontal lobe necrosis: 2 patients with grade 1 (1 with bilateral necrosis) and 2 patients with bilateral grade 2. Overall, TLN rates of any grade, ≥grade 2, and ≥grade 3 were 5.6% (N = 13), 2.1% (N = 5), and 0.9% (N = 2), respectively. The estimated 2-year actuarial TLN rate was 4.6%, and the 2-year rate of any brain necrosis was 6.8%. All grade 1 patients had radiographic TLN without clinical symptoms. Of 3 grade 2 patients, 2 patients had radiographic TLN before their clinical presentation of nausea

Table 1. Patient characteristics.

	Patients with no TLN, N = 221 (%[a])	Patients with TLN, N = 13 (%[a])	*P* Value[b]
Age, median (range), years	59 (14-88)	54 (23-71)	.128
Sex			1.000
Male	55.20	53.80	
Female	44.80	46.20	
Primary sites			<.001
Major salivary glands	35.30	0	
Sinonasal	31.20	23.10	
Nasopharynx	13.10	23.10	
Ears and skin	10.00	15.40	
Other minor salivary glands[c]	1.80	0	
Oral cavity	4.10	38.50	
Others	4.50	0	
Histology			.010
SCC	32.60	46.20	
ACC	19.90	53.80	
Sarcoma	5.00	0	
Esthesioneuroblastoma	2.30	0	
Others	40.30	0	
T stage			.153
T1-T2	42.50	23.10	
T3-T4	50.20	76.90	
Tx[d]	7.20	0	
N stage			.414
N0-N1	74.70	76.90	
N2-N3	15.40	23.10	
Nx	10.00	-	
Comorbidities			
Hypertension	34.80	38.50	.773
Diabetes	9.50	23.10	.136
Smoking			.780
Yes	43.90	38.50	
No	56.10	61.50	
Concurrent chemotherapy			.252
Yes	43.00	61.50	
No	57.00	38.50	
Type of radiation			.694
Proton only	86.40	84.60	
IMRT + proton boost	13.60	15.40	
Proton technique			.773
US	65.20	61.50	
PBS	34.80	38.50	
Radiation dose, median (range)			
Proton only, GyRBE	66 (45-77)	70 (66-76)	.001
Proton boost, GyRBE	20 (10-48.8)	26	.145
IMRT + proton boost, GyRBE	70 (60-76)	76	.104
Median dose per fraction, GyRBE	2 (1.8-2.12)	2 (2.0-2.12)	.518
Temporal lobe dose-volume parameters, median (IQR)[e]			
aV40	1.9 (0-8.7)	20.0 (11.3-31.6)	<.001
aV50	0.6 (0-5.0)	16.3 (8.4-24.3)	<.001
aV60	0 (0-1.3)	7.3 (4.8-17.4)	<.001

Table 1. Continued.

	Patients with no TLN, N = 221 (%[a])	Patients with TLN, N = 13 (%[a])	*P* Value[b]
aV70	0 (0)	1.8 (0.5-11.2)	<.001
Dmean	7.3 (0.4-16.7)	24.5 (12.6-33.9)	<.001
Dmax	54.9 (15.8-68.6)	76.0 (70.6-80.8)	<.001
D0.5cm^3	50.9 (8.3-63.2)	74.9 (71.1-79.7)	<.001
D1cm^3	46.3 (5.6-61.0)	74.0 (70.3-79.2)	<.001
D2cm^3	33.5 (1.8-55.9)	70.0 (65.0-78.1)	<.001

Abbreviations: TLN, temporal lobe necrosis; SCC, squamous cell carcinoma; ACC, adenoid cystic carcinoma; IMRT, intensity-modulated radiation therapy; US, uniform scanning; PBS, pencil-beam scanning; IQR, interquartile range; aV40, aV50, aV60, and aV70, absolute volume of the temporal lobe receiving 40, 50, 60, 70 GyRBE, respectively, in cm^3; D0.5cm^3, D1cm^3, and D2cm^3, dose to the 0.5 cm^3, 1 cm^3, and 2 cm^3 volume, respectively, receiving the maximum dose in GyRBE; Dmean, mean dose in GyRBE; Dmax, maximum dose in GyRBE.

[a]Percentages are rounded to 1 decimal place.

[b]*P* value <.05 was considered statistically significant.

[c]Other minor salivary glands included primary sites of lacrimal duct, orbit, and parapharyngeal space.

[d]Tx consisted of unknown primary cancers, schwannoma, paraganglioma and chordoma.

[e]Left and right temporal lobes were considered separately.

and intermittent headache, respectively. The other grade-2 patient presented with confusion preceding her radiographic TLN. One patient developed grade 3 TLN at 14.4 months with cognitive impairment and hemiparesis. Brain MRI showed a right temporal lobe mass requiring craniotomy and removal of the mass. Histopathology tests confirmed the diagnosis of TLN. At 30.7 months, another patient presented with seizure at an outside hospital. Brain MRI showed a right temporal lobe mass with uncal herniation resulting in an urgent craniotomy with resection of the mass. The pathology report later confirmed brain necrosis. Due to a life-threatening condition and urgent procedure, this patient was scored grade 4. The median time to TLN was 20.9 months (range = 4.4-47, interquartile range = 14.1-32.7). The median time to any brain necrosis was 20.3 months (range = 4.4-47, interquartile range = 14.1-32.7). Findings for all patients with TLN are summarized in Table 2. All dose-volume parameters in the TLN group were statistically significantly higher than in those without TLN as shown in Table 1.

The UVA showed that higher values of all dose-volume parameters were associated with greater TLN incidence. All clinical parameters (gender, age, comorbidities, concurrent chemotherapy, and smoking) as well as proton techniques (PBS vs US) and types of RT showed no correlation with TLN (Table 3) and with any brain necrosis in an additional analysis. To prevent

Table 2. Summary of characteristics of patients with temporal lobe necrosis.

Case	Laterality	CTCAE v5.0 grade	Time to TLN (months)	aV50 (cm^3)	D2cm^3 (GyRBE)	Types of RT	Proton technique
1	Left	1	25.1	14.4	61.8	Proton	US
2	Right	1	38.5	18.0	68.2	Proton	US
3	Left	1	34.8	22.0	75.2	Proton	PBS
4	Right	1	4.4	11.0	69.8	Proton	PBS
5[a]	Right	1	20.9	28.2	78.0	Proton	US
6	Right	1	13.7	12.6	69.4	Proton	PBS
7	Left	1	27.6	0.8	61.2	Proton	US
8	Left	1	46.0	4.1	54.2	Proton	US
9	Right	2	14.5	12.9	77.6	IMRT+proton	US
10	Right	2	20.3	50.7	83.7	Proton	PBS
11	Left	2	12.4	5.7	70.0	Proton	PBS
12	Right	3	14.4	16.3	78.3	IMRT+proton	US
13	Right	4	30.7	26.5	79.2	Proton	US

Abbreviations: CTCAE, Common Terminology Criteria for Adverse events; TLN, temporal lobe necrosis; aV50, absolute volume of the temporal lobe receiving 50 GyRBE; D2cm^3, dose to the 2 cm^3 volume receiving the maximum dose; RT, radiation; IMRT, intensity-modulated radiation therapy; US, uniform scanning; PBS, pencil-beam scanning.

[a]Patient with synchronous cerebellar necrosis.

Table 3. Univariate and multivariate analysis for temporal lobe necrosis.

		Univariate analysis		Multivariate analysis	
Parameter	**Variable**	**OR (95% CI)**	***P* Value[a]**	**OR (95% CI)**	***P* Value[a]**
Gender	Male vs female	0.95 (0.31-2.91)	.924	-	-
Age	Continuous	0.98 (0.95-1.01)	.209	-	-
Concurrent chemotherapy	Yes vs no	2.12 (0.67-6.69)	.199	2.18 (0.72-6.54)	.166
Hypertension	Yes vs no	1.17 (0.37-3.70)	.791	-	-
Diabetes	Yes vs no	2.86 (0.73-11.20)	.132	2.91 (0.80-10.61)	.105
Smoking	Yes vs no	0.80 (0.25-2.52)	.702	-	-
Type of RT	IMRT+proton vs proton only	1.16 (0.24-5.48)	.854	-	-
Proton technique	PBS vs US	1.17 (0.37-3.70)	.791	-	-
aV40	Continuous	1.12 (1.08-1.17)	<.001	1.13 (1.10-1.18)	<.001
aV50	Continuous	1.16 (1.10-1.22)	<.001	1.16 (1.10-1.24)	<.001
aV60	Continuous	1.20 (1.10-1.31)	<.001	1.21 (1.10-1.33)	<.001
aV70	Continuous	1.41 (1.20-1.65)	<.001	1.44 (1.22-1.70)	<.001
Dmean	Continuous	1.08 (1.03-1.13)	.001	1.08 (1.04-1.13)	.001
Dmax	Continuous	1.20 (1.06-1.34)	.003	1.21 (1.06-1.37)	.005
$D0.5cm^3$	Continuous	1.22 (1.06-1.40)	.006	1.24 (1.06-1.44)	.006
$D1cm^3$	Continuous	1.22 (1.07-1.39)	.003	1.25 (1.07-1.44)	.004
$D2cm^3$	Continuous	1.22 (1.10-1.36)	<.001	1.25 (1.10-1.42)	<.001

Abbreviations: OR, odds ratio; CI, confidence interval, RT, radiation; IMRT, intensity-modulated radiation therapy, PBS, pencil-beam scanning; US, uniform scanning; aV40, aV50, aV60, and aV70, absolute volume of the temporal lobe receiving 40, 50, 60, 70 GyRBE, respectively, in cm^3; Dmean, mean dose in GyRBE; Dmax, maximum dose in GyRBE; $D0.5cm^3$, $D1cm^3$, and $D2cm^3$, dose to the 0.5 cm^3, 1 cm^3, and 2 cm^3 volume, respectively, receiving the maximum dose in GyRBE.

[a]*P* value < .05 was considered statistically significant.

multicollinearity, 1 temporal lobe dose-volume covariate was entered at a time in the MVA. Higher dose in $D0.5cm^3$, $D1cm^3$, $D2cm^3$, Dmean, Dmax, and higher volume of aV40, aV50, aV60, and aV70 were identified as risk factors for TLN in the MVA. Diabetes and concurrent chemotherapy were found in higher proportion of patients with TLN than in patients without TLN; however, there was no statistical significance in the UVA and MVA. In the ROC analysis, all dose-volume parameters gave high AUC values as shown in Table 4. Among volume parameters, aV50 gave maximum AUC (0.921), and $D2cm^3$ gave the highest AUC (0.935) among dose parameters indicating the maximum predictive power for TLN. The cutoff values for all temporal lobe covariates that gave maximum Youden's Index results are shown in Table 4. The 11-cm^3 cutoff for aV50 showed 83.3% sensitivity and 89.3% specificity, while the 62-GyRBE cutoff dose for $D2cm^3$ gave 91.7% sensitivity and 82.6% specificity. The dose-volume relationship among aV50, $D2cm^3$, and TLN status is shown in Figure 1. In our population,

Table 4. AUC of each dose-volume parameter.

				95% CI		Cutoff		
Parameter	**AUC**	**SE**	***P* value[a]**	**Lower**	**Upper**	**values**	**Sensitivity, %**	**Specificity, %**
aV40	0.904	0.030	<.001	0.845	0.964	14.2	83.3	85.8
aV50	0.921	0.026	<.001	0.870	0.972	11.0	83.3	89.3
aV60	0.896	0.056	<.001	0.787	1.000	3.7	91.7	86.1
aV70	0.868	0.068	<.001	0.735	1.000	0.9	83.3	90.7
Dmean	0.857	0.040	<.001	0.778	0.936	11.0	100	62.3
Dmax	0.888	0.041	<.001	0.808	0.967	72.3	83.3	83.6
$D0.5cm^3$	0.913	0.036	<.001	0.843	0.984	70.8	83.3	89.3
$D1cm^3$	0.923	0.031	<.001	0.861	0.984	70.0	83.3	90.7
$D2cm^3$	0.935	0.027	<.001	0.882	0.987	62.0	91.7	82.6

Abbreviations: AUC, area under the curve; SE, standard error; CI, confidence interval; aV40, aV50, aV60, and aV70, absolute volume of the temporal lobe receiving 40, 50, 60, 70 GyRBE, respectively, in cm^3; Dmean, mean dose in GyRBE; Dmax, maximum dose in GyRBE; $D0.5cm^3$, $D1cm^3$, and $D2cm^3$, dose to the 0.5 cm^3, 1 cm^3, and 2 cm^3 volume, respectively, receiving the maximum dose in GyRBE.

[a]*P* value < .05 was considered statistically significant.

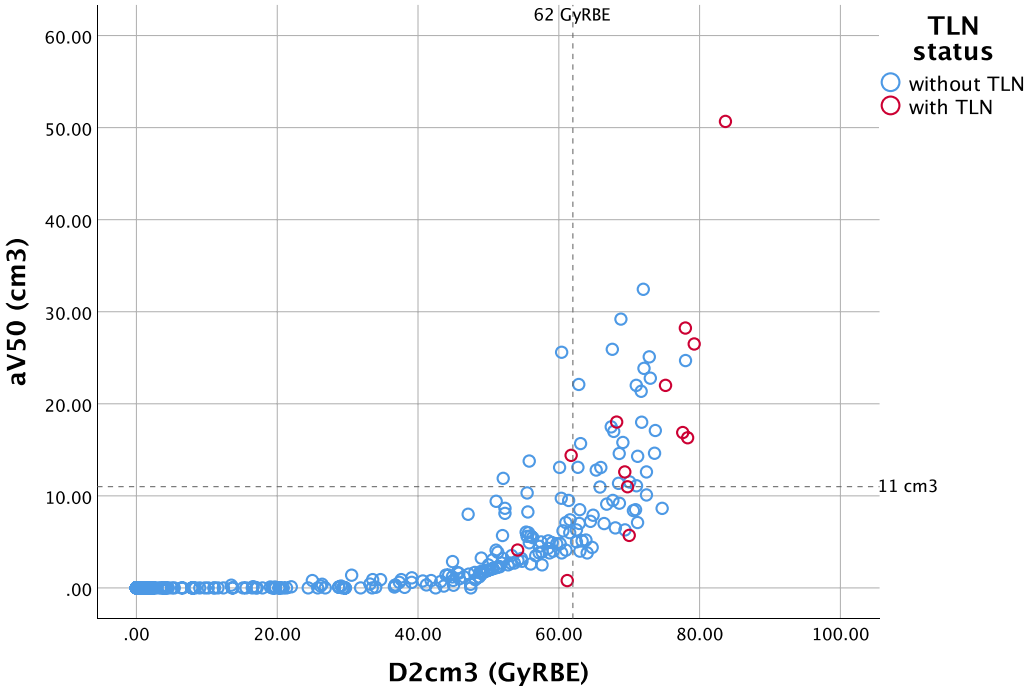

Figure 1. Demonstrated temporal lobe necrosis (TLN) and its relationship to aV50 (an absolute volume of the temporal lobe receiving 50 GyRBE), and D2cm^3 (dose to the 2 cm^3 volume receiving the maximum dose). The dash lines demonstrate the cutoff values of each parameter.

temporal lobes receiving aV50 >11 cm^3 had TLN in 23.1% compared with 1.6% in those with aV50 ≤11 cm^3. TLN developed in approximately 14% of temporal lobes receiving D2cm^3 >62 GyRBE and in 0.9% of those with D2cm^3 ≤62 GyRBE.

Discussion

With a median follow-up time of 22.5 months, the observed rate of any TLN in this study was 5.6%, with an estimated 2-year actuarial rate of 4.6%. This finding is similar to the rate reported by Santoni et al at the same follow-up period in which the TLN rate was 7.6% [22]. For other proton studies with approximately 3-year follow-up time, overall TLN rates ranged from 12.4% to 17.1% [23–25]. In IMRT studies, researchers reported crude TLN rates of 3.48% to 8.1% at 3 to 4 years [16, 26, 27], 7.5% to 13.2% at 5 years [10, 12], and 8.5% to 15% at >5 years of follow-up time [14, 28]. In comparison, the rate of TLN was more frequent in patients receiving proton therapy than IMRT at the same follow-up time. The lack of conformality at the high-dose region with older proton techniques versus IMRT may account for the higher rates of TLN. Secondly, another plausible explanation was different dose prescription. Proton dosing prescription tended to be higher than IMRT (median prescribed dose 66-70.2 Gy in IMRT [10, 13–16, 26, 27, 29], 65-75.6 GyRBE in proton [22–25, 30]). Moreover, the total dose delivered with proton may in fact be higher than anticipated if the RBE is higher than 1.1 at the distal edge. Thirdly, the increasing availability of MRI as a follow-up modality facilitated early detection of radiographic changes, hence, as expected, increasing the overall TLN rate in modern studies.

Most patients who developed brain necrosis in our study had grade 1 disease. Three studies also reported higher rates of grade 1-2 than grade 3-4 of proton-associated TLN [23–25]. For grade 1 patients, the literature suggests the latent nature with subsequent stability or regression in the majority of lesions after following up [17, 23]. However, 1 of our grade 1 TLN patients showed enlargement of an enhancing temporal lobe lesion 1 year after TLN diagnosis but remained asymptomatic. For grade 2 TLN, 2 of 3 grade 2 patients in our cohort had progression in sizes of enhancing temporal lobe lesions on the follow-up dedicated MRI/MR perfusion of the brain; 1 patient also had new enhancing lesion despite steroid intervention. Therefore, careful evaluation of the temporal lobes is essential in all patients undergoing proton therapy for early TLN detection and for studying TLN evolution. Incidence of grade 3-5 TLN was reportedly low at a rate of 1.9% to 6.8% in IMRT cohorts. Our rate of ≥grade 3 TLN was less than the rate of approximately 6% (4/66 patients) reported by McDonald et al [24]. Note that 10/15 (66.7%) TLN patients in our study received US and 5 (33.3%) received PBS, while all TLN patients in the study by McDonald et al [24] received double scattering, which is effectively identical to US. Both patients who developed grade 3 and 4 TLN in our study were treated with US. Although we could not demonstrate US as a TLN risk factor, this observation emphasizes the

possibility that newer proton techniques allowing advanced optimization might result in lower high-dose complications and warrant further exploration.

Our study identified a median time to TLN of 20.9 months, but the onset can occur as early as 4.4 months, as seen in 1 patient with grade 1 TLN. Other proton studies showed similar median time to radiographic TLN of 17 to 24 months with the earliest onset seen at 6 months after proton initiation [25] and 8 to 9 months after proton completion [23, 24]. A study in patients with central nervous system tumor receiving proton therapy reported a median time to TLN at 12 months [31]. The median time to TLN was earlier in proton cohorts ($\leq$24 months) compared with conventional radiation and IMRT with median time to onset of $\geq$24 months (range = 24-38) [10, 13–16, 28, 29].This early onset could be partly a result of more frequent use of follow-up MRI in recent series as discussed earlier.

Age [9], concurrent chemotherapy [9, 10], and male gender [22] were previously identified as risk factors for TLN but showed no association with TLN in our study. Diabetes and concurrent chemotherapy were found more frequent in TLN patients, although not statistically significant as risk factors. Nevertheless, caution of possible TLN and more stringent dose constraint should be considered when giving these patients proton therapy. There were higher proportions of ACC and T3-T4 stage in the TLN group as the dose used to treat these patients at the skull base in the entire population was escalated compared with other histologies and other T stages. (median dose in GyRBE: ACC vs non-ACC 70 vs 66, *P* value .094; T3-4 vs others 70 vs 66, *P* value $<$ .001).

We identified that higher values of all dose-volume parameters were correlated with higher risk of TLN in proton therapy patients. While patients with head and neck cancer inevitably received high radiation dose, minimizing the dose as low as possible to the OARs remains the basic principle. In proton therapy planning, aV50 $\leq$11 cm^3, D2cm^3 $\leq$ 62 GyRBE, and other cutoff values can be applied as strict dose constraints to prevent any grade TLN and can be used to define patients who are at higher risk of developing TLN. All patients whose temporal lobe(s) unavoidably received higher doses than these thresholds should be carefully monitored with MRI after proton therapy. The Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) study did not specify any dose constraints to the brain but stated a risk of brain necrosis of 5% at 5 years when partial brain was irradiated to 72 Gy, and in some cases, at as low as 60 Gy [8]. However, most data were derived from 2-dimensional or 3-dimensional radiation era. Multiple dose-volume parameters for temporal lobes have been suggested in the IMRT literature [9, 10, 12–14, 16] (supplementary table A). Limited numbers of studies have explored the dose-volume relationship associated with TLN in proton therapy [22–25, 30, 32]. Most studies used non–pencil beam 3-dimensional technique as shown in supplementary table B. A study by McDonald et al [24] found a sharply increased risk of TLN when aV60 exceeded 5.5 cm^3 or aV70 exceeded 1.7 cm^3. It is still unclear whether incorporating the same dose-volume constraints for OARs from photon to proton therapy planning will yield the comparable clinical outcomes. Despite the same endpoints, the cutoff values were different across IMRT and proton studies. In a proton study by McDonald et al [24], aV40 cut point of 16.5 cm^3 was reported to predict 15% TLN risk at 3 years, while an IMRT study by Su et al [14], presenting an actual crude TLN rate of 15% at 3 years, used aV40Gy of 5 cm^3. The cutoff point for aV40 in our study was 14.175 cm^3 to give 83.3% sensitivity and 85.8% specificity. Our result was in accordance with those of McDonald et al [24]. Hence, more proton-specific studies are needed to ensure result homogeneity. We encourage reporting an absolute volume (aV) of temporal lobe receiving radiation dose rather than relative volume allowing variety in temporal lobe contouring and boundary definition.

Despite the small number of toxicities $\geq$grade 3, any means to avoid these complications should be taken by the treating physicians. Utilization of dose-volume constraints for the temporal lobes and beam angle optimization to avoid RBE uncertainty near the critical organs should be strongly considered. There is still an ongoing debate about the increased linear energy transfer (LET) at the end and distal to the proton Bragg peak, which leads to RBE variation of more than the conventional value of 1.1 [33, 34]. In patients with head and neck cancer involving the skull base, this effect could lead to a substantial increase in biological response if the uncertainty is placed near the adjacent brain tissue [35]. Further, as tumors respond to proton therapy during treatment, the delivered dose to the normal structure may differ from the planned dose due to the uncertainty of beam path as a result of changes in filling of air cavities in the sinuses. Some studies showed the correlation between increased LET and imaging changes of the brain in patients after proton therapy [36, 37]. Thus, incorporating LET distribution to the planning optimization may not be negligible, as historically suggested, but may be important for further investigation.

To our knowledge, this study is the largest analysis reporting TLN in radiation-naïve patients with head and neck cancer treated with proton therapy in conventional fractionation where the radiation field involved the skull base. While our population was heterogeneous, the findings emphasize that every patient treated to the skull base are at risk of TLN, regardless of

primary site and histology. Limitations of this study included its retrospective nature, the heterogeneity of primary sites and histology with various treatment approaches, no routine MRI surveillance after 3 months, and relatively short follow-up time.

In conclusion, we report an estimated 2-year TLN rate of 4.6% with a low rate of toxicities ≥grade 3 after proton therapy to the skull base. We propose aV50 $\leq$11 cm^3, D2cm^3 $\leq$62 GyRBE, and other cutoff values as temporal lobe constraints in proton therapy planning to minimize the risk of any grade TLN. All patients whose temporal lobe(s) unavoidably received higher doses than these thresholds should be carefully monitored with MRI after proton therapy.

ADDITIONAL INFORMATION AND DECLARATIONS

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