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Scientific Article

Phantosmia Among Pediatric, Adolescent, and Young Adult Patients Receiving Proton Beam Therapy

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Abstract

Purpose: Phantosmia, an underreported toxicity of brain radiation therapy (RT), is defined as an olfactory disorder resulting in a malodorous phantom smell. This study aimed to characterize the incidence of phantosmia in patients treated with intensity modulated proton therapy (IMPT).

Methods and Materials: In this institutional review board–approved retrospective study, the electronic medical record of a pencil beam scanning-only proton center was queried for patients ≤39 years of age who received IMPT for primary intracranial, metastatic intracranial, skull base, nasopharyngeal or sinonasal neoplasms between August 2019 and December 2020. Patient, clinical, and phantosmia-related characteristics were collected. The olfactory region was defined to include the olfactory bulb and tract. Phantosmia severity was graded by intervention use (mild, no intervention; moderate, supportive treatment; severe, RT discontinuation).

Results: Ninety-nine patients met the inclusion criteria. Twelve patients (12.1%) reported phantosmia. Patients described perceiving a "chlorine," "broccoli," "stale water," "metallic," or "noxious" smell. Of the patients who reported phantosmia, median age was 17 (12-33) years, 66.7% were male, and 91.7% had intracranial tumors. None of the patients had prior RT. Chemoradiotherapy treatment did not correlate with phantosmia development (odds ratio, 1.09; 95% confidence interval, 0.32-3.70; P = .90). Ten patients experienced accompanying toxicities, including taste changes (n = 3), vision disturbances (n = 5), and nausea/emesis (n = 7). Phantosmia was mild (n = 7) or moderate (n = 5). All patients completed their RT course. Sixty-seven percent received craniospinal irradiation (CSI) while 33% received focal brain RT, with the olfactory region receiving doses as low as 0.5 Gy. Notably, 8 of 27 patients who received CSI (30%) reported phantosmia (odds ratio, 7.66; 95% confidence interval, 2.07-28.34; P = .002).

Conclusions: In the first-ever study examining radiation-induced phantosmia among children and young adults treated with IMPT, all affected patients received irradiation dose to the olfactory region. Physician awareness of phantosmia, especially in the context of CSI,

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may improve the patient experience and treatment compliance. A prospective study is needed to elucidate frequency, severity, and phantosmia mechanism.

Introduction

Phantosmia is characterized as a qualitative olfactory disorder resulting in the perception of a foul-smelling odor without odorant stimulus. Phantom smell has been reported in cases of psychiatric disorders, head injuries, intake of drugs with varying mechanisms of action, and seizures.[1] Olfaction begins when receptors in the olfactory epithelium are activated, which triggers a complex sequence of biochemical reactions that ultimately send a signal to the olfactory bulb. This signal is, in turn, translated into an odor perception by the olfactory cortex located in the inferior frontal and medial temporal lobes. The cause of phantosmia is still largely unknown; however, research has suggested that peripheral phantosmia is due to impaired olfactory receptor and neuron function while central phantosmia is caused by damaged cortical olfactory pathways. Medical and surgical treatments have been explored in the management of phantosmia; however, results and techniques have varied, leaving phantosmia diagnosis and treatment without strong and thorough guidelines to date.[2]

Radiation-induced phantosmia has been reported as a side effect of radiation therapy (RT) in children, adolescents, and young adults (AYAs) with a variety of intracranial neoplasms. Phantosmia can greatly affect the patient's quality of life during and after treatment and can also disrupt a treatment regimen, especially in younger patients.[3,4] Additionally, other side effects of cranial RT, such as taste disturbances, blurry vision, flashing lights, and nausea, have been reported to accompany phantosmia and, as a result, increase toxicity burden of this unique patient population.[5,6] For example, prior reports have shown that in some patients with radiation induced sensory changes, taste acuity may only partially recover or not recover at all, leading to excessive weight loss and a significant effect on patients' quality of life.[7]

A variety of clinical, tumor, and treatment-related characteristics may affect olfactory perception of patients receiving cranial RT.[5,8] Understanding these characteristics, as well as examining incidence and effect of radiation-induced phantosmia, is critical to improving care of pediatric and AYA patients, an increasingly large proportion of whom are treated with proton beam therapy (PBT) for their intracranial tumors. However, clinical data characterizing olfactory disturbances during PBT are limited. Therefore, we conducted a study to examine and characterize the phenomenon of phantosmia in a large cohort of pediatric and AYA patients treated with pencil beam scanning (PBS) PBT to intracranial, base of skull, nasopharyngeal, and sinonasal tumors. We also aimed to identify potential clinical and treatment-related characteristics that may correlate with the development of phantosmia in this population. We hypothesized that pediatric and AYA patients who receive PBS-PBT to tumors located in or adjacent to the olfactory cortex are more likely to develop phantosmia than patients receiving PBS-PBT elsewhere intracranially. To the best of our knowledge, this is the first study that has examined radiation-induced phantosmia among children and AYAs treated with PBS-PBT.

Methods and Materials

This was a retrospective study of phantosmia reported by pediatric and AYA patients receiving PBS-PBT to intracranial, base of skull, nasopharyngeal, and sinonasal tumors. All consecutive patients treated at a PBS-only proton center from August 1, 2019, to December 31, 2020, who met the inclusion criteria were included in the study. Inclusion criteria were (1) patients with intracranial primary neoplasms, intracranial metastatic neoplasms, skull base neoplasms, or nasopharyngeal/sinonasal neoplasms, who were (2) treated with PBS-PBT, and (3) age 39 and younger. Those patients who were 40 years of age and older at the time of proton therapy and/or received anesthesia during treatment were excluded from the study. Patients who were sedated during treatment were excluded, as in our institution phantosmia has been noted to occur largely during RT sessions, requiring patients to be conscious during treatment to make note of phantosmia symptoms. These criteria resulted in the inclusion of 99 patients in the analysis.

Phantosmia-specific variables of interest included: presence of phantosmia before treatment; development of phantosmia at the time of treatment; timing of event in relation to RT; severity, frequency, and duration of each phantosmia episode; description of phantosmia symptoms; progression of symptoms; timing of odor resolution; and interventions used. The severity of phantosmia was graded by the intervention needed (mild, no intervention; moderate, supportive treatment; severe, discontinuation of radiation). Phantosmia-specific variables were obtained from on-treatment visit (OTV) notes. As phantosmia is not a standard toxicity reviewed during OTVs, phantosmia was recorded only if patients reported this toxicity during OTVs and it was subsequently

documented by the provider. Additionally, data on patient's age; gender; Karnofsky performance scale score; tumor histology; radiation field; RT dose; use of other treatments such as chemotherapy, surgery and/or antiepileptic drugs; and development of other acute or subacute toxicities (Common Terminology Criteria for Adverse Events v5.0 grade ≥2) were collected for analysis.

To account for variations in reported performance scores, Karnofsky performance scale scores were converted to Eastern Cooperative Oncology Group (ECOG) performance scores. Dose to the olfactory region, which was defined to include the olfactory bulb and tract, was obtained from external beam treatment plans (Eclipse; Varian Medical Systems, Palo Alto, CA) of patients who experienced phantosmia. Univariate analysis comparing patient, clinical, and treatment-related characteristics between patients who experienced phantosmia and those who did not was performed using the χ^2 test and Kruskal-Wallis test for categorical and continuous variables, respectively. Parameters significantly associated with development of phantosmia ($P < .1$) or deemed a priori to be clinically relevant were selected for inclusion on multivariable logistic regression models. As the mechanism of radiation-induced phantosmia is unknown, an odds ratio (OR) was calculated to elucidate the correlation of the use of chemotherapy, antiepileptic drugs, and craniospinal irradiation (CSI) treatment with the development of phantosmia. We hypothesized that chemotherapy may increase the risk of developing phantosmia, potentially suggesting a biochemical mechanism underlying this unusual phenomenon. We also hypothesized that antiepileptic drugs may correlate with a decreased risk of phantosmia if we assume that the mechanism responsible for phantosmia is similar to the one responsible for focal seizures. Finally, we hypothesized that CSI treatment may increase the risk of developing phantosmia, suggesting a radiation-induced mechanism within a specific brain region. $P < .05$ was considered to be statistically significant.

Results

A total of 99 patients were included in the data set (Table 1). The median age of patients was 18 years old (2-39), 60.6% were male, and 56.6% had an ECOG score of 0. The most common tumor histologies were medulloblastoma (14.1%), rhabdomyosarcoma (13.1%), low-grade glioma (11.1%), high-grade glioma (10.1%), and germinoma (8.1%). Nearly three-quarters (73.7%) of patients were treated for primary disease, whereas 24.2% were treated for recurrent disease and 2.0% for metastatic disease. Ten patients (10.1%) had received prior RT, 29.3% underwent surgery, 25.3% received chemotherapy either before or concurrently with RT, and 34.3% underwent both chemotherapy and surgery. Twenty-six (26.3%)

Table 1 Patient, tumor, and treatment-related characteristics

		N = 99 (%)
Age, y, median (range)		18 (2-39)
Gender	Female	39 (39.4)
	Male	60 (60.6)
ECOG	0	56 (56.6)
	1	20 (20.2)
	2	6 (6.1)
	3	1 (1.0)
	Unknown	16 (16.2)
Primary tumor histology	Medulloblastoma	14 (14.1)
	Rhabdomyosarcoma	13 (13.1)
	Low grade glioma	11 (11.1)
	High-grade glioma	10 (10.1)
	Germinoma	8 (8.1)
	Ependymoma	5 (5.1)
	Nasopharyngeal Carcinoma	5 (5.1)
	Meningioma	3 (3.0)
	Neuroblastoma	3 (3.0)
	Oligodendroglioma	3 (3.0)
	Pituitary adenoma	3 (3.0)
	Pleomorphic Xanthoastrocytoma	3 (3.0)
	Other	18 (18.2)
Disease	Primary	73 (73.7)
	Recurrent	24 (24.2)
	Metastatic	2 (2.0)
Tumor location	Intracranial	64 (64.6)
	Skull base	16 (16.2)
	Nasopharyngeal	12 (12.1)
	Sinonasal	7 (7.1)
Prior RT	No	89 (89.9)
	Yes	10 (10.1)
Radiation alone	No	88 (88.9)
	Yes	11 (11.1)
Other treatment	Chemotherapy	25 (25.3)
	Surgery	29 (29.3)
	Chemotherapy and surgery	34 (34.3)
	None	11 (11.1)
Use of chemotherapy Concurrently or before RT	No	43 (43.4)
	Yes	56 (56.6)
Seizures before/during RT	No	86 (86.9)
	Yes	13 (13.1)
Concurrent use of antiepileptics	No	79 (79.8)
	Yes	20 (20.2)
Radiation field	Partial brain	73 (73.7)
	Whole brain	26 (26.3)
Craniospinal irradiation	No	73 (73.7)
	Yes	26 (26.3)
RT cumulative dose, Gy CGE, median (range)		45 (14.8-74)
RT dose per fraction, Gy CGE, median (range)		1.8 (1.5-3.7)

Abbreviations: CGE = cobalt gray equivalent; ECOG = Eastern Cooperative Oncology Group; RT = radiation therapy.

Table 2 Acute toxicity events, CTCAE grade 2 or higher

		All patients N = 99 (%)	Toxicity grade 2	3
Toxicity	No	52 (52.5)		
	Yes	47 (47.5)		
Toxicity grade	2	47 (47.5)		
	3	4 (4.0)		
Acute weight loss	No	93 (94.0)		
	Yes	6 (6.0)	5	1
Pain	No	91 (91.9)		
	Yes	8 (8.1)	7	1
Nausea	No	87 (87.9)		
	Yes	12 (12.1)	12	-
Emesis	No	95 (96.0)		
	Yes	4 (4.0)	4	-
Radiation dermatitis	No	92 (92.9)		
	Yes	7 (7.1)	7	-
Blurred vision	No	97 (98.0)		
	Yes	2 (2.0)	2	-
Alopecia	No	82 (82.8)		
	Yes	17 (17.2)	17	-
Skin erythema	No	96 (97.0)		
	Yes	3 (3.0)	3	-
Fatigue	No	79 (79.8)		
	Yes	20 (20.2)	20	-
Headache	No	94 (94.9)		
	Yes	5 (5.1)	4	1
Lethargy	No	98 (99.0)		
	Yes	1 (1.0)	1	-

Abbreviation: CTCAE = Common Terminology Criteria for Adverse Events.

patients underwent CSI. The median cumulative RT dose was 45 (14.8-74) Gy cobalt gray equivalents (CGE) and the median dose per fraction was 1.8 (1.5-3.7) Gy (CGE).

Selected acute grade 2 or higher toxicities for all patients are described in Table 2. Not including phantosmia, 47 patients experienced at least one acute toxicity of grade 2, and 4 patients experienced at least one acute toxicity of grade 3. The most common reported grade ≥2 toxicities were fatigue (20.2%), alopecia (17.2%), nausea (12.1%), pain (8.1%), and radiation dermatitis (7.1%).

Of the 99 included patients, 12 patients reported phantosmia symptoms. Univariate analysis comparing patient, tumor, and treatment-related variables is described in Table 3. A larger proportion of patients who reported phantosmia received whole brain irradiation (as part of CSI treatment) compared with patients who did not report phantosmia (66.7% vs 20.7%, P = .002), respectively. There were no significant differences in age, gender, ECOG score, tumor location, history of prior RT, history of prior surgeries, use of prior or concurrent chemotherapy, use of antiepileptics, or median dose per fraction between patients who did and did not report phantosmia. Alopecia was a more common acute toxicity in patients with phantosmia compared with patients who did not experience phantosmia (41.7% vs 13.8%, P = .046). On multivariate analysis, no included variable predicted a higher probability of developing phantosmia.

Clinical and treatment-related variables of patients who reported phantosmia are described in Table 4. None of the patients had experienced a phantom smell before RT. The median age of patients reporting phantosmia was 17 years (12-33); 12.5% of patients <18 years old versus 11.5% of patients ≥18 years of age reported phantosmia (P = 1.0). Eight (66.7%) patients were male and 11 (91.7%) had intracranial tumors. Among those who experienced phantosmia, 4 patients were taking antiepileptic drugs during the course of RT (33.3%; OR, 2.22; 95% confidence interval [CI], 0.59-8.28; P = .24), 2 of whom had a history of seizures. Seven (58.3%) patients received chemotherapy (OR, 1.09; 95% CI, 0.32-3.70; P = .90). Chemotherapy regimens included vincristine (n = 4), temozolomide (n = 1), carboplatin-etoposide (n = 1), and carboplatin-etoposide-ifosfamide (n = 1). Ten (83.3%) patients underwent surgery before RT. None of the patients previously received RT.

All patients who reported phantosmia received some dose of radiation to the olfactory region. Eight of the 26 patients who received CSI (30%) reported phantosmia, indicating a significant correlation with development of phantosmia (OR, 7.66; 95% CI, 2.07-28.34; P = .002). Seven of the 8 patients with phantosmia who received CSI reported symptom resolution upon completion of the whole brain portion of treatment. The other 4 patients who reported phantosmia and did not receive CSI, received focal brain RT, with the olfactory region receiving doses as low as 0.5 Gy (0.5-5.0). The average cumulative radiation dose and dose per fraction among patients who developed phantosmia was 28.4 Gy CGE (18-54) and 1.8 Gy CGE (1.8), respectively.

Phantosmia-related variables are described in Table 5. The phantom odor was described as a "chlorine," "broccoli," "stale water," "metallic," or "noxious" smell. Ten patients (83.3%) experienced accompanying toxicities, including taste changes (n = 3), visual disturbances (n = 5) such as flashing and purple lights, and nausea/emesis (n = 7). Six patients reported other acute toxicities, including alopecia (n = 5), fatigue (n = 2), and headache (n = 1). All patients noted phantosmia to begin during the RT treatment. The phantosmia symptoms remained stable for 66.7% of patients, improved with more fractions for 25% of patients, and worsened for 8.3% of patients. All patients were able to complete their RT course as planned without treatment breaks.

Table 3 Comparison of patient, tumor, and treatment-related characteristics between patients who experienced and did not experience phantosmia

		No phantosmia n = 87 (%)	Phantosmia n = 12 (%)	*P* value
Age, y, median (range)		19 (2-39)	17 (12-33)	.771
Gender	Female	35 (40.2)	4 (33.3)	.886
	Male	52 (59.8)	8 (66.7)	
ECOG	0	48 (55.2)	8 (66.7)	.862
	1	18 (20.7)	2 (16.7)	
	2	6 (6.9)	0 (0.0)	
	3	1 (1.1)	0 (0.0)	
	Unknown	14 (16.1)	2 (16.7)	
Primary tumor histology	Medulloblastoma	10 (11.5)	4 (33.3)	.072
	Rhabdomyosarcoma	13 (14.9)	0 (0.0)	
	Low grade glioma	10 (11.5)	1 (8.3)	
	High-grade glioma	9 (10.3)	1 (8.3)	
	Germinoma	4 (4.6)	4 (33.3)	
	Ependymoma	5 (5.7)	0 (0.0)	
	Nasopharyngeal Carcinoma	5 (5.7)	0 (0.0)	
	Meningioma	3 (3.4)	0 (0.0)	
	Neuroblastoma	3 (3.4)	0 (0.0)	
	Oligodendroglioma	3 (3.4)	0 (0.0)	
	Pituitary adenoma	3 (3.4)	0 (0.0)	
	Pleomorphic Xanthoastrocytoma	3 (3.4)	0 (0.0)	
	Other	16 (18.4)	2 (16.7)	
Disease	Primary	62 (71.3)	11 (91.7)	.317
	Recurrent	23 (26.4)	1 (8.3)	
	Metastatic	2 (2.3)	0 (0.0)	
Tumor location	Intracranial	53 (60.9)	11 (91.7)	.197
	Skull base	15 (17.2)	1 (8.3)	
	Nasopharyngeal	12 (13.8)	0 (0.0)	
	Sinonasal	7 (8.0)	0 (0.0)	
Prior RT	No	77 (88.5)	12 (100.0)	.467
	Yes	10 (11.5)	0 (0.0)	
Radiation alone	No	76 (87.4)	12 (100.0)	.414
	Yes	11 (12.6)	0 (0.0)	
Other treatment	Chemotherapy	23 (26.4)	2 (16.7)	.416
	Surgery	24 (27.6)	5 (41.7)	
	Chemotherapy and surgery	29 (33.3)	5 (41.7)	
	None	11 (12.6)	0 (0.0)	
Use of chemotherapy concurrently or before RT	No	38 (43.7)	5 (41.7)	1
	Yes	49 (56.3)	7 (58.3)	
Seizures before/during RT	No	76 (87.4)	10 (83.3)	1
	Yes	11 (12.6)	2 (16.7)	
Concurrent use of antiepileptics	No	71 (81.6)	8 (66.7)	.409
	Yes	16 (18.4)	4 (33.3)	
Acute toxicity, grade 2 or higher	No	46 (52.9)	6 (50.0)	1
	Yes	41 (47.1)	6 (50.0)	
Radiation field	Partial brain	69 (79.3)	4 (33.3)	.002
	Whole brain	18 (20.7)	8 (66.7)	
Craniospinal irradiation	No	69 (79.3)	4 (33.3)	.002
	Yes	18 (20.7)	8 (66.7)	
RT cumulative dose, Gy CGE, median (range)		46 (14.8-74)	23.4 (18-54)	.001
RT dose per fraction, Gy CGE, median (range)		1.8 (1.5-3.7)	1.8 (1.8-1.8)	.239

Abbreviations: CGE = cobalt gray equivalent; ECOG = Eastern Cooperative Oncology Group; RT = radiation therapy.

Table 4 Patient, tumor, and treatment-related characteristics of patients who reported phantosmia

Gender	Age, y	Primary diagnosis	Disease	Tumor location	Prior RT	Other treatment	Type of chemotherapy	Use of antiepileptic drugs	Seizures (prior or during)	Radiation field	CSI	RT cumulative dose (Gy CGE)	RT dose per fraction (Gy CGE)
Male	14	Germinoma	Primary	Intracranial	No	Surgery	-	No	No	Whole brain	Yes	1800	180
Female	16	Medulloblastoma	Primary	Intracranial	No	Chemotherapy and surgery	Vincristine	Yes	No	Whole brain	Yes	2340	180
Male	21	Germinoma	Primary	Intracranial	No	Surgery	-	Yes	No	Partial brain	No	1800	180
Male	33	Low grade glioma	Recurrent	Intracranial	No	Chemotherapy	Temozolomide	No	No	Partial brain	No	5400	180
Male	19	Medulloblastoma	Primary	Intracranial	No	Chemotherapy and surgery	Vincristine	No	No	Whole brain	Yes	2340	180
Male	13	Germinoma	Primary	Skull base	No	Chemotherapy and surgery	Carboplatin-etoposide	No	No	Partial brain	No	1800	180
Male	18	High-grade glioma	Primary	Intracranial	No	Surgery	-	Yes	Yes	Partial brain	No	5400	180
Female	12	Medulloblastoma	Primary	Intracranial	No	Surgery	-	No	No	Whole brain	Yes	1800	180
Female	26	HGNET	Primary	Intracranial	No	Surgery	-	No	No	Whole brain	Yes	2340	180
Male	14	PPTID	Primary	Intracranial	No	Chemotherapy and surgery	Vincristine	No	No	Whole brain	Yes	3600	180
Female	23	Medulloblastoma	Primary	Intracranial	No	Chemotherapy and Surgery	Vincristine	Yes	Yes	Whole brain	Yes	2340	180
Male	15	Germinoma	Primary	Intracranial	No	Chemotherapy	Carboplatin, etoposide, and ifosfamide	No	No	Whole brain	Yes	3060	180

Abbreviations: CGE = cobalt gray equivalent; CSI = craniospinal irradiation; HGNET = high-grade neuroepithelial tumor; PPTID = pineal parenchymal tumor of intermediate differentiation; RT = radiation therapy.

Table 5 Phantosmia-related variables for patients who reported phantosmia

					Sensory and/or other disturbances								Intervention					
Phantosmia before RT	Severity	First phantosmia reported	Timing of phantosmia	Accompanying sensory disturbances	Flashing lights	Taste changes	Nausea	Emesis	Purple lights	Description of phantosmia symptoms	Phantosmia progression during RT	Intervention used	Essential oil	Vicks	Chewing gum	Antiemetics	Timing of phantosmia resolution	Other acute toxicities (grade 2)
No	Moderate	1st week	During RT delivery	Yes	No	Yes	Yes	Yes	No	NA	Worsened	Yes	Yes	No	No	No	Completion of CSI	Alopecia
No	Moderate	2nd week	During and after RT delivery	Yes	No	Yes	Yes	Yes	No	NA	Stable	Yes	Yes	No	Yes	Yes	Completion of CSI	Nausea, alopecia, fatigue
No	Mild	1st week	During RT delivery	Yes	No	No	No	No	Yes	Chlorine	Improved w/ additional fractions	No	No	No	No	No	Completion of RT	None
No	Mild	2nd week	Sometime after RT delivery	No	No	No	No	No	No	Broccoli	Stable	No	No	No	No	No	Completion of RT	None
No	Mild	1st week	During RT delivery	No	No	No	No	No	No	Chlorine	Improved w/ additional fractions	No	No	No	No	No	4 weeks into treatment	None
No	Mild	1st week	During RT delivery	Yes	No	No	Yes	No	No	Chlorine	Stable	No	No	No	No	No	1 report during boost	None
No	Mild	1st week	During varying RT delivery	Yes	No	Yes	No	No	No	Indescribable	Stable	No	No	No	No	No	Completion of RT	None
No	Moderate	1st week	During RT delivery	Yes	Yes	No	Yes	Yes	No	NA	Stable	No	No	No	No	Yes	Completion of CSI	Headache
No	Moderate	2nd week	During and after RT delivery	Yes	Yes	No	Yes	Yes	No	Noxious	Stable	Yes	No	Yes	No	Yes	Completion of CSI	Alopecia
No	Mild	1st week	During RT delivery	Yes	No	No	Yes	No	No	Stale Water	Stable	No	No	No	No	No	Completion of CSI	Alopecia, fatigue
No	Mild	1st week	During RT delivery	Yes	Yes	No	No	No	Yes	Chlorine	Improved w/ additional fractions	No	No	No	No	No	Completion of CSI	None
No	Moderate	1st week	During RT delivery	Yes	Yes	No	Yes	No	No	Metallic	Stable	Yes	Yes	No	No	No	Completion of CSI	Alopecia

Abbreviations: CSI = craniospinal irradiation; RT = radiation therapy.

Phantosmia was categorized as mild for 7 patients and moderate for 5 patients. The 5 patients who experienced moderate phantosmia required an intervention to continue treatment; 3 patients received essential oils to smell during treatment, 1 of whom required the addition of chewing gum and oral antiemetic ondansetron. The 2 other patients also required oral antiemetic ondansetron, one of whom used Vicks VapoRub applied to the nasolabial fold during treatment as well. The other 7 patients did not require any intervention to complete therapy.

Discussion

This is the first study evaluating radiation-induced phantosmia in pediatric and AYA patients receiving cranial irradiation with PBT. Our study identified phantosmia toxicity to be reported in 12% of children and AYA patients treated with PBS proton therapy for primary intracranial, metastatic intracranial, skull base, nasopharyngeal, or sinonasal neoplasms. All patients who developed phantosmia reported smell symptoms during their RT treatment, and in most patients these symptoms remained stable until the completion of RT. CSI was significantly correlated with development of phantosmia; furthermore, phantosmia symptoms did not resolve until completion of the whole brain component of the CSI. Considering these findings, it is important that physicians treating patients with cranial RT discuss phantosmia as a potential side effect of PBT, ask patients about olfactory disturbances during weekly OTVs, and be prepared to adequately manage moderate to severe phantosmia. In our study, 42% of patients who experienced phantosmia had moderate symptoms requiring interventions that allowed them to complete the entire treatment course without interruption. Further understanding of the mechanisms and risk factors for the development of olfactory toxicities associated with cranial proton irradiation may help improve patients' quality of life and compliance with treatment.[9]

One of the first reports of radiation-induced phantosmia in pediatric patients treated with cranial RT was published in 2012 by Yang et al. [3] The authors described findings of olfactory disturbances in a 6-year-old boy with diffuse intrinsic pontine glioma treated with a 6-week course of involved field photon RT concurrently with vorinostat, and a 15-year-old male with gliomatosis cerebri who received a course of photon RT of 54 Gy in 1.8 Gy fractions with concurrent temozolomide. The first patient initially reported an abnormal smell at day 22 of treatment, while the second patient reported phantosmia at day 2 of treatment. Although both patients received chemotherapy, the time-course of reported phantosmia aligned with the start and end of radiation treatment.

There have been recent retrospective studies characterizing radiation-induced phantosmia in patients treated with photon-based techniques. In 2019, Obinata et al[10] assessed the reported abnormal olfactory sensations of 191 patients with primary brain tumors treated with photon RT. A total of 3.7% of patients reported unpleasant olfactory sensations during irradiation. The authors of the study found no difference in dose to the olfactory region or target volume of radiation between patients who reported phantosmia and those who did not. However, they did find that a majority of patients with unusual olfactory perception were younger than 20 years old. In another retrospective study aimed at determining the prevalence of olfactory side effects in patients receiving photon RT to the olfactory system, Sagar et al[5] sent a questionnaire to patients whose treatment volumes included the olfactory region and to those whose treatment volumes excluded the olfactory region (ie, a control group). Their results suggested that radiation to the olfactory region, including the maxillary antrum, nasopharynx, pituitary gland, and frontal lobe, as well as whole brain irradiation, induced a smell toxicity in a significant number of cases compared with the control group, which experienced no smell toxicity. Additionally, in 2014, Leyrer et al[6] conducted a prospective study of 22 patients with low- and high-grade gliomas treated with cranial RT, which found an association between development of taste toxicity and smell disturbances and that patients with temporal lobe tumors or radiation dose to the nasopharynx have a higher probability of experiencing smell toxicities. Our study suggests that any dose to the olfactory region, even as low as 0.5 Gy, is sufficient to induce a phantom smell, which is consistent with previous research.

The mechanism of radiation-induced phantosmia is still largely unknown. It was previously suggested that phantom odor is due to the environmental ozone formed in the proximity of the radiation beams; however, another study by Costello et al[11] found the ozone level concentration was too low to produce a phantom odor.[5] Rather, it is likely that phantosmia is the result of other proposed mechanisms, such as hyperactive olfactory receptor neurons or inactive inhibitory neurons.[2]

In our study, one-third of patients who experienced phantosmia required intervention, including essential oils, Vicks, chewing gum, and antiemetics, to continue PBT. Currently, there is no standardized treatment strategy for patients developing radiation-induced olfactory toxicity. A recent study by Raghavan et al[12] described the use of propofol total intravenous anesthesia as a treatment for severe radiation-induced phantosmia. The patient described in the report was a 16-year-old girl diagnosed with myxopapillary ependymoma treated with proton therapy treatment. Without the total intravenous anesthesia intervention, the patient was nauseous, gagging, and vomiting because of the unpleasant odor during radiation

treatments; however, with anesthesia, these distressing symptoms completely resolved. Obinata et al[10] documented the use of various interventions to combat the foul smell with RT delivery. One patient filled their nasal cavity with swabs, 3 smelled essential oils before each treatment, and 1 initially smelled essential oils but eventually needed sedation to continue treatment. No adverse effects were reported from the sedation. Other potential interventions for radiation-induced phantosmia that have not yet been studied but were described in the literature on the management of nonradiation-induced olfactory disorders include topical cocaine; propofol in subanesthetic antiemetic doses; antipsychotic, antimigraine, and antiepileptic medications; and magnetic stimulation.[2,12] Prospective studies are needed to identify both effective and safe interventions that will constitute a standard practice for treating patients suffering from radiation-induced phantosmia.

Although this is the first study investigating phantosmia among pediatric and AYA patients undergoing cranial PBT, the retrospective design of this study poses major limitations. Odorous smells are not a standard radiation toxicity; therefore, there is a likelihood that phantosmia was underreported in this study, as patients who were not asked about these symptoms may not have reported them unprompted to the medical staff. Additionally, physicians may not have documented smell toxicities, as smell toxicities are not included in the standard OTV. Importantly, whenever the treating radiation oncologist did report phantosmia, details describing specific types of smell, intensity, timing, and length of phantosmia were sparsely documented in OTV notes. Additionally, it was beyond the scope of our study to evaluate a comprehensive dose-volumetric analysis of parameters associated with the risk of radiation-induced phantosmia; therefore, future research is needed to elucidate the association of radiation dose to the olfactory region and volume of the irradiated olfactory bulb and olfactory disturbances. Prospective studies are needed to accurately characterize and understand this toxicity. As younger children may have difficulty understanding and conveying information about olfactory side effects to their treating physician, special consideration should be made to involve child life specialists, therapists, and nursing staff, as well as parents to ensure that olfactory disturbances of the entire pediatric patient population are being accurately captured. Additionally, further research is needed to identify patients at risk for developing phantosmia, which will allow for timely intervention and, in turn, will enable completion of treatment without interruptions and/or significant decrement in patients' quality of life.

Conclusion

This is the largest retrospective study to date investigating phantosmia among pediatric and AYA patients and the first such study in patients receiving cranial PBTs. All patients who developed phantosmia received some radiation dose to the olfactory region. Additionally, there was a significant association between CSI treatment and the development of phantosmia toxicity. To improve patients' experience and treatment compliance, physician awareness of radiation-induced olfactory disturbances is necessary. Physicians treating pediatric and AYA patients with cranial RT should discuss phantosmia as a potential side effect of treatment, ask patients about it during weekly status checks, and be prepared to manage it in a timely fashion. Prospective studies are needed to elucidate mechanisms of phantosmia and further examine its incidence and associated risk factors.

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