

Unusual olfactory perception during radiation sessions for primary brain tumors: a retrospective study

Mika Obinata*, Kana Yamada and Keisuke Sasai

Department of Radiation Oncology, Graduate School of Medicine, Juntendo University

*Corresponding author: Department of Radiation Oncology, Faculty of Medicine, Juntendo University, 2-1-1 Hongo, Bukyo-ku, 113-8421, Tokyo, Japan.

Email: m-obinata@juntendo.ac.jp

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ABSTRACT

During irradiation sessions for brain tumors or head and neck cancers, some patients experience abnormal olfactory sensations. To date, the frequency of such sensations during these treatment sessions has not been investigated. We analyzed abnormal olfactory sensations in patients who underwent radiation therapy at our institution for primary brain tumors, excluding malignant lymphoma, between January 2009 and January 2018. A total of 191 patients who were awake during radiation treatment and capable of communicating were analyzed in this retrospective medical study. Of these patients, 7 were aware of olfactory sensations during irradiation. The median age of these 7 patients was 13 (range 8–47) years. Six were <20 years of age, accounting for 10% of the total population of similar age ($n = 60$). However, only 1 of 131 patients aged ≥ 20 years complained of strange olfactory sensations. Four of seven patients had germ cell tumors, but none had a medulloblastoma. We investigated patients who experienced light sensation, as an internal standard to ascertain the accuracy of this study. Only 10 patients experienced light sensation during their irradiation sessions. This suggests that the frequency of these sensations was possibly underestimated in our study. In conclusion, a considerable number of patients experienced unusual olfactory sensations during radiation treatment. Further prospective studies on abnormal olfactory sensations during irradiation are needed to clarify the underlying mechanism of this sensation.

Keywords: olfactory perception; phantosmia; phosphene; brain tumor; radiation

INTRODUCTION

With recent rapid advances in radiation therapy, multi-directional beams are commonly used in intensity-modulated radiation therapy (IMRT) and volumetric-modulated arc therapy (VMAT). Therefore, unexpected exposure of the eyes and/or olfactory organs to ionizing radiation frequently occurs. During irradiation sessions for brain tumors or head and neck cancers, some patients experience abnormal sensations of light or smell [1–6]. There have been several studies on anomalous visual perception, that is sometimes known as phosphene, and the authors of those studies have suggested that this effect is due to Cherenkov emissions [4–6].

On the other hand, although two cases of olfactory sensation were reported at the Memorial Sloan Kettering Cancer Center in 2012 [3], there has been no report on the frequency of such sensations during radiation sessions or related factors in the modern era of precise treatment. The cause of this phenomenon is unclear: Patients may smell a

substance such as ozone generated by the radiation [1] or may have a phantosmia [3], which is the sensation of an unpleasant odor that does not exist. Such unusual perceptions may disrupt radiation therapy. Predicting the risk of such sensations in advance would make it possible to take measures to prevent the interruption of radiation therapy. Furthermore, patients could then be relieved of such odors. In this retrospective medical chart study, we analyzed abnormal sensations during irradiation sessions in patients who underwent radiotherapy for primary brain tumors at our institution.

MATERIALS AND METHODS

Between January 2009 and January 2018, 218 consecutive patients with primary brain tumors, excluding malignant lymphoma, received radiation therapy at our institution. Among them, 15 were children (between 1 and 7 years old) treated under sedation, and 12 were suffering from mental deterioration due to the tumors themselves.

Table 1. Patient characteristics and frequencies of abnormal sensations experienced

Characteristics	Number of cases	Abnormal olfactory sensations	Abnormal light sensations
	191	7 (3.7)	10 (5.2)
Age median (range)	46 (4–88)		
<20 years old	60	6 (10)	1 (1.6)
>20 years old	131	1 (0.8)	9 (6.9)
Sex			
Male	101	5 (5.0)	3 (3)
Female	90	2 (2.2)	7 (7.7)
Primary disease			
Gliomas and glioblastoma	102	0 (0)	6 (5.9)
Ependymoma	11	2 (18)	0 (0)
Medulloblastoma	17	0 (0)	0 (0)
Germinoma	23	4 (17)	1 (4.3)
Meningioma	16	0 (0)	1 (6.2)
Pituitary adenoma	7	1 (14)	2 (29)
Others	15	0 (0)	0 (0)
Site of lesions			
Cerebrum			
Frontal lobe	35	0 (0)	1 (2.9)
Parietal lobe	23	0 (0)	2 (8.7)
Occipital lobe	9	0 (0)	0 (0)
Temporal lobe	42	1 (2.3)	4 (9.5)
Lateral ventricle	4	0 (0)	0 (0)
Basal ganglia and/or hypothalamus	6	1 (17)	0 (0)
Pineal body	15	3 (20)	1 (6.7)
Posterior fossa	40	1 (2.5)	0 (0)
Pituitary gland or suprasellar	16	1 (6.2)	2 (13)
Others	1	0 (0)	0 (0)
Method for confirmation of pathological diagnosis			
Craniotomy and tumorectomy	154	3 (1.9)	7 (4.5)
Tumorectomy through the nose	7	1 (14)	2 (29)
Craniotomy and biopsy	1	1 (13)	0 (0)
Endoscopic biopsy	15	2 (13)	1 (6.7)
Unexamined	6	0 (0)	0 (0)
Radiation therapy technique			
Conventional	33	1 (3.0)	0 (0)
3D-CRT	90	2 (2.2)	1 (1.1)
IMRT	67	4 (6.0)	8 (12)
SRT	1	0 (0)	1 (100)

Values in brackets are percentages. 3D-CRT = 3D conformal radiation therapy, IMRT = intensity-modulated radiation therapy, SRT = stereotactic radiation therapy.

Therefore, 191 patients who were awake during irradiation and were able to communicate with other people were analyzed. Table 1 shows the characteristics of the patients and details of their treatment.

Patients were irradiated with 6 or 10 MV X-rays from a linear accelerator (Clinac 21 EX or True Beam; Varian, Palo Alto, CA, USA or TomoTherapy; Accuray, Sunnyvale, CA, USA). Patients with high-grade gliomas including glioblastoma usually received radiation therapy with a generous field size up to 50 Gy in 25 fractions, followed by a boost of 10 Gy in 5 fractions. They also received concurrent chemotherapy using temozolomide with or without other agents. Children with medulloblastoma received craniospinal irradiation of 23.4–39.6 Gy depending on their risk grade and a boost to the

posterior fossa and/or tumor bed. Patients with germinoma received chemotherapy initially and then received whole-ventricle or generous field radiation therapy of 23.4–30.6 Gy in 13–17 fractions. Patients with ependymomas received localized field radiation therapy. Clinical target volumes for pituitary adenoma are almost the same as the gross tumor volume. Almost all patients were irradiated with 3D conformal radiation therapy (3D-CRT), IMRT or VMAT. Whole-brain irradiation was performed with a pair of opposing fields but with the beams angled so that the anterior edges were parallel. Additional fields were added to compensate for dose inhomogeneity.

Patients' medical records were retrospectively investigated. During radiation therapy, patients were evaluated by radiation oncologists

at least once a week. Other physicians and medical staff, including radiation therapy technicians, also saw patients and recorded their observations. Abnormal olfactory sensations during irradiation and the time at which medical staff became aware of patients' complaints, the primary disease, the radiation therapy modality (target, irradiation technique, dose administered) and countermeasures were studied. Steidley *et al.* reported that all patients who received radiation in their eyes reported experiencing phosphene [4]. Therefore, patients who complained of perceptions of light during irradiation sessions were also identified as an internal standard to evaluate the accuracy of this study. Radiation oncologists, other physicians or medical staff discussed these sensations with their patients only if the patients mentioned them voluntarily.

The radiation dose delivered to a specific anatomical site is important. Therefore, we recalculated the dose distribution using Eclipse ver. 13.6.32 with AAA (Varian Medical Systems, Palo Alto, CA, USA) for True Beam/Clinac 21 EX, or Planning Station ver. 2.1.3 (Accuray, Sunnyvale, CA, USA) for TomoTherapy. The dose distributions to these sites were very heterogeneous, and the highest dose would be an important cause of unusual sensations. Therefore, we selected D_2 (Gy)/fraction as the representative dose delivered to the olfactory region or orbit. D_2 is the minimum absorbed dose of the hottest 2% volume of the region of interest [7]. The olfactory region extends over the upper 10 mm of the septum, over the superior concha, and includes the lateral walls above the concha [1, 8]. Therefore, these areas of the nasal cavity were contoured just before the sphenoid sinus and visualized under a lung window/level (see Supplementary Figure 1, available as online Supplementary material).

The study protocol was approved by the institutional review board (#17–310) of our hospital, and the need for informed consent was waived. This study was conducted in accordance with the Declaration of Helsinki and Japanese ethical guidelines for epidemiologic research.

RESULTS

Of a total of 191 patients, 7 (3.7%) were aware of abnormal unpleasant olfactory sensations during irradiation sessions. Tables 1 and 2 show the patient details. Five patients experienced an odor during irradiation only and one experienced an odor during his stay in the radiotherapy room. Another patient (#7) initially experienced an odor during the irradiation session only but later insisted that he could also smell the odor in the corridor in front of the radiotherapy room.

The first day that patients complained of an abnormal sensation ranged from day 3 to day 23 (median day 11) after the commencement of radiation therapy. The complaints of 4 patients were recorded on the chart only once. Two patients required nothing to relieve the odor, 1 stuffed their nasal cavities with swabs, 3 sniffed essential oils and 1 patient initially sniffed essential oils but ultimately required sedation.

The median age of the 7 patients was 13 years (8–47 years) at the start of radiation therapy. Six were <20 years of age, i.e. 10% of the 60 total patients of similar age. On the other hand, only 1 (0.7%) of 131 patients aged ≥ 20 years complained of such odors during irradiation sessions.

Four of the 7 patients had a germ cell tumor, but none had a medulloblastoma. There was no tendency in either type of surgery before radiation therapy or target volume of radiation. Conventional

radiation therapy, including 3D-CRT, was used to treat 3 patients, while IMRT including VMAT was used for 4 patients.

The D_2 (Gy) values of the olfactory region in each patient who experienced olfactory sensations during their irradiation sessions are given in Table 2. We compared D_2 values of the olfactory regions between the patients who experienced abnormal olfactory sensations and those who did not; no significant difference was detected between the groups (Table 3,A). When we focused exclusively on germ cell tumors, 4 patients experienced olfactory sensations, whereas the remaining 19 did not; however, there was no significant difference in olfactory region D_2 values between these two patient groups (Table 3,A).

Ten patients reported phosphenes during radiation sessions (Table 1). Of these, 9 were >20 years old and 6 had been irradiated for glioma or glioblastoma. Eight were treated with IMRT or VMAT. There was no significant difference in the radiation dose delivered to the orbit between the patients who experienced abnormal light sensations and those who did not (Table 3,B). Of the 42 patients with temporal lesions, 4 experienced phosphenes. There was no significant difference in the orbit radiation dose between the patients who did and those who did not experience the sensation (Table 3,B).

DISCUSSION

In all, 7 (3.7%) of 191 patients who received radiation therapy for a primary brain tumor experienced an abnormal olfactory sensation during the treatment sessions in this study.

The results of our literature review on anomalous olfactory sensations during irradiation sessions are presented in Table 4. Sagar *et al.* described how irradiation of the olfactory region triggered such odors in patients [1]. Among 25 patients whose treatment volumes included the olfactory region, 15 complained of an abnormal smell during irradiation. However, among 40 patients whose treatment volumes excluded those organs, no patients complained of any unusual sensation. Costello *et al.* reported that there was no relationship between detection of the odor and the radiation field [2]. In the present study, no patients with D_2 to the olfactory region of <0.4 Gy experienced the abnormal sensation. However, there were no significant differences in D_2 values of the olfactory region between patients with and without awareness of any sensation, as shown in Table 3. Fifteen patients received whole-ventricle irradiation, and three of them (20%) reported such an odor. However, among 26 patients who underwent whole-brain irradiation, only 1 (4%) complained of an odor. Focusing on patients <20 years of age, 13 underwent whole-ventricle irradiation and 3 of them (20%) reported such odors. Twenty patients underwent whole-brain irradiation and 1 (5%) suffered from an odor. Radiation fields for whole-brain irradiation encompass entire ventricles. The D_2 values of the olfactory region were not related to the awareness of any sensation, as shown in Table 3. As these sensations occurred during irradiation, the relationship between a specific point and the radiation dose rate at that point may be much more important than the cumulative dose. We identified no relationship between the frequency of olfactory or visual sensations experienced and the radiation doses delivered to the olfactory region or orbits. It was difficult to ascertain which directional

Table 2. Characteristics of the patients who experienced abnormal olfactory sensations during radiation treatment

Sex/age (years)	Primary disease/location	Surgery/Biopsy	Radiation therapy		Dose/fraction (Gy)	First day recorded (treatment days/cumulative dose (Gy))	D2 of the olfactory region (Gy) ^a	Counter measure
			CTV	Technique				
1	F/17	GCT hypothalamus	Craniotomy and biopsy	CSI	1.8	3/5.4	1.8	Stuff up the nose
2	F/8	GCT pineal body	Craniotomy and biopsy	WV	2.0	3/6.0	1.3	None
3	M/12	GCT pineal body	Endoscopic biopsy	WV	1.8	11/14.4	0.74	Essential oils
4	M/13	Ependymoma temporal lobe	Craniotomy and tumorectomy	LF	1.8	23/30.6	1.1	Essential oils
5	M/47	Pituitary A Pituitary G	Tumorectomy through the nose	LF	1.8	8/10.8	1.8	None
6	M/14	GCT pineal body	Endoscopic biopsy	WV	1.8	20/27	1.3	Essential oils
7	M/11	Ependymoma posterior fossa	Craniotomy and tumorectomy	LF	1.8	12/14.4	0.50	Sedation

^a Gy/fraction. M = male, F = female, GCT = germ cell tumor, pituitary A = pituitary adenoma, pituitary G = pituitary gland, CSI = craniospinal irradiation, WV = whole ventricle, LF = localized field, 3D-CRT = 3D conformal radiation therapy, IMRT = intensity-modulated radiation therapy.

Table 3. A: Radiation doses of the olfactory regions in patients with and those without abnormal olfactory sensations. B: Radiation doses of the orbits in patients with and those without abnormal visual sensations

Abnormal olfactory sensation	Number of patients	D ₂ (Gy) ^a	P
A: All patients	191		
With abnormal olfactory sensation	7	1.3(0.50–1.8)	0.28
Without abnormal olfactory sensation	184	0.90 (0.0–2.5)	
Germ cell tumor	23		
With abnormal olfactory sensation	4	1.2 (0.28–2.0)	0.94
Without abnormal olfactory sensation	19	1.3 (0.73–1.8)	
B: All patients	191		
With abnormal visual sensation	10	0.54 (0.20–1.4)	0.42
Without abnormal visual sensation	181	0.69 (0.0–2.3)	
Lesions in temporal lobes	42		
With abnormal visual sensation	4	0.54 (0.32–1.1)	0.32
Without abnormal visual sensation	38	0.92 (0.0–2.0)	

^aD₂: the minimum absorbed dose of the hottest 2% volume of the region of interest, values given as median (range)

Table 4. Reports of unusual olfactory sensations during irradiation sessions

Author	Total no of patients	No of patients with olfactory sensations
Steidley <i>et al.</i> [4]	10 (To areas other than the head and neck)	1
Sagar <i>et al.</i> [1]	25 (Volume included olfactory mucosa)	15 (60%)
	40 (Volume did not include olfactory mucosa)	0 (0%)
Costello <i>et al.</i> [2]	7 (Volume included olfactory mucosa)	1 (14%)
	46 (Volume did not include olfactory mucosa)	2 (4.3%)
Yang <i>et al.</i> [3]		Two-case report
Obinata M <i>et al.</i> (the present study)	191 (Primary brain tumors)	7 (3.6%)

beam caused the sensation due to the retrospective nature of this study.

There are two possible explanations for the cause of this abnormal sensation: ozone synthesis and direct stimulation of the olfactory system and nerve tracts by radiation [1–3]. Radiation treatment technicians or other medical staff were unable to detect any abnormal odor when patients complained of it. Irradiation of atmospheric air produces ozone, nitrogen oxides and other molecules. Ozone has a very specific, sharp odor somewhat resembling chlorine-based bleach. Sagar *et al.* demonstrated that ozone is detectable even at low concentrations if it is produced adjacent to the olfactory receptors, which are located in the olfactory region [1]. Most people can detect the odor of ozone even at 0.01 parts per million (ppm) [9]. Costello *et al.* measured the concentration of ozone produced during a working day within a bunker [2]. They reported that the maximum concentration was less than 0.15 ppm, and that exposure to 0.1 to 1 ppm ozone produced headaches, burning eyes and irritation to the respiratory passages. The actual measured concentration of ozone reached the sensing capability threshold of humans. Although it is difficult to determine the concentration in the nasal cavity, it may reach >0.01 ppm under the right conditions.

Almost all patients who complained about an odor were <20 years old in this study. In 2013, Yang *et al.* reported 2 patients, who were 6 and 15 years old, who complained about an odor during irradi-

ation [3]. The Olfaction in Catalonia (OLFACAT) study demonstrated that the detection of smells showed a progressive decrease during the human lifespan [10]. Among the potential mechanisms proposed for age-related olfactory loss are the replacement of olfactory mucosa with respiratory epithelia caused by disease or pollutant exposure [11], cribriform plate calcification [12], olfactory bulb atrophy [13], decreased number of glomeruli/mitral cells in the olfactory tract [14] and/or volume loss in temporal lobes of the cerebrum [15].

Although 4 out of 23 patients with a germ cell tumor in the present study experienced an odor, no patients with medulloblastoma had such a sensation. For primary brain tumors, the peak age at onset, primary sites, therapeutic strategy and target volume of radiation therapy differ according to disease. Therefore, it is possible that not only age but also a variety of other factors associated with primary disease play a part in the occurrence of this phenomenon.

Many factors including surgery, trauma, environmental causes, medications (particularly antiepilepsy drugs), cancer treatment and even general anesthesia influence olfactory functions [16]. Generally, patients with germ cell tumors in our study underwent biopsy only to confirm the diagnosis before irradiation. Biopsy is currently performed endoscopically without craniotomy. On the other hand, patients with medulloblastoma received more invasive surgeries, such as total or subtotal resection of the tumors. The greater the

operative stress, the more the patient may experience olfactory dysfunction.

One patient (#7) claimed that his pain was caused by an odor during irradiation, which became stronger as the radiation therapy progressed; later, he began to complain of the odor in the corridor in front of the radiotherapy room. Ultimately, he was unable to continue with the treatment while remaining conscious. This may, however, be a learned response, such as anticipatory vomiting in patients who receive chemotherapy [17].

This study had a major limitation in that the medical records were reviewed retrospectively. Therefore, there was a possibility that some patients experienced an odor but did not report it to medical staff, or staff did not record it. Patients with medulloblastomas may have been too young to complain of any sensation. Adults may have deliberately not complained of an odd sensation. Costello *et al.* and Sagar *et al.* administered questionnaires about such sensations to patients who received radiation therapy and reported a much higher frequency (Table 3) [1,2]. We investigated patients who complained of phosphenes as an internal standard to know how accurate this study was. There were only 10 patients who experienced a sensation of light. Steidley *et al.* reported that all patients who received irradiation to their eyes reported such a phenomenon [4]. Therefore, our study probably underestimated the frequencies of the olfactory and visual perceptions. In this study, only the adults complained of phosphenes. The reason why children did not report these sensations is unclear. The light could have been too faint to qualify as unpleasant, or the patients may have misunderstood that the x-rays were visible.

CONCLUSIONS

A considerable number of patients complain of unusual olfactory sensations during irradiation. Further prospective studies on abnormal olfactory sensation during radiation sessions are needed to understand the underlying causes of these sensations.

SUPPLEMENTARY DATA

Supplementary data is available at *Journal of Radiation Research* online.

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CONFLICT OF INTEREST

None declared.

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