

## Critical Review

# Olfactory Sensations During Radiation Sessions: A Review

Keisuke Sasai, MD, PhD<sup>a,b,\*</sup>

<sup>a</sup>Department of Radiation Therapy, Misugikai Satou Hospital, Hirakata, Japan; and <sup>b</sup>Department of Radiation Oncology, Graduate School of Medicine, Juntendo University, Tokyo, Japan

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## Abstract

**Purpose:** During radiation therapy sessions, certain patients may perceive smells, particularly in younger populations. The sense of smell generally does not interrupt treatment; hence, it has attracted limited attention from oncologists worldwide. However, in certain cases, the prevention of smell perception may be necessary when treating pediatric patients. In this regard, this study reviewed previous studies pertaining to this unusual phenomenon of smell perception during radiation sessions.

**Methods and Materials:** A PubMed search using the terms “radi\*” AND (“olfaction” OR “odor” OR “smell” OR “phantosmia”) was performed, and 9 articles related to this sensation were identified. Furthermore, through the references in these 9 articles, 3 additional related studies were identified.

**Results:** Perception of smell during radiation treatment sessions was first reported in 1989. This phenomenon entails the perception of a pungent, repulsive, and unpleasant smell and is generally only observed in the presence of radiation beams. Occasionally, these smell perceptions are also accompanied by visual and gustatory sensations. Patients complain about this sensation more frequently when their olfactory regions are irradiated. Nevertheless, some patients have also reported experiencing this sensation when these areas are not included in the radiation field. Although the intensity of this sensation is low, intervention is required to prevent it. The cause of this perception remains unclear and requires further investigation.

**Conclusions:** During radiotherapy sessions, certain patients may perceive smells. The cause of this perception remains unclear and requires further investigation.

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## Introduction

During radiation treatment sessions, predominantly for intracranial and/or head and neck tumors, certain patients may perceive smells,<sup>1,2</sup> especially in pediatric

oncology. The smell is detected only by the patient; others, including staff at radiation therapy facilities, cannot smell anything. Even among adults, several participants in the cancer survivor’s network of the American Cancer Association stated that they experienced such a smell during radiation sessions.<sup>3</sup> Thus far, this phenomenon remains poorly understood. Patients may smell substances such as ozone synthesized by radiation or experience phantosmia, that is, the perception of a smell in the absence of an odorant stimulus.<sup>1</sup> The sense of smell generally does not interrupt treatment; therefore, it has attracted limited attention from oncologists worldwide. Preventing this perception is occasionally necessary in pediatric patients, such as by using essential oils,<sup>1,4</sup> and

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\*Corresponding author: Keisuke Sasai, MD, PhD; E-mail: [ksasai@juntendo.ac.jp](mailto:ksasai@juntendo.ac.jp)

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certain patients may not be able to continue the session without sedation or anesthesia.<sup>1,5,6</sup> To better characterize the occurrence of the sensation of smell during radiation treatment and draw attention to this unusual phenomenon, this study reviews the unusual smells experienced during radiation sessions, focusing on related literature, phenomenon frequency, and possible causes.

## Methods and Materials

A literature survey was performed using the following inclusion criteria: original article, review, case report, or correspondence describing the phenomenon in which patient(s) perceive smell in the presence of radiation beams, but other persons cannot detect it in the treatment room. On May 31, 2022, a PubMed search using the terms “radi\*” AND (“olfaction” OR “odor” OR “smell” OR “phantosmia”) was performed, revealing 2765 studies; among these, only 9 studies were based on this sensation.<sup>1,2,4-10</sup> Three other related reports were identified based on the references in these articles.<sup>11-13</sup> Table 1 presents the details of these studies.

## History of study

Through a 1989 study on the visual sensations induced by radiation therapy, Steidley et al<sup>12</sup> was the first to report a patient who complained of an ozone smell during radiation sessions. However, a detailed description of this phenomenon has not been reported. In 1991, Sagar et al<sup>7</sup> systematically reported this phenomenon. They sent questionnaires to 40 patients who had received irradiation at their olfactory regions, and 24 patients responded; 15 of these patients complained of experiencing smells during the radiation sessions. Costello et al<sup>8</sup> published a correspondence to Sagar’s report in 1992 and reported that 3 out of 53 patients experienced such smells. Thereafter, no related studies were reported.

In 2012, 2 pediatric patients at the Memorial Sloan-Kettering Cancer Center were reported to have experienced unpleasant smells during radiation sessions using modern radiation techniques, such as conformal radiation therapy.<sup>5</sup> In 2015, Blumenthal et al<sup>13</sup> reported 3 patients who experienced visual sensations during radiation sessions; among them, 2 patients also perceived smells.

We reported in 2019 that 7 out of 191 patients who received radiation therapy for intracranial lesions were aware of smell during irradiation.<sup>1</sup> Since then, 5 research groups, including ours, have published 6 articles on this topic. Among these, 2 were prospective observational studies,<sup>2,10</sup> 2 were retrospective chart reviews,<sup>4,9</sup> and 2 were case reports.<sup>6,11</sup>

## Sensation characteristics

In particular, these smells were only experienced in the presence of radiation beams and usually ceased

immediately after the radiation was terminated.<sup>2,7</sup> Some patients complained about experiencing these smells before and/or after the treatment sessions. Yang et al<sup>5</sup> reported a case of a 15-year-old boy who complained of an odor like halitosis for an entire day. An 11-year-old boy complained of an odor during irradiation, the intensity of which increased as radiation therapy progressed, and he subsequently began to complain of the same smell in the corridor in front of the radiation therapy room. Another patient experienced a smell during his stay in the radiation therapy room.<sup>1</sup>

Smell is a highly subjective sensation. Although patients generally describe the smell sensation as pungent, repulsive, and unpleasant, various descriptions have been reported (Table 1). Patients primarily reported smells resembling the burning of materials such as plastic or rubber or chemicals such as ozone. In particular, one patient who was a former worker in an industry that involved the use of ozone informed us that the smell he perceived was identical to that of ozone.

Recently, Mizumoto et al<sup>10</sup> conducted a prospective study in which patients were asked to identify the smell of preprovided examples. Among the 51 patients, 32 (63%) reported a burnt smell, 8 (16%) reported a chemical smell, 2 (4%) reported a sour smell, and 9 reported other smells.

Another concern is the intensity of these smells. Among the 7 patients involved in our retrospective chart analyses, 5 required interventions.<sup>1</sup> Other reports have also mentioned that some patients are unable to continue radiation therapy without anesthesia.<sup>5,6</sup> The interventions are described further in subsequent sections. The intensity of smell is generally low. Mizumoto et al’s<sup>10</sup> prospective study, in which patients were required to rate the intensity of the smells on a 6-point scale, classified the intensity as very weak or medium.

## Perceptions experienced simultaneously with smell

Sense of smell has been reported to occur as an isolated sensation or in combination with other perceptions (Table 1). Sagar et al<sup>7</sup> reported that 6 out of 14 patients with smell perception also complained of visual sensations. In our prospective series, 12 of 13 patients reported visual sensations.<sup>2</sup> Other investigators have described visual sensations combined with a sense of smell. A few patients also reported other perceptions, such as gustatory sensations, although the frequency of such sensations was lower than that of the visual sensations (Table 1). The cause of this visual sensation has not yet been determined. Nevertheless, there are 2 possible causes: Cherenkov radiation in the vitreous of the eye or direct stimulation under ionizing irradiation to the optic nerve or visual areas.<sup>2</sup> The visual and olfactory systems are located adjacent to each other,<sup>9</sup> and higher-dose-rate beams

**Table 1 Reports of smell during radiation sessions**

First author year	Study type	Treatment beam	Total number of pts: Radiation target or irradiation volume	Total number of pts with perception	Ages of pts who perceived the smell (y)	Characteristics of olfaction
Steidley <sup>12</sup> 1989	Prospective	Electron/photon	10: Other than H & N	1 (10%)	NA	Ozone
Sagar <sup>7</sup> 1991	Retrospective	Photon	25: Including OR 60: Not including OR	14 (56%) 0 (0%)	NA	Bleach, ozone, gas, chlorine, ammonia, acid, celery, burning, pungent
Costello <sup>8</sup> 1992	Retrospective	Photon	7: Including OR 46: Not including OR	1 (14%) 2 (4.3%)	NA	
Yang <sup>5</sup> 2013	Case report	Photon	1: Pons 1: F, O, T	2	6, 15	Halitosis-like, water, and rubbing alcohol
Blumenthal <sup>13</sup> 2015	Case report	Photon	1: Whole brain 1: F	2	52, 42	Alcohol, metal white smell
Obnata <sup>1</sup> 2019	Retrospective	Photon	191: Primary brain tumor	7 (3.7%)	8, 11, 12, 13, 14, 17, 47	Unpleasant
Raghavan <sup>6</sup> 2020	Case report	Proton	1: Craniospinal irradiation	1	16	Noxious
Narici <sup>9</sup> 2020	Retrospective	Proton	183: NA	9 (4.9%)	NA	Burning, bleach, chemical, metallic electrical, strong, unpleasant
Hara <sup>2</sup> 2021	Prospective	Photon	38: Intracranial or near orbital tumor	13 (34%)	44 (25-78) <sup>†</sup> 64 (15-86) <sup>‡</sup>	Burning plastics or rubber stimulating, unpleasant, aura of forest
Mizumoto <sup>10</sup> 2022	Prospective	Photon/ proton	96: Including NC 524: Not including NC	26 (27%) 25 (4.8%)	NA	Burning, chemical smell, sour
Rosenzweig <sup>4</sup> 2022	Retrospective	Proton	99: Intracranial, base of skull, nasopharyngeal, and sinonasal tumors	12 (12%)	17 (12-33) <sup>  </sup>	Chlorine, broccoli, stale water, metallic, noxious
Kosugi <sup>11</sup> 2022	Case report	Photon	1: OR and F	1*	35	Foul odor

*(continued on next page)*

**Table 1** (Continued)

First author year	Study type	Treatment beam	Total number of pts: Radiation target or irradiation volume	Total number of pts with perception	Ages of pts who perceived the smell (y)	Characteristics of olfaction
<b>Other sensations simultaneously perceived with olfaction</b>	<b>Intervention</b>	<b>Doses to specific areas or irradiated regions</b>	<b>Additional comments</b>			
		NA				
6: Visual		OR NA				
2: Gustatory						
1: Visual	2: Anesthesia	1.8 Gy/fraction 1.8 Gy/fraction				
2: Visual		3 Gy/fraction 2 Gy/fraction				
1: Visual 1: Visual and gustatory	5 needed essential oil, stuff up the nose, sedation	No significant difference in radiation doses to OR				
	Anesthesia	1.8 Cobalt gray equivalents/fraction ?				
5: Visual 1: Gustatory		Higher doses in orbito-frontal cortex, temporal lobe, and visual tracts				
12: Visual		No significant differences in doses to the specific sites <sup>§</sup> between patients who perceived the smell and those who did not	Patients who perceived the smell were younger than those who did not.			
		NC dose was significant factor	Age ( $P < .001$ ), and photon RT ( $P = .018$ ) were identified as significant factors			

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**Table 1** (Continued)

First author year	Study type	Treatment beam	Total number of pts: Radiation target or irradiation volume	Total number of pts with perception	Ages of pts who perceived the smell (y)	Characteristics of olfaction
	5 needed essential oils, Vicks drop, chewing gum, antiemetics	A larger proportion of patients who reported phantosmia received whole brain irradiation compared with patients who did not	No significant differences in age (cutoff: 17 years old)			
			The olfactory epithelium, olfactory nerves, and bulbs were resected, and she had no olfaction at all before RT			

*Abbreviations:* F = frontal lobe; H & N = head and neck; NA = not available; NC = nasal cavity; O = occipital lobe; OR = olfactory region; pts = patients; RT = radiation therapy; T = temporal lobe.

\* This patient was reported in another reference (Hara et al 2021<sup>2</sup>).

† Median (range).

‡ Ages of patients who did not perceive the smell.

§ These sites include retina, eyes, optic nerves, optic chiasm, olfactory region, olfactory tract, and olfactory or visual cortex.

|| Ages of 99 patients.

pass through these organs simultaneously. Therefore, it is reasonable that patients might experience both sensations simultaneously.<sup>2,9</sup>

Focusing on cases where gustatory sensations were combined with smell sensations may help clarify the causes of these sensations evoked by ionizing irradiation, because the 2 systems are not located adjacently. This may give us a hint to understand the smell sensation in the future.

## Frequency of sensation

The reported incidence estimate of this phenomenon is 3.7% to 35%. Sagar et al<sup>7</sup> first reported the frequency of this phenomenon. They revealed that 14 (56%) of the 25 patients who received radiation at their olfactory regions and answered the questionnaire experienced olfaction, whereas none of the 60 patients whose radiation fields excluded these regions experienced a sense of smell. However, this was a retrospective study; they supposed that the frequencies were overestimated and were actually between 35% (14 of the 40 patients who received the questionnaire on this phenomenon experienced during radiation) and 56%. Other investigators have reported significantly lower incidence rates of this phenomenon in retrospective studies (3.7%-14%).

Generally, in prospective studies, the frequency of this sensation is higher than that in retrospective studies. Hara et al<sup>2</sup> and Mizumoto et al<sup>10</sup> reported that approximately 30% of patients who received radiation therapy to the nasal cavity or brain region perceived a smell.

## Sex and age

There was no significant difference between sexes in terms of the frequency of detecting this perception. Younger patients frequently complained about experiencing this sensation. Obinata et al<sup>1</sup> reported that 6 out of 7 patients who reported the sensation were less than 20 years old, accounting for 10% of the total of 60 patients of similar age. Conversely, only 1 of 131 patients aged  $\geq 20$  years complained of such sensations. In our second prospective study, we found that patients who experienced a smell were younger than those who did not.<sup>2</sup> Mizumoto et al<sup>10</sup> reported that age was a significant factor associated with smell sense. Although Rosenzweig et al<sup>4</sup> reported that there was no significant difference in age between patients who experienced smell and those who did not, the analyzed population was 39 years old or younger. In the 2 case reports of patients who needed anesthesia, all the patients were from the younger population.<sup>5,6</sup>

The reason for this predominance in younger patients for sensing smell during radiation is unclear. Generally, smell detection decreases during the human lifespan,<sup>1,10</sup>

and various potential mechanisms have been proposed for this age-related olfactory loss.<sup>1</sup>

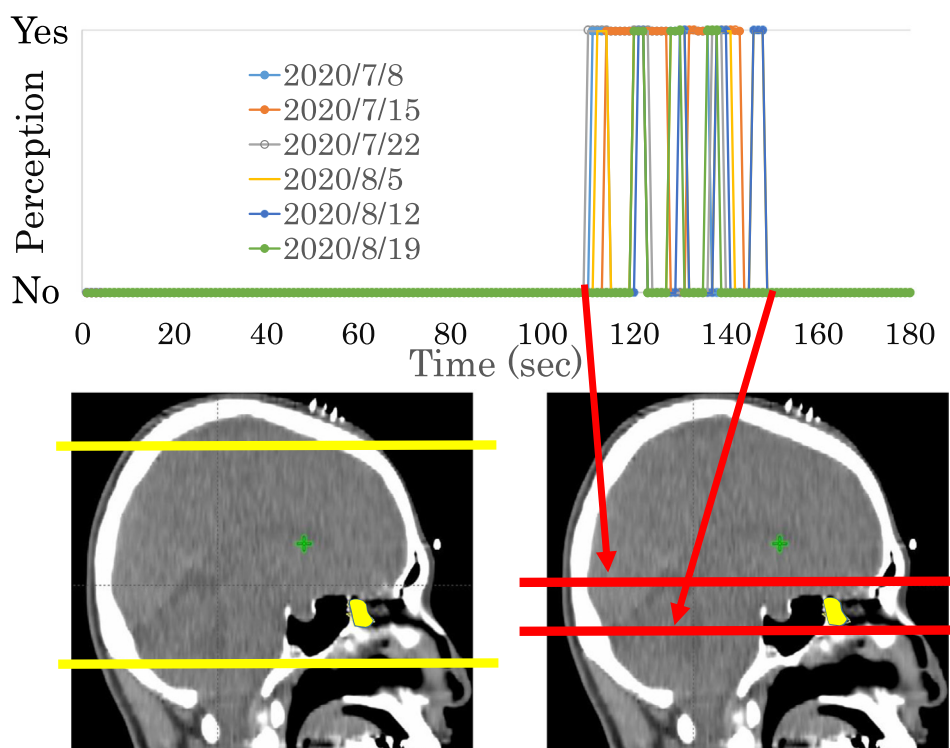
## Photon or particle therapy

The type of ionizing irradiation that causes this phenomenon has garnered considerable interest. Originally, this sensation was reported by photon institutions; however, several related reports have recently been presented in the field of particle therapy. This phenomenon, caused by particle beams, has attracted attention in the field of space science. In 2 retrospective studies of patients treated with proton beams, the frequencies were approximately 5% to 12%.<sup>4,9</sup> In a prospective study, Mizumoto et al<sup>10</sup> compared the frequencies of smell sensations experienced under photon and proton beams and concluded that patients who received photon therapy sensed these smells (43/415; 10.4%) more frequently than those treated with proton beam therapy (8/205; 3.9%). It appears that proton beams induce fewer smell perceptions than photon beams; however, these studies are inconclusive because the backgrounds of the patients treated with photon and proton beams were different.

## Cause of perception

Sagar et al<sup>7</sup> reported that only patients who received radiation therapy at the olfactory region perceived smell. We attempted to identify the organ responsible for this perception in patients who received radiation therapy using helical tomotherapy and found that almost all patients reported experiencing this sensation when x-rays passed through the olfactory epithelium and/or ethmoid sinus level (Fig. 1).<sup>2</sup> These findings suggest that the olfactory epithelium, location olfactory receptors, or olfactory nerves may play a role in inducing this phenomenon.

Conversely, Costello et al<sup>8</sup> and Mizumoto et al<sup>10</sup> reported that patients who did not receive radiation therapy at their olfactory regions also perceived these smells. Mizumoto et al<sup>10</sup> reported that 14 (8.0%) of 174 patients who received irradiation to their chest and 8 (3.6%) of 219 patients who received irradiation to their pelvis reported the smell, whereas 28 (27%) of 105 patients who were irradiated to their nasal cavities perceived the smell. Considering these findings, it is suggested that substances such as ozone contribute to this phenomenon. Therefore, we measured ozone concentrations during x-ray and electron irradiation.<sup>14</sup> Although the direct beam did not synthesize a sufficient concentration of the substance, its concentration in the treatment bank reached a detectable level in humans 1 hour after commencing daily irradiation. Costello et al<sup>8</sup> also measured the concentration of ozone in the treatment field, which did not reach the threshold for human detection.



**Figure 1** Representative case of a smell perception during radiation therapy. A 48-year-old woman with pituitary adenoma was treated with tomotherapy. The patient indicated the use of a button when a sensation commenced and ended. Data were recorded electronically and collated with treatment logs. The upper column indicates when the patient experienced the sensation. The lower column shows the beam positions that overlapped the sagittal views of treatment-planning computed tomography. Red lines indicate the start and end of the sensation. The yellow area indicates the olfactory epithelium. This figure was reproduced from Hara et al<sup>2</sup> with permission.

Notably, we encountered a patient who experienced an interesting course of events: a 35-year-old woman who had undergone resection of her olfactory epithelium, olfactory nerves, and bulbs; therefore, she had no olfaction. The patient complained of smells during radiation therapy for a recurrent tumor in the olfactory region.<sup>11</sup> This suggests that the central nervous system of the patient detected x-rays during radiation sessions, although this hypothesis remains to be confirmed.

The relationship between the radiation doses to specific regions and the frequency of this phenomenon is another concern. Recent studies have revealed that cumulative radiation doses to specific regions are unrelated to the incidence of this sensation.<sup>1,2</sup> Even doses less than 0.4 Gy to the olfactory regions induced the sense of smell.<sup>2,4</sup> Thus, it is likely that the dose rate is significantly more important for inducing this phenomenon than the per-fraction dose.<sup>2</sup> In modern radiation therapy techniques such as intensity modulated radiation therapy, the per-fraction dose is composed of multidirectional beamlets. Therefore, the dose rate of each beamlet is more important than the fractional dose in this setting.<sup>2</sup>

In summary, the mechanism underlying this phenomenon remains unclear. We propose 2 possible hypotheses

as follows; however, neither of them can explain the phenomenon completely.

Because patients perceive the smell not only when the olfactory area is irradiated but also when other parts of the body are irradiated, we first tried to explain that phenomenon as the patient smelling substances such as ozone generated by ionizing radiation.

The measured concentration of ozone was lower than the human detection threshold.<sup>14</sup> One patient who did not have either the olfactory epithelium or olfactory nervous system also complained of the smell.<sup>2,11</sup> Now, a hypothesis can be posited that the central nervous system itself is stimulated by x-rays directly or by the oxidative species generated by ionizing radiation. The biggest weakness of this hypothesis is that it cannot explain why a patient who is irradiated not to his/her brain but to another part of the body can have this phenomenon.

## Intervention

As mentioned previously, the intensity of smell is generally low. However, several patients, especially pediatric patients, require intervention to prevent this phenomenon



(Table 1). Obinata et al<sup>1</sup> reported that 5 pediatric patients required interventions, mainly through the topical use of essential oils, and 1 patient required intravenous sedation. Rosenzweig et al<sup>4</sup> showed that 5 patients required several types of interventions, including the use of essential oils, Vicks drops, chewing gums, and antiemetics. Yang et al<sup>5</sup> and Raghavan et al<sup>6</sup> reported that patients could not continue treatment without general anesthesia.

## Limitations

The phenomenon presented in this review has not been well recognized for a long time. The available literature is too limited to draw definite conclusions, including the incidence and mechanism of the phenomenon and its effective interventions.

Only our group tried to identify the organ responsible for this smell, but the number of patients in that study was limited.<sup>2</sup> Other investigators only revealed the incidence of the phenomenon, primarily in a retrospective manner, and a few of them indicated radiation dose distributions to specific organs.

It was difficult to show how many patients required intervention. It is important to note that some patients required an effective intervention for this phenomenon. Otherwise, the patients could not receive radiation therapy. Although patients underwent various procedures, they were not sufficient, except for systemic anesthesia/sedation. Therefore, efforts must be made to unveil the cause of this phenomenon and to develop an effective intervention.

## Conclusion

During radiation therapy, certain patients may perceive smells, especially in younger populations. This smell is described as pungent, repulsive, and unpleasant and is predominately noted in the presence of radiation beams. Patients more frequently complained of this sensation when their olfactory regions were irradiated; however, some patients reported experiencing this phenomenon

when these areas were not included in the radiation fields. Although the intensity of sensation was low, interventions were required to prevent this phenomenon in certain cases. The cause of this perception remains unclear and requires further investigation.

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