Radiotherapy and Oncology 132 (2019) 109–113

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

Occurrence and mechanism of visual phosphenes in external photon beam radiation therapy and how to influence them

Willy de Kruijf [a,*], Anke Timmers [a], Janita Dekker [a], Florian Böing-Messing [b,c], Tom Rozema [a]

[a] Instituut Verbeeten, Tilburg; [b] Department of Methodology and Statistics, Tilburg University; and [c] Jheronimus Academy of Data Science, The Netherlands

ARTICLE INFO

Article history:
Received 4 July 2018
Received in revised form 30 October 2018
Accepted 17 November 2018
Available online 21 December 2018

Keywords:
Visual phosphenes
Cherenkov radiation
Light flashes
Photoreceptor proteins
Photon beam radiation therapy

ABSTRACT

Background and purpose: Two plausible mechanisms to explain the appearance of visual phosphenes are: direct activation of the photochemicals in the retina and the generation of Cherenkov radiation in the vitreous humour. In this clinical trial we investigated the occurrence of visual phosphenes in external photon beam radiation therapy.

Material and methods: Logistic regression analysis is used to examine whether seeing light flashes and seeing steady light depended on the ambient light intensity and the dose.

Results: In total, 465 treatments of 25 patients were analysed. The odds of seeing light flashes multiply by 0,926 as the ambient light intensity increases by 10 lux. Similarly, the odds multiply by 1,604 as the dose to the retina increases by 10 cGy. The odds of seeing steady light multiply by 1,540 as the dose to the vitreous humour increases by 10 cGy.

Conclusions: We postulate that one should reduce the dose rate, instruct patients to keep the eyes open and increase the illuminance in the treatment room to reduce the probability of experiencing visual phosphenes. We hypothesize that melanopsin is involved in the visual phosphenes and that fatigue of patients might be correlated with the observation of visual phosphenes.

The first visual phosphene due to radiation has been discovered in 1896 by Brandes and Dorn who treated a blindfolded aphakic person with X-rays [1]. Giesel was the first who was able to isolate a large amount of fairly pure radium [2]. He discovered that a very clear glow was perceived when radium was attached to the eye, even with the eyelid closed. In the early years after the discovery of X-rays by Röntgen, many experiments were performed with test persons on visual phosphenes. Experiments ended after the harmful effects of radiation became clear. In 1955 a thorough literature review on visual phosphenes, including his own experimental work, was given by Lipetz [3]. He postulates the hypothesis that the "X-ray phosphenes" in the dark-adapted retina are produced through a direct action of the X-rays on the rhodopsin ("visual purple") in the retina. He postulates that the "Radium phosphene" consists of two phosphenes; the main one caused by the beta particles that act by producing fluorescence within the eye, and a much dimmer one from the gamma rays, that act like the X-rays by breaking down the photochemicals in the retina. Later, Steidley showed that the radium phosphene as described by Lipetz, is not caused by fluorescence in the eye, but is due to the Cherenkov effect by means of decaying daughters of Radium [4].

Cherenkov radiation is emitted when charged particles are moving faster than the speed of light in a particular medium. The ionizing radiation polarizes the medium. When the medium turns back to its ground state electromagnetic waves are emitted. The number of the Cherenkov photons arising from a medium is given by the Frank–Tamm formula: $\frac{dN}{d\lambda dx} = 2\pi\alpha\mu_r(\lambda)\frac{1}{\lambda^2}\left(1-\frac{1}{\beta^2 n(\lambda)}\right)$, where dN equals the number of the Cherenkov photons produced per interval wavelength $d\lambda$ and travelled distance dx, the fine structure constant $\alpha \cong 1/137$; μ_r is the relative permeability of the medium, n the refractive index of the medium; and $\beta = v/c$, in which v is the velocity of the charged particle in the medium and c is the speed of light in vacuum [5]. For external beam photon radiation therapy, the threshold energy of an electron to generate Cherenkov radiation in the vitreous humour of the eye ($n = 1.336$) is 0.260 MeV. The number of the Cherenkov photons increases with photon energy (decreasing wave length), so Cherenkov radiation is perceived by humans as blue. With increasing energy outside the visual spectrum, the intensity decreases to zero as the refraction index also decreases with photon energy.

The interest in visual phosphenes reappeared after the first report on light flashes by Buzz Aldrin on the Apollo-11 space flight [6]. Astronauts in deep space observed light flashes, presumably as a result of the passage of heavy cosmic-ray nuclei through the eye. The retina was again identified as the most probable locus of

* Corresponding author at: Instituut Verbeeten, Postbus 90120, 5000 LA, Tilburg, The Netherlands.
E-mail address: kruijf.de.w@bvi.nl (W. de Kruijf).

https://doi.org/10.1016/j.radonc.2018.11.010
0167-8140/

interaction with radiation [7], but it was also stated that Cherenkov radiation could be the cause of the visual phosphenes. Experiments with a particle accelerator able to deliver a single beam particle to the target showed that the detection efficiency for individuals was much higher for particles that generated Cherenkov radiation, whereas the linear energy transfer (LET) was similar. Point-like flashes, streaks and diffuse flashes were observed, but the diffuse flashes were only observed when the particle moved fast enough to generate Cherenkov radiation [8].

So, there seem to be two plausible mechanisms in producing visual phosphenes by radiation. The first one is direct activation of the photochemicals in the retina. The second one is the generation of Cherenkov radiation in the vitreous humour. The question is whether both phenomena also occur in external beam radiation therapy.

Schardt et al. investigated light flashes in patients treated with a scanning carbon ion beam, offering the opportunity to investigate the correspondence between the perception of light flashes by the patient and the area where the beam energy was deposited [9]. The energy of the carbon beam is too low to generate Cherenkov radiation. They concluded that the main mechanism of visual phosphenes was the direct energy deposition by charged particles in the retina. Steidley et al. studied a group of ten patients who were irradiated with electron beams [10]. They concluded that the dominant mechanism of the phosphene was the Cherenkov effect based on the colour seen. Newman et al. calculated the number of Cherenkov photons per second hitting the retina for a portal image of 100 MU/min [11]. They concluded that this would cause more than enough Cherenkov radiation to bring about a visual sensation. In a case report by Blumenthal et al. describing external radiation therapy with 6 MV photons for 3 patients, visual phosphenes are attributed to Cherenkov radiation [12]. Farzin et al. report the radiation phosphene experience for 20 patients [13]. The experience varies a lot between the patients, ranging from light, flashes, blinks, and stripes in different colours, but mainly blue (12) and white (11). Moreover, the experience does not occur in every fraction for all patients. They conclude that Cherenkov radiation may cause the effect, but that this effect may also be due to radiation treatment in different parts of the visual pathway. Thariat et al. [14] summarize findings on the phosphenes in patients receiving radiotherapy. They report that up to 70% of patients with ocular melanoma receiving radiotherapy report visual phosphenes. They also report transient mydriasis (dilation of the pupil) after initiation of proton beam therapy occurring in half the patients experiencing visual phosphenes but seldom in the patients without phosphenes, suggesting involvement of melanopsin in the ganglion cells.

Patients may experience and report these phenomena as very unpleasant. Our research was initiated by individual reports of patients who asked their radiation oncologist not to be treated on a specific treatment machine, because they experienced these phenomena only during treatment fractions at this treatment machine. Because we could not explain this, we investigated the occurrence of visual phosphenes in our patient population. In a preliminary study we asked 66 patients who were treated at least 3 fractions to fill in a questionnaire [15]. We hypothesized that there are two different visual phosphenes: direct stimulation of the retina, mainly perceived as light flashes, and generation of Cherenkov radiation in the vitreous humour, mainly perceived as steady light. Therefore, we asked the patients whether they had experienced light flashes and/or steady light. Moreover, we asked them to describe the phenomenon. In our population, 68% of patients reported seeing light flashes or steady light at least in one fraction. When a visual phosphene is observed for at least one fraction, it happens in 71% of the fractions. Surprisingly, again a difference was observed between the treatment machine for which individual patients had complained and other treatment machines. After excluding dosimetric differences between the treatment machines, we hypothesized that this difference is caused by the ambient lighting level in the treatment room. Therefore, we designed a clinical trial in which we have treated the patients on a single treatment machine with varying ambient lighting levels. This paper reports on the results of that clinical trial.

Materials and method

Patients to be treated with radiation therapy on the head were asked to participate in the study to investigate their experiences of seeing steady light and/or light flashes during radiation treatment. The radiation oncologist included patients whose treatment consisted of a minimum of four fractions. All treatments started between October 2015 and December 2016. In case of participation, informed consent was signed. To exclude differences caused by the treatment room one specific treatment room was used for the study, equipped with a TrueBeam (Varian Medical Systems, Palo Alto, CA, USA). Patients were treated with a photon beam energy of 6 or 10 MV with either conformal fields or a volumetric modulated arc treatment. For each fraction the ambient light intensity was set randomly at a level between 1 and 6, while the participants were not informed about this changing condition. Table 1 shows the average measured illuminance associated with the different levels for the duration of the trial, using a lux meter (CD LUX Meter, PTW, T54003D – 1180). After each treatment, a questionnaire was filled in by the patient to assess how often they saw light and light flashes, the colour and a description of the light and the condition of the eyes (open/closed).

Model and software

We used logistic regression analysis to examine whether visual phosphenes depend on the ambient light intensity and the dose. We fitted logistic regression models with random intercepts to take into account that repeated observations on the same patient are potentially correlated. These models estimate patient-specific effects by conditioning on patient-specific random intercepts [[16], Chapter 10]. A separate random intercept logistic regression model was fitted for each of the two dichotomous outcomes of seeing light flashes (no, yes) and seeing steady light (no, yes). For the analysis of light flashes, we used ambient light intensity and maximum dose to the retina as predictors, whereas the model for the analysis of steady light included ambient light intensity and maximum dose to the vitreous humour as predictors. The models were fitted in R using the lme4 package [17,18].

Results

In total, 508 treatments were administered to 25 patients (15 males, 10 females). The average age of the patients was 55 with a standard deviation of 13. For 43 treatments there was a missing value on at least one of the variables seeing light flashes, seeing

Table 1
The ambient light was set randomly at an intensity level between from 1 to 6.

Ambient light intensity level	Average measured illuminance (lux)
1	9.0
2	34.6
3	80.0
4	130.3
5	175.8
6	217.6

steady light, and ambient light intensity. The 43 treatments with missing values were removed, resulting in a final data set containing 465 treatments of 25 patients (i.e. for every patient there was at least one treatment for which all variables were observed).

Patients reported divergent perceptions about light and light flashes. The descriptions varied from short flashes, flashes fading away, kind of lightning to a cloud of changing colour and stains. Table 2 gives an overview of the characteristics of the tumour and the number of fractions for these patients with the observations: nothing, light flashes, steady light, or both.

Table 3 shows the results of the logistic regression analyses for the outcomes of seeing light flashes and seeing steady light. Confidence intervals and *p*-values that indicate a significant effect at the 0.05 level are flagged with an asterisk (*). We first discuss the results of the analysis of light flashes. The *p*-values from this analysis indicate that both illuminance and dose are significantly related to the outcome at the 0.05 level. The estimates of the odds ratios have the following conditional interpretation. When conditioning on a patient-specific random intercept, the odds of seeing light flashes multiply by 0.926 as the illuminance increases by 10 lux, that is, the odds decrease by 7%. Similarly, the odds of seeing light flashes multiply by 1.604 as the dose increases by 10 cGy, which means that the odds increase by 60%. The 95% confidence intervals (CI's) give a range of likely values for the odds ratios. Similar to the *p*-values, we can conclude from the CI's that both predictors are significantly related to the outcome since the value 1 falls outside the CI's. The results of the analysis of steady light are similar to those of the analysis of light flashes. It can be seen that the estimates of the odds ratios are in the same direction, only weaker in magnitude (i.e., the odds ratios are closer to the value 1). However, only the predictor dose is significantly related to the outcome at the 0.05 level.

Fig. 1 visualizes the results of the logistic regression analyses on the probability scale for the outcomes of seeing light flashes (Fig. 1a) and seeing steady light (Fig. 1b). On the *x*-axis we have the dose in cGy and on the *y*-axis we have the probability of seeing light flashes and steady light, respectively. The lines show the probabilities for different values of the ambient light intensity. The plots show that the probability of seeing light flashes and steady light increases as the dose increases. Furthermore, it can be seen that the probability of seeing phosphenes decreases as the ambient light intensity increases. Note that this is only statistically significant for the outcome of seeing light flashes (Table 3). We also expect an effect by instructing patients to keep the eyes open, but our study does not show this. Preferably, the condition of the eyes (open, closed) should have been assigned randomly as well.

Discussion

Based on the observations of the patients and based on literature we conclude that there are two different mechanisms for visual phosphenes in external beam photon therapy, direct activation of the photoreceptor proteins ("X-ray phosphene") and the production of Cherenkov radiation in the vitreous humour (main contributor to the "Radium phosphene").

It may be difficult for patients to distinguish the different phenomena as they occur simultaneously. Moreover, the observation of the patients may be influenced by the treatment technique that is used. We included volumetric modulated arc treatments and conventional whole brain treatments. In a volumetric modulated arc treatment specific segments may cause visual phosphenes during a short period of time, whereas in a conventional treatment the visual phosphenes may last much longer.

Table 2
Overview of observations. Out of 25, 16 patients (64%) report light flashes and/or coloured light at one or more fractions. If it is reported, it is seen in on average 66% of the fractions.

Patient	Tumour site	Beam energy (MV)	Treatment technique	Dose to retina (cGy)	Dose to vitreous humour (cGy)	Number of fractions with observations				
						Only light flashes	Only coloured light	Both	Nothing	Total
1	Right frontal	6	Conformal	34.9	23.7	0	2	3	26	31
2	Left temporal	6	Conformal	48.9	32.8	0	0	0	10	10
3	Bifrontal	6	Conformal	34.8	24.6	4	0	0	16	20
4	Right frontal	6	Conformal	3.6	3.5	0	19	1	7	27
5	Cerebellum	6	Rapid Arc	36.5	30.9	0	0	1	25	26
6	Left frontal	6	Conformal	2.4	2.3	0	0	0	24	24
7	Left temporal	6	Conformal	19.5	18.4	0	0	0	30	30
8	Right temporal	6	Rapid Arc	42.6	32.5	0	16	1	14	31
9	Frontotemporal	6	Conformal	38.9	30.1	3	0	7	2	12
10	Right temporal	6	Conformal	91.4	74.0	0	0	0	14	14
11	Right eye	6	Conformal	408.4	399.8	0	0	3	0	3
12	Right eye	6	Rapid Arc	91.6	62.6	0	0	0	27	27
13	Left temporal	6	Conformal	47.4	47.6	0	2	0	17	19
14	Prophylatic cranial irradiation	10	Conformal	209.7	135.2	0	0	9	0	9
15	Right sphenoid	6	Rapid Arc	101.8	83.5	0	11	1	9	21
16	Clivus	6	Rapid Arc	65.9	49.1	0	8	0	2	10
17	Right parietal	6	Conformal	20.0	17.6	0	2	27	2	31
18	Left parietotemporal	6	Conformal	19.2	18.5	0	0	0	27	27
19	Left frontal	6	Rapid Arc	37.6	26.9	0	0	0	21	21
20	Left sphenoid	6	Rapid Arc	163.8	139.5	0	0	0	10	10
21	Prophylatic cranial irradiation	10	Conformal	192.8	140.7	3	0	5	0	8
22	Prophylatic cranial irradiation	10	Conformal	198.4	138.0	0	0	7	0	7
23	Prophylatic cranial irradiation	10	Conformal	187.7	126.5	0	0	5	1	6
24	Left frontal	6	Conformal	42.6	38.6	0	0	0	29	29
25	Frontal	6	Rapid Arc	81.7	70.7	0	1	9	2	12

Note that in the preliminary study these numbers were very similar (respectively 68% and 71%).

Table 3
Results of random intercept logistic regression analyses for the outcomes of seeing light flashes and seeing steady light. A * denotes statistical significance ($p < 0.05$).

	Light flashes			Steady light		
Variable	Odds ratio	95% CI	*p*-Value	Odds ratio	95% CI	*p*-Value
Illuminance	0.926	[0.863, 0.990]*	0.027*	0.956	[0.909, 1.003]	0.071
Dose	1.604	[1.231, 2.484]*	0.004*	1.540	[1.118, 2.575]*	0.033*

Note: Ambient light intensity and dose were divided by 10 prior to the analysis to facilitate the interpretation of the odds ratios. The point estimates for the (fixed) intercept on the logit scale were 0.004 for the light flashes outcome and 0.018 for the steady light outcome. The 95% confidence intervals (CI's) were computed using the profile method. The *p*-values are based on the Satterthwaite degrees of freedom approximation.

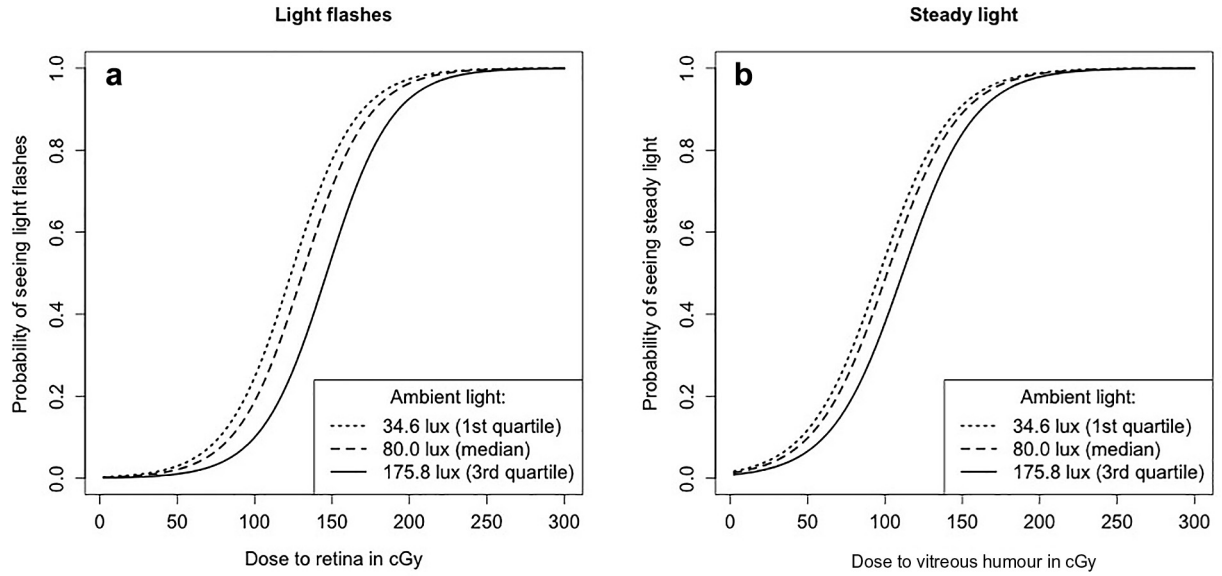

Fig. 1. Results of the logistic regression analyses on the probability scale for (a) the outcome of seeing light flashes and (b) the outcome of seeing steady light. The lines show the probabilities as a function of dose for a random intercept of 0 and different values of the ambient light intensity.

The mechanism behind Cherenkov radiation is known, but the question is how to understand the direct activation of the photoreceptor proteins. Rods are responsible for monochromatic vision in low-light conditions. Rhodopsin is the photoreceptor protein, that is found in the rods of the retina. Cones are responsible for coloured vision and function better than rods in bright light conditions. The cones of the retina have three different photoreceptor proteins, photopsin type I, II, and III, with each their specific absorption spectrum. Some ganglion cells contain melanopsin, which is not used for image formation, but contributes to various reflexive responses in the presence of light and contributes to the circadian rhythm. All photoreceptor proteins contain the chromophore 11-cis-retinal which upon photon activation changes into the isomer all-trans-retinal (photoisomerization), which induces a signal transduction cascade leading to a stimulus of the brain. So, the direct activation of the retina is most probably the activation of 11-cis-retinal, the same mechanism as for visual light. The absorption spectrum of the photochemical depends on the protein that contains 11-cis-retinal. The absorption spectra for the different photoreceptor proteins for wavelengths below visible light are not known. Since dark adaptation is known for the high-energy beams of astronauts [19] and is shown by us for radiotherapy treatments, the involvement of photoreceptor cells seems obvious. The more difficult question is whether charged particles are able to directly activate the photoreceptor proteins or all phenomena can be explained by photons interacting with photoreceptor proteins.

Assuming that the isomerization step of 11-cis-retinal cannot be triggered by charged particles directly, we could in fact have 4 physical mechanisms for visual phosphenes, being:

(a) Direct activation of photoreceptor proteins by the primary or scattered radiation photon beam.
(b) Indirect activation of photoreceptor proteins by Cherenkov radiation produced in the eye.
(c) Indirect activation of photoreceptor proteins by photons produced by the charged particles in the radiation beam (excitation, bremsstrahlung).
(d) Indirect activation of photoreceptor proteins by photons produced by chemiluminescence [20].

The findings of our patients treated with photons support our hypothesis of at least the two different physical mechanisms: direct activation of the photon beam (a) and Cherenkov radiation (b).

Fuglesang et al. [19] conclude that for astronauts a small fraction of the light flashes is caused by Cherenkov radiation with the majority caused by direct interaction with elements in the retina. Casolino et al. [21] report that there are two separate components of the cosmic rays: heavy nuclei and protons. Both these results and the findings of Schardt et al. [9] seem to indicate that direct interactions of charged particles with the retina are possible. However, we lack the fundamental understanding of such an interaction.

Although physical mechanisms might be similar, the radiation quality in space or in heavy-ion therapy is different from that in a typical radiation treatment photon beam [22,23]. The high-energy heavy charged particles in space and in heavy-ion therapy have a high linear energy transfer with low linear energy transfer components of the δ-rays produced. One expects more localized spots of lights produced by the radiation in space and with

heavy-ion radiation therapy than with a typical radiation treatment photon beam. Moreover, heavy-ion radiation therapy often uses scanning-beam techniques leading to spot-size treatments and thus spot-size observations.

To model the occurrence of visual phosphenes is a big challenge. First, one needs a time-dependent dose calculation because the delivery of the beam with VMAT techniques is time dependent. This is not possible with our treatment planning system. Second, we need all physics involved in the calculation, which is more than is necessary for dose calculations, since it is important to know the complete spectrum of photons including the visible spectrum.

And finally, the observation of visual phosphenes does not only depend on the physical mechanism, but also on the type and location and absorption spectra (complete photon spectrum) of the photoreceptor proteins:

1. Rhodopsin in rods, mainly used for monochromatic vision in low-light conditions.
2. Photopsin type I, II, and III in cones, mainly used for coloured vision in bright-light conditions.
3. Melanopsin in some retinal ganglion cells, contributing to the pupillary reflex and the circadian rhythm [24].

There seem to be some indications of the involvement of melanopsin in visual phosphenes. Fuglesang et al. [19] state that part of the astronauts reported that light flashes sometimes disturbed their sleep, and 1 astronaut even reported occasionally waking up. Moreover, there is an unexplained effect that during Moon flights more light flashes are observed while flying to the Moon, compared with the return flight. Could this be related to the disturbance of the circadian rhythm of the astronauts?

As stated in the introduction, our research started when individual patients complained about visual phosphenes at one specific treatment machine. Unfortunately, we ignored part of their complaints, which was fatigue on days that these patients were treated at this particular treatment machine. We thought these complaints were coincidental findings because we were unaware of the possible link between visual phosphenes and the circadian rhythm, and because fatigue is a common complaint for these patients. Visual phosphenes might be correlated with fatigue in radiation therapy. More research is needed to determine whether such a relationship exists.

Conclusions

Visual phosphenes during external beam photon radiation therapy, which are unpleasant for patients, are caused by photon activation of photochemicals in the retina, probably either by the direct or scattered photon beam or by the generation of Cherenkov radiation in the vitreous humour. We expect the direct photon activation to be associated with the observation of light flashes and Cherenkov radiation to be associated with the observation of steady light, although it may be difficult for patients to distinguish the two phenomena. Illuminance and maximum dose to the retina are good predictors of seeing light flashes. As the ambient light intensity increases, the probability of seeing light flashes decreases. For the observation of steady light only the dependence on maximum dose to the vitreous humour is statistically significant.

This study shows that the occurrence of visual phosphenes can be influenced by reducing dose to the retina and vitreous humour and by illuminating the treatment room. We postulate that one should reduce the dose rate, instruct patients to keep the eyes open and increase the illuminance in the treatment room to reduce the probability of experiencing visual phosphenes.

Conflicts of interest

None.

Acknowledgements

We would like to acknowledge D.B.P. Eekers, who initiated the research by noticing that for some of her patients the occurrence of visual phenomena depended on the treatment unit.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2018.11.010.

References

[1] Brandes G, Dorn E. Ueber die Sichtbarkeit der Röntgenstrahlen. Ann Phys 1897;296:478–90.
[2] Giesel F. Einiges über das Verhalten des radioactiven Baryts und über Polonium. Ann Phys 1899;305:91–4.
[3] Lipetz L. The x-ray and radium phosphenes. Br J Ophthalmol 1955;39:577–98.
[4] Steidley K. The radiation phosphene. Vision Res 1990;30:1139–43.
[5] Frank I, Tamm I, Coherent visible radiation of fast electrons passing through matter; 1991.
[6] Fazio GG, Jelley JV, Charman WN. Generation of Cherenkov light flashes by cosmic radiation within the eyes of the apollo astronauts. Nature 1970;228:260–4.
[7] Tobias CA, Budinger TF, Lyman JT. Radiation-induced light flashes observed by human subjects in fast neutron, X-ray and positive pion beams. Nature 1971;230:596–8.
[8] McNulty P, Pease V, Bond V. Visual phenomena induced by relativistic carbon ions with and without Cerenkov radiation. Science 1978;201:341–3.
[9] Schardt D, Kavatsyuk O, Krämer M, Durante M. Light flashes in cancer patients treated with heavy ions. Brain Stimul 2013;6:416–7.
[10] Steidley KD, Eastman RM, Stabile RJ. Observations of visual sensations produced by Cerenkov radiation from high-energy electrons. Int J Radiat Oncol Biol Phys 1989;17:685–90.
[11] Newman F, Asadi-Zeydabadi M, Durairaj V, Ding M, Stuhr K, Kavanagh B. Visual sensations during megavoltage radiotherapy to the orbit attributable to Cherenkov radiation. Med Phys 2008;35:77–80.
[12] Blumenthal D, Corn B, Shtraus N. Flashes of light-radiation therapy to the brain. Radiother Oncol 2015;116:331–3.
[13] Farzin M, Molls M, Astner S, Reitz S, Kreiser K, Kampfer S. Light seeing in patients with brain tumors and head and neck malignancies treated with radiotherapy Mostafa. Eur J Oncol 2016;21:254–9.
[14] Thariat J, Leal C, d'Ascoli A, Jardel P, Caujolle JP, Herault J, et al. Phosphenes in patients receiving radiotherapy. Lancet Oncol 2016;17:869–71.
[15] Timmers A, De Kruijf WJM, Rozema T. Occurrence of visual phosphenes during radiation therapy of the head. Radiother Oncol 2016;119.
[16] Agresti A. An introduction to categorical data analysis. Hoboken, NJ, (USA): Wiley-Interscience; 2007.
[17] R Core Team, R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2016.
[18] Bates D, Maechler M, Bolker B, Walker S. Fitting linear mixed-effects models using lme4. J Stat Softw 2015;67:1–48.
[19] Fuglesang C, Narici L, Picozza P, Sannita WG. Phosphenes in low earth orbit: survey responses from 59 astronauts. Aviat Space Environ Med 2006;77:449–52.
[20] Narici L, De Martino A, Brunetti V, Rinaldi A, Sannita WG, Paci M. Radicals excess in the retina: a model for light flashes in space. Radiat Meas 2009;44:203–5.
[21] Casolino M et al. Dual Origins of light flashes seen in space. Nature 2003;422:680.
[22] Durante M, Cucinotta FA. Heavy ion carcinogenesis and human space exploration. Nat Rev Cancer 2008;8:465–72.
[23] Durante M, Orecchia R, Loeffler JS. Charged-particle therapy in cancer: clinical uses and future perspectives. Nat Rev Clin Oncol 2017;14:483–95.
[24] Lane Brown R, Robinson PR. Melanopsin – Shedding light on the elusive circadian photopigment. Chronobiol Int 2004;12:189–204.