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Original Article

Radiation-induced optic neuropathy after stereotactic and image guided intensity-modulated radiation therapy (IMRT)

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ABSTRACT

Background/purpose: To quantify the risk of radiation-induced optic neuropathy (RION) after stereotactic/image-guided positioning and intensity-modulated radiotherapy (IMRT) with ≥50 Gy to the anterior visual pathway (AVP).

Methods: Patients irradiated with ≥50 Gy to the AVP using stereotactic/image-guided positioning between 2002 and 2011 in Mannheim were identified. Detailed dosimetric data were collected and patients or family members were retrospectively asked to rate visual acuity and visual disorders.

Results: 125 patients fulfilled the eligibility criteria. Average maximum equivalent point dose (D_{max}-EQD-$2_{[\alpha/\beta=1.6]}$) to the AVP was 53.1 ± 3.9 Gy. 99 patients received ≥50 Gy bilaterally (chiasm or both optic nerves), resulting in 224 (99x2 bilateral plus 26 unilateral) visual-fields-at-risk (VFAR) for RION. Eighty-two patients provided pre/post-IMRT visual status information (n = 151 VFARs). Permanent visual deterioration occurred in 18 (22%) patients. In seven, visual deterioration was possibly related to radiotherapy (two-sided deterioration in one patient) for a crude incidence of 8.5% (7/82 patients) and 5.3% (8/151 VFARs). Two cases were caused by chronic keratitis/conjunctivitis; in five patients RION could not be excluded (one two-sided). In one of 13 patients with D_{max}-EQD-2 > 58 Gy, RION could not be excluded. In all affected patients, visual acuity post-IMRT had decreased only mildly (1–2 points on the 5-point-scale). One patient with relevant baseline visual impairment (3/5) developed unilateral blindness (crude incidence of blindness on patient-/VFAR-level: 1.2% and 0.66%; competing risk-adjusted/actuarial 24-month incidence: patient/VFAR-level: 1.8% and 0.95%).

Conclusion: Risk of RION was low in this cohort with accurate positioning and precise dosimetric information. Less conservative tolerance doses may be considered in patients with high risk of recurrence.

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Radiation-induced neuropathy (RION) is a serious side-effect which can lead to loss of visual acuity or visual field deficits after irradiation to the anterior visual pathway (AVP). In conventionally fractionated radiotherapy, the incidence of RION primarily depends on the total radiation dose [1,2]. Certain baseline factors such as diabetes mellitus (DM) [3], gender [2], tumor compression [4] or chemotherapy [2,5] have been reported to be associated with an increased risk. These associations, however, were mainly reported in Asian populations [2,3,5] but not observed in a Western case–control study [1]. Nevertheless, there is consensus on the importance of cumulative radiation dose as a risk factor [6–10]. Typically, a maximum point dose (D_{max}) of up to 54–55 Gy in 1.8–2 Gy fractions is recommended based on the observation that the incidence of RION increases markedly at doses >60 Gy [10] although presumed RIONs have also been reported at lower doses [11].

Onset of RION peaks at ~2 years post-radiotherapy but cases within 3 months have also been reported [12]. Much of the

Abbreviations: 3DCRT, 3D-conformal radiation therapy; AVP, anterior visual pathway; CBCT, cone-beam computed tomography; DM, diabetes mellitus; D_{max}, maximum point dose; EQD-2, biologically equivalent dose; IMRT, intensity-modulated radiation therapy; MRI, magnetic resonance imaging; OS, overall survival; RION, radiation-induced optic neuropathy; VFAR, visual field at risk.

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available evidence has been gathered using older radiation techniques with some recent studies focusing on single-fraction or hypofractionated stereotactic radiosurgery [13]. Reports on conventionally fractionated intensity-modulated radiotherapy (IMRT) are scarce with the largest series encompassing 75 patients with 3D-conformal radiation therapy (3DCRT; $n = 19$ had IMRT). [14] Comparability of hypofractionated with conventionally fractionated data depends on accuracy of α/β-estimates [15] which are hard to verify due to the low number of cases. [13] With the current study, we quantified the RION risk in patients treated with IMRT under stereotactic or image-guided conditions with reliable contouring and well documented 3D-plan dosimetry. All patients were prescribed a dose of $\geq$50 Gy to any structure of the AVP. Image-guided radiotherapy (IGRT) was either done using rigid immobilization with stereotactic frame-based setup and weekly portal imaging or, more recently, using cone-beam CT (CBCT).

Materials and methods

Patients

After institutional review board approval (2015-591N-MA), all patients treated at the Department of Radiation Oncology of the University Medical Center Mannheim between 07/2002

Table 1
Baseline characteristics of patients with a nominal prescription dose of 50 Gy or more to the AVP.

Baseline patient factor or risk factor		Results
Primary tumor	Glioblastoma	29 (23.2%)
	Squamous Cell Carcinoma	23 (18.4%)
	Meningioma	20 (16%)
	Astrocytoma or oligodendroglioma (grade II and III)	11 (8.8%)
	Adenocarcinoma (incl. metastases)	8 (6.4%)
	Sarcoma	7 (5.6%)
	Other*	27 (21.6%)
Age at radiotherapy	Mean	56.7
	Median (minimum–maximum)	59.0 (12–92)
Gender	Female (%)	58 (46.4%)
	Male (%)	67 (53.6%)
Tumor localization	Right eye (%)	36 (28.8%)
	Left eye (%)	52 (41.6%)
	Midline/chiasm (%)	36 (28.8%)
	Multiple locations (%)	1 (0.8%)
Diabetes mellitus	Yes (%)	15 12%)
	No (%)	106 (84.8%)
	Unknown (%)	4 (3.2%)
Neurodegenerative disease	Yes (%)	3 (2.4%)
	No (%)	119 (95.2%)
	Unknown (%)	3 (2.4%)
Hypercholesterolemia	Yes (%)	25 (20%)
	No (%)	93 (74.4%)
	Unknown (%)	7 (5.6%)
Alcohol consumption	Yes (%)	15 (12%)
	No (%)	105 (84%)
	Unknown (%)	5 (4%)
Smoking	Yes (%)	51 (40.8%)
	No (%)	71 (56.8%)
	Unknown (%)	3 (2.4%)
Arterial Hypertension	Yes (%)	67 (53.6%)
	No (%)	56 (44.8%)
	Unknown (%)	2 (1.6%)
Surgery of the optic nerve or chiasm prior to radiation?	Yes (%)	15 (12%)
	No (%)	106 (84.8%)
	Unknown (%)	4 (3.2%)
Surgery of the orbital cavity prior to radiation?	Yes (%)	24 (19.2%)
	No (%)	97 (77.6%)
	Unknown (%)	4 (3.2%)
Number of surgical interventions at the AVP	1	74 (59.2%)
	2	20 (16%)
	3	10 (8%)
	4	2 (1.6%)
Chemotherapy concurrent to radiation therapy	Yes (%)	73 (58.4%)
	No (%)	51 (40.8%)
	Unknown (%)	1 (0.8%)
Visual acuity deficit at start of radiation therapy	Yes (%)	40 (32%)
	No (%)	67 (53.6%)
	Unknown (%)	18 (14.4%)
Any other visual deficit at start of radiation therapy	Yes (%)	58 (46.4%)
	No (%)	55 (44%)
	Unknown (%)	12 (9.6%)
Direct tumor infiltration in the AVP?	Yes (%)	45 (36%)
	No (%)	71 (56.8%)
	Unknown (%)	9 (7.2%)

* Other tumors: Esthesioneuroblastoma, sarcomatoid carcinoma, schwannoma/neurinoma ($n = 2$), Non-Hodgkin's lymphoma (other than Burkitt's, $n = 3$), Burkitt's lymphoma, adenoid cystic carcinoma ($n = 2$), other neuroblastoma ($n = 2$), lymphoepithelial carcinoma ($n = 4$), melanoma, sinonasal undifferentiated carcinoma, pilocytic astrocytoma, gliosarcoma, other high-grade glioma, myoepithelial carcinoma (malignant myoepithelioma), epidermoid tumor, pituitary adenoma ($n = 2$), plasmacytoma ($n = 2$).

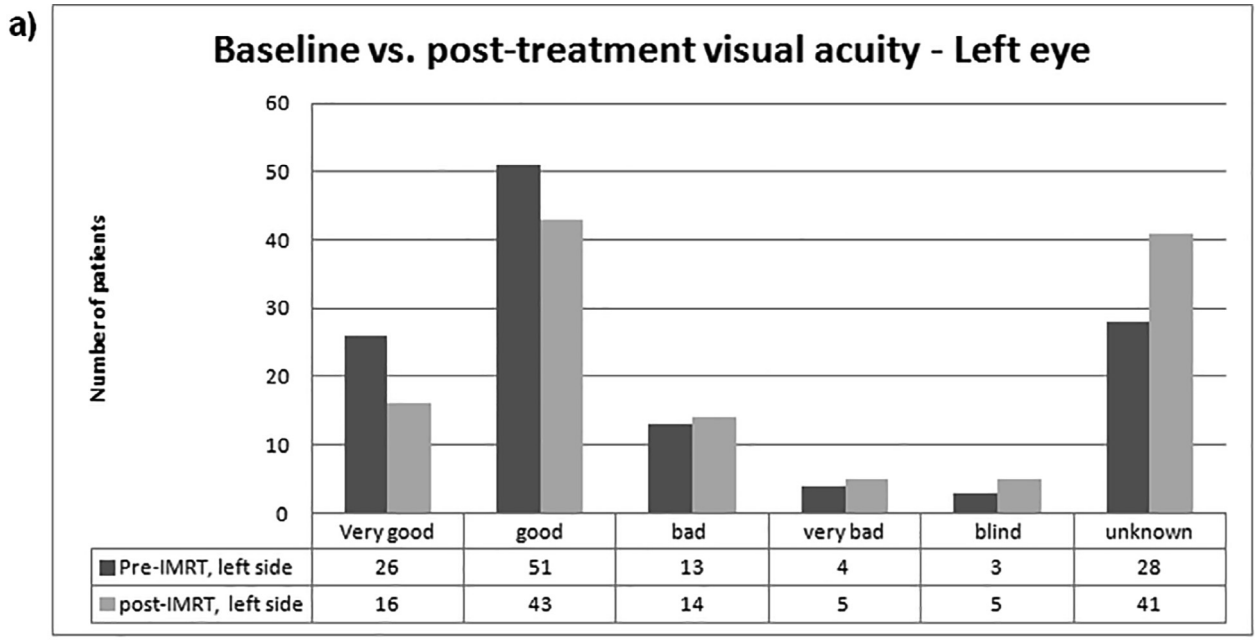
(introduction of IMRT) and 12/2011 (≥5 years follow-up) were reviewed retrospectively for a nominal prescribed dose to any AVP structure (optic nerves, chiasm, eyeballs) of ≥50 Gy. Cumulative doses of ≥50 Gy after re-irradiation were excluded.

Radiotherapy

Planning was CT-based, positioning was done with a rigid mask after stereotactic frame-based isocenter localization (n = 36; 28.8%) or with a thermoplastic mask (n = 89; 71.2%) and IGRT with CBCT [16], initially with CORVUS™ (Nomos, Pittsburgh, PA, USA; pencil-beam dose-calculation), later with MONACO™ (Elekta AB, Sweden). All patients had highly conformal IMRT plans. Dose prescription was dose–volume based, in line with the ICRU-83. Median PTV dose was reported as prescription dose. To calculate the biologically equivalent dose (EQD-2), we used an α/β of 1.6 as proposed by Jiang et al. [15].

Statistics:

Statistics were performed using SPSS (V15.0, SPSS, Chicago IL/IBM New York, USA), or "R" (https://www.r-project.org/). [17] Curves for overall survival (OS) and side-effects were calculated using the Kaplan–Meier analyses. Differences between variables were tested using the Mantel–Cox log-rank statistics. We analyzed patient-level events but additionally performed an analysis with all *visual fields at risk* (VFAR). VFARs were defined for each patient to reflect AVP structures prescribed ≥50 Gy; e.g. patients with a D_{max} of ≥50 Gy to both optic nerves or the chiasm (potentially leading to 2-sided blindness/bitemporal hemianopsia) would have two VFARs. A D_{max} of ≥50 Gy to one side (e.g. optic nerve/eyeball)



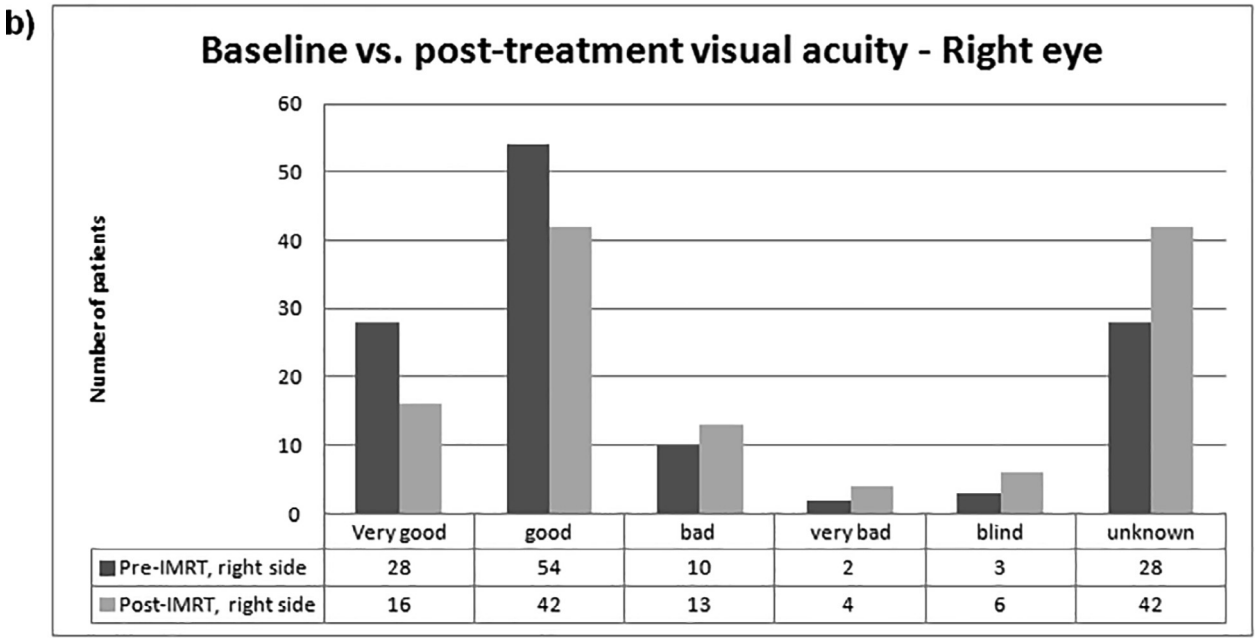
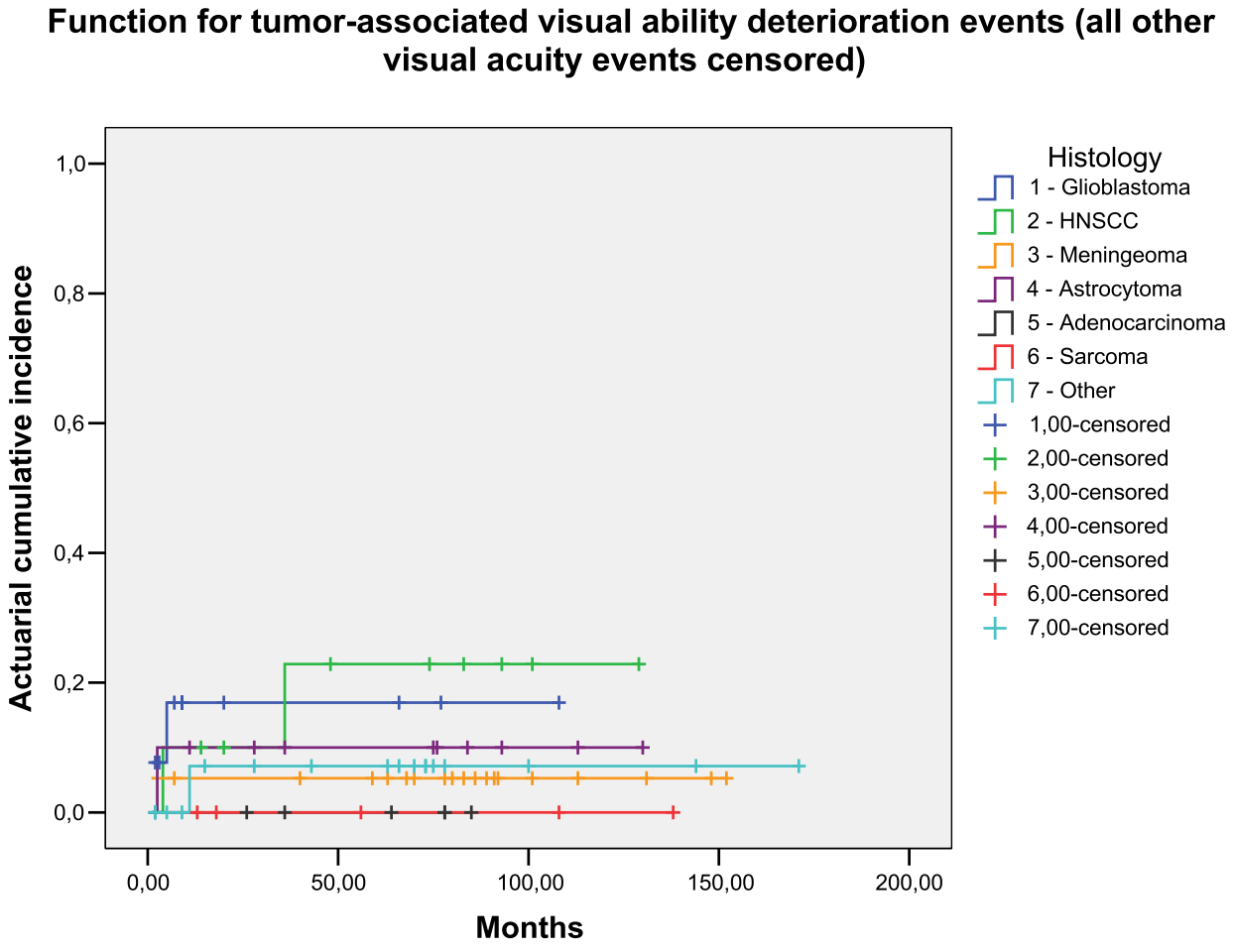


Fig. 1. (a, b) Pre-IMRT and post-IMRT visual acuity ratings are shown for the left eye (a) and for the right eye (b). Changes are not specifically tumor-related or treatment-related but include changes in visual acuity due to age-related diseases or symptoms such as presbyopia or diabetes.

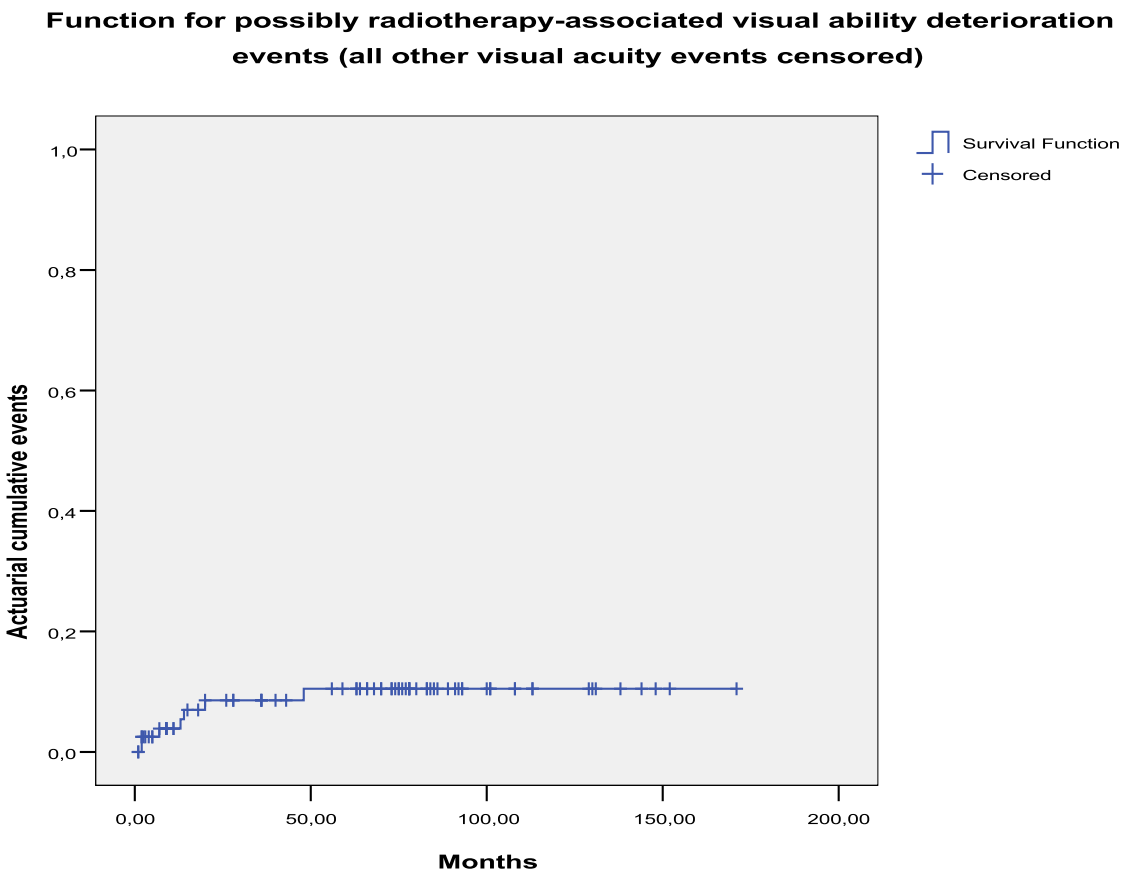


Patients at risk

	0 months	50 months	100 months	150 months	200 months
1. Glioblastoma	13	3	1	0	0
2. HNSCC	10	5	2	0	0
3. Meningeoma	19	16	5	1	0
4. Astrocytoma	10	6	2	0	0
5. Adenocarcinoma	7	4	0	0	0
6. Sarcoma	5	3	2	0	0
7. Other	18	10	3	1	0

P=0.61 for differences in tumor-associated blindness between groups

Fig. 2. (a) Tumor-associated deterioration in visual ability for all patients with visual acuity data ($n = 82$) is shown as actuarial incidence. Other visual events such as cataract, presbyopia, and RION were censored for this analysis. Graphs are stratified by tumor-types: 1: Glioblastoma; 2: Squamous cell carcinoma; 3: Meningioma; 4. Astrocytoma; 5. Adenocarcinoma; 6. Sarcoma; 7: Other tumors. b) Cumulative incidence of patients with deterioration of visual ability over time for all patients with visual acuity data ($n = 82$). This graph only shows cases that were deemed possibly related to radiation therapy; all other cases were censored. Two patients had conjunctivitis, and keratitis; five patients had visual acuity deterioration deemed possibly related to RION.



Patients at risk

	0 months	50 months	100 months	150 months	200 months
All patients with full visual acuity data	82	47	15	2	0

Fig. 2 (*continued*)

results in one VFAR. VFAR calculations were done for the RION endpoint to adjust for the higher risk of blindness after two-sided AVP-exposure with ≥50 Gy. Percentages mentioned in the results section apply to the number of evaluable cases at the time of evaluation; this translates to different percentages for right/left eye for the same number of cases (e.g. after enucleation, the eye was censored for the cataract analysis).

Questionnaires

Patients, family members (for passed patients) and ophthalmologists were contacted to obtain information on visual acuity on a 5-point scale encompassing a patient-reported, "very good" to "blind" scale. Pre-radiotherapy visual status was evaluated retrospectively from patients, family members and ophthalmologists. Details on risk factors, including DM, arterial hypertension, smoking, alcohol abuse, and neurological or eye diseases were obtained. Patients were asked to provide access to their ophthalmologist's record.

Definition of RION as an endpoint

Patients were classified as possible RION events in case of visual deterioration not explained by other factors such as tumor recurrence or surgical interventions directly associated with visual deterioration. Patients with visual deterioration were evaluated by two senior radiation oncologists. Severe RION was defined as blindness of an eye or hemianopsia or deterioration of visual acuity by ≥2 points, regardless of initial visual status.

Results

134 patients with ≥50 Gy were identified; however, 9 of them had received the required dose only after two courses of IMRT and were excluded from this study.

Baseline factors

The remaining 125 patients were included in the analysis after a mean follow-up of 51.5 (median: 37) months. Most common histologies included glioblastoma (23.2%), head-and-neck squamous cell carcinoma (18.4%), and meningioma (16%; Table 1). Tumors were adjacent to the right eye/optic nerve, left eye/optic nerve, and chiasm in 36 (28.8%), 52 (41.6%), and 36 (28.8%) of patients, respectively (multiple: $n = 1$, 0.8%). Direct infiltration in AVP structures was observed in 45 (36%) patients with 9 close/unknown cases (7.2%). Median age was 59 years. 46.4% of patients were female. Patient-reported data were obtained from 44 patients (35.2%) and from interviews with family members in 49 cases (39.2%). Indirect sources of information were the only source of information in 32 cases (25.6%; primarily health records and ophthalmologists). Non-tumor, non-treatment related risk factors for blindness were present in 95 (76%) of patients. Risk factors included

Table 2
Details on patients with decreased visual acuity possibly associated with RION. The localization "eyeball" was used in cases in which doses of ≥50 Gy could not be excluded at proximal parts of the optic nerve (i.e. possible optic head dose ≥50 Gy).

Pat.-No./ VFAR	Histology	Baseline risk factors?	Baseline eye disorders	Systemic tumor therapies prior or concurrent with IMRT	Nominal D_{max} (EQD-2-D_{max}) Localization	Onset of symptoms (month)	Decrease in acuity (points, pre-IMRT → post-IMRT)	Symptoms[±]
1 Right	Meningioma	Hypertension	Exophthalmos, Ptosis, Ocular motility disorder, pupillary dysfunction	None	51.6 Gy (49.3 Gy)[#] right optic nerve	7	3 → 5 (blind)	Periorbital edema, loss of vision that developed after prior displacement of optic nerve by tumor (stable disease at time of blindness).
2 Left	Sarcoma	No	Ocular motility disorder, exophthalmos	Prior to IMRT: VIDE (x6), VAI (x3)[##]	58.2 Gy (54.4 Gy) left eyeball[**]	13	1 → 3	Incipient cataract, epiphora, loss of visual acuity.
3 Right	Non-Hodgkin Lymphoma	No	Myopia, lacrimal duct stenosis, intraocular lens implant (cataract), transient partial visual field loss	None prior to visual deterioration[§§]	51.4 Gy (54.7 Gy) right eyeball	2	2 → 3	Retinal detachment and retinal foramen, cyclitis, epiphora, macular edema, possible temporary visual field loss after IMRT with subsequent loss of visual acuity
4 Left[§]	Plasmacytoma[*]	Hypertension	Transient blindness after central vein thrombosis, ptosis: periorbital edema, macular edema	Melphalan and stem cell transplantation[††]	52.6 Gy (54.1 Gy) left eyeball	2	3 → 4[§]	Reduction of visual acuity, furthermore, surgically treated cataract
5 right	HNSCC (nasopharynx)	Hypertension Hypercholesterolemia	Double images, cataract	Concurrent radio-/ chemotherapy with 5-fluorouracil and carboplatin	56.9 Gy (55.3 Gy) right optic nerve[†]	20	2 → 4	Loss of visual acuity, blurred vision
5 left			Double images, cataract		64.8 Gy (67.7 Gy) left optic nerve[†]	20	3 → 4	Loss of visual acuity, blurred vision, retina color changes, cotton wool foci, bleeding, pale papilla, ectropion and concomitant conjunctivitis

[*] The patient was in complete remission after chemotherapy and stem cell transplantation before infiltration of atypical plasma cells in the left eye was diagnosed. As there was no other systemic recurrence at the time of radiation therapy, high-dose radiation therapy of the eye with 50 Gy was recommended.
[§] This patient had an improvement of visual acuity on the right side (mild improvement on the right: 3 → 2, mild deterioration on the left: 3 → 4); the reported scores were congruent with objective changes in visual acuity testing by an ophthalmologist in both eyes of the patient.
[#] Contralateral EQD-2-D_{max} was higher: 53 Gy.
[**] Left eye ball had the highest dose but doses ≥50 Gy were also recorded at the left optic nerve, the right optic nerve, and the chiasm.
[†] The patient had doses ≥50 Gy on all AVP structures besides the right eyeball which only received 37.4 Gy.
[±] All recorded disorders and symptoms are listed. There was no patient with reduction in visual acuity without accompanying eye disorders.
[##] VIDE: vincristine, ifosfamide, doxorubicin, etoposide was given in 6 cycles until 12 months prior to IMRT; VAI: vincristine, actinomycin, ifosfamide until 6 months prior to IMRT.
[§§] After onset of RION, the patient received rituximab and bendamustine.
[††] The patient had high-dose melphalan and autologous stem cell transplantation with near-complete remission 16 months prior to IMRT.

DM (12%), neurodegenerative diseases (2.4%), arterial hypertension (53.6%), hypercholesterolemia (20%), alcohol abuse (12%), and smoking (40.8%). Visual acuity deficits were present in 43 patients (34.4%; unknown: 9.6%) at diagnosis and in 40 (32%, unknown 14.4%) at start of IMRT. Baseline deficits were deemed tumor-related in 25 patients (=41%; 34.4% unknown but possibly related; 24.6% unrelated). For baseline patient characteristics, see Table 1.

Other visual, eye, or ocular motility deficits were present in 58 patients (46.4%). Symptoms in patients with other deficits included ocular motility disorder, diplopia, and partial visual field loss in 19%, 12.1%, 8.6%, respectively; 24 patients (41.4%) with other visual, eye, or ocular motility deficits had multiple disorders; 46 were deemed tumor-related (79.3%).

Very good or good pre-IMRT visual acuity scores for the right and left eye were recorded in 84.5% and 79.4%, respectively (28 unknown cases for each side, three blind patients each side; Fig. 1a–b).

Chemotherapy and surgery

Most patients had chemotherapy during the course of disease (62.4%; one unknown case). 90.4% of patients had surgery or biopsy. Surgery, potentially directly affecting AVP structures, was done in 84.8% of patients (25.6% had ≥2 interventions). Surgical complications were recorded in 12.8% of patients, including 5 severe cases of cerebral nerve injury, and one visual field loss.

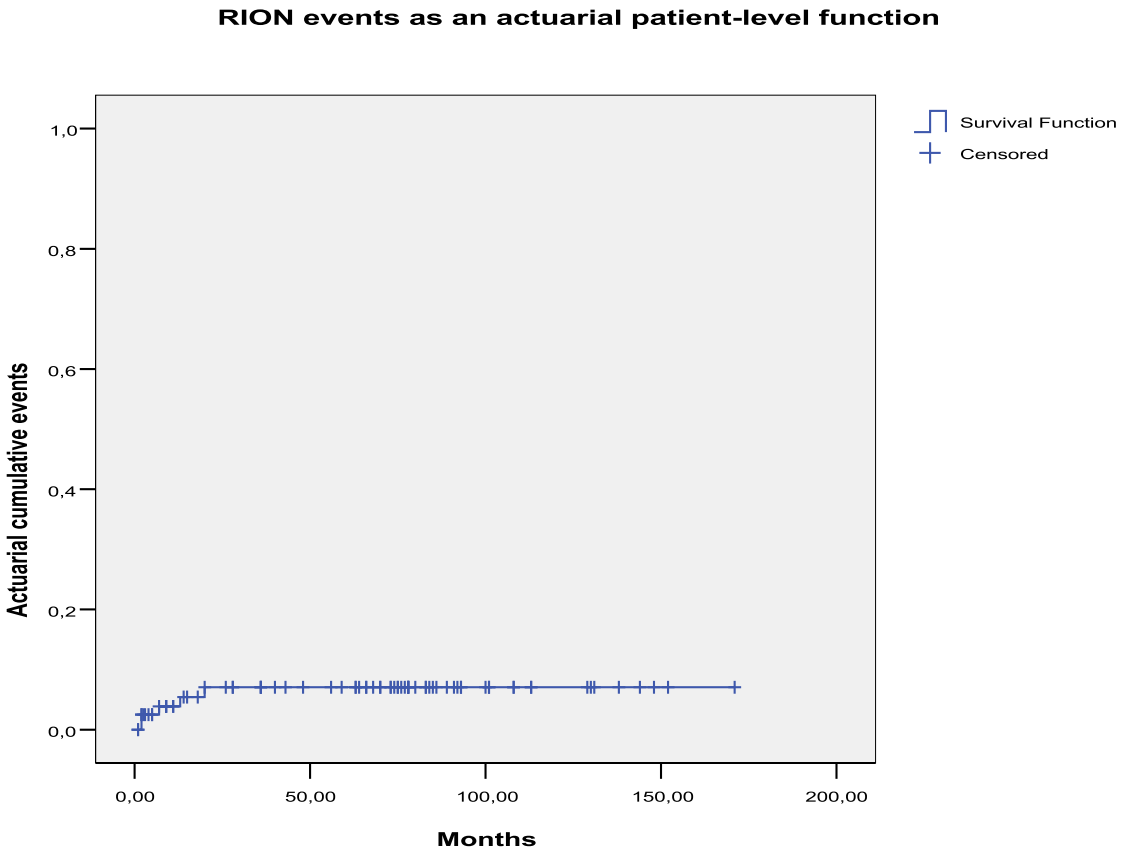
Radiotherapy

All 125 patients included in the primary analysis had a nominal prescription D_{max} of ≥50 Gy to at least one AVP structure. 99 patients had 50 Gy bilaterally or at the chiasm for 224 VFARs. Mean tumor prescription dose was 60.5 Gy (median: 60 Gy; range 46–86 Gy). Number of fractions ranged from 23-41 (median 30, mean 30.8). Median D_{max}-EQD-2 $_{[\alpha/\beta=1.6Gy]}$ calculated for the highest AVP dose in 125 patients was 51.8 Gy (mean: 52.2 Gy, range: 43.6–69.2 Gy). 19 out of 82 patients with post-IMRT visual acuity data had a D_{max} of ≥55 Gy (including n = 13 with ≥58 Gy; highest D_{max}-EQD-2$_{[\alpha/\beta=1.6\ Gy]}$ = 69.2 Gy).

Median VFAR-level (n = 224) D_{max} EQD-2 $_{[\alpha/\beta=1.6\ Gy]}$ was 51.8 Gy (mean: 52.4 Gy, range: 43.6–69.2 Gy). Post-IMRT visual acuity data were available for 151 VFARs; 27 had received a dose of ≥55 Gy (including n = 15 with ≥58 Gy). Details on irradiation doses and dose-level stratifications are shown in Supplementary Fig. SF-1a-b.

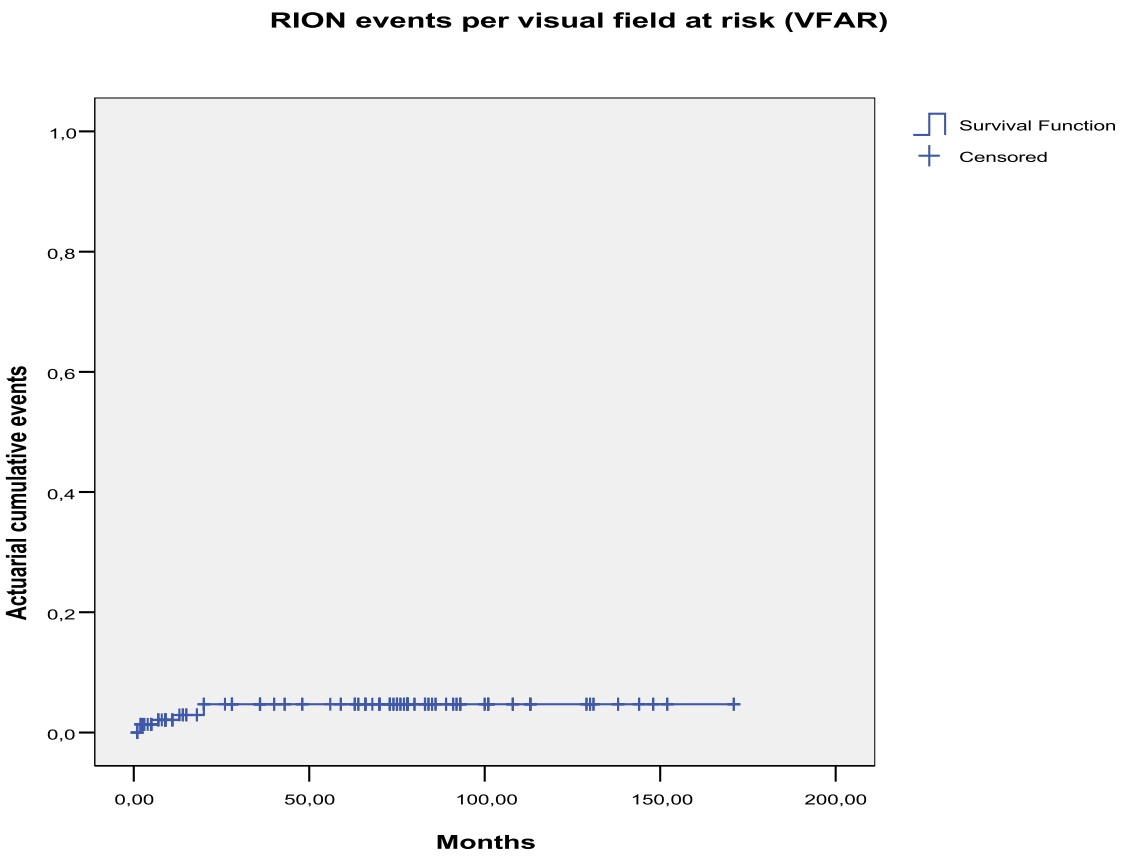
Efficacy outcomes

Efficacy outcomes such as OS and tumor-specific survival were collected to evaluate competing risks to RION. Mean OS was 88.7 months (74.1–103.4; median 60 months). Most deaths were tumor-related (78.5%; unrelated: 6.2%; unknown: 15.4%). Detailed



	0 months	50 months	100 months	150 months	200 months
All patients with full visual acuity data	82	47	15	2	0

Fig. 3. (a, b) RION incidence curves over time are shown for patients with full visual acuity data as patient-level analysis (3a; n = 82) and VFAR-level data (3b; n = 151). Five patients in total developed visual acuity deterioration possibly related to RION. One patient had decreased visual acuity on both eyes for a total of six VFAR lesions. Only one patient with bad visual acuity at baseline developed blindness, thereby fulfilling the criteria for severe RION in our study; all other possible RIONs were mild or modest reductions in visual acuity (1–2 points on the 5-point scale).



	0 months	50 months	100 months	150 months	200 months
All VFARs with full visual acuity data	151	89	29	2	0

Fig. 3 (*continued*)

graphs for survival events stratified for histology and stratified for dose levels are shown in Supplementary Figs. SF-2a-f.

Visual outcomes

Most patients with evaluable data (right side: 83, left side 81 patients) rated their visual acuity as good or very good at the time of the follow-up (right side: 71.6%, left side: 71.1%). Bad, very bad vision, or amaurosis was observed in 16%, 4.9%, or 7.4% on the right side and 16.9%, 6%, or 6% on the left side, respectively. One patient had enucleation after local recurrence on the right side, 2 on the left side. Detriment in visual acuity due to presbyopia was recorded in 12 (14.5%) patients. Cataracts occurred in 22 (23.2%) patients on the left and in 20 patients (21.5%) on the right side, respectively. Most cataracts were deemed possibly related to radiotherapy (left side, $n = 18$; 81.8%; right side, $n = 19$, 95%). Actuarial incidence curves for cataract or presbyopia are shown in Supplementary Fig. SF-3a-c.

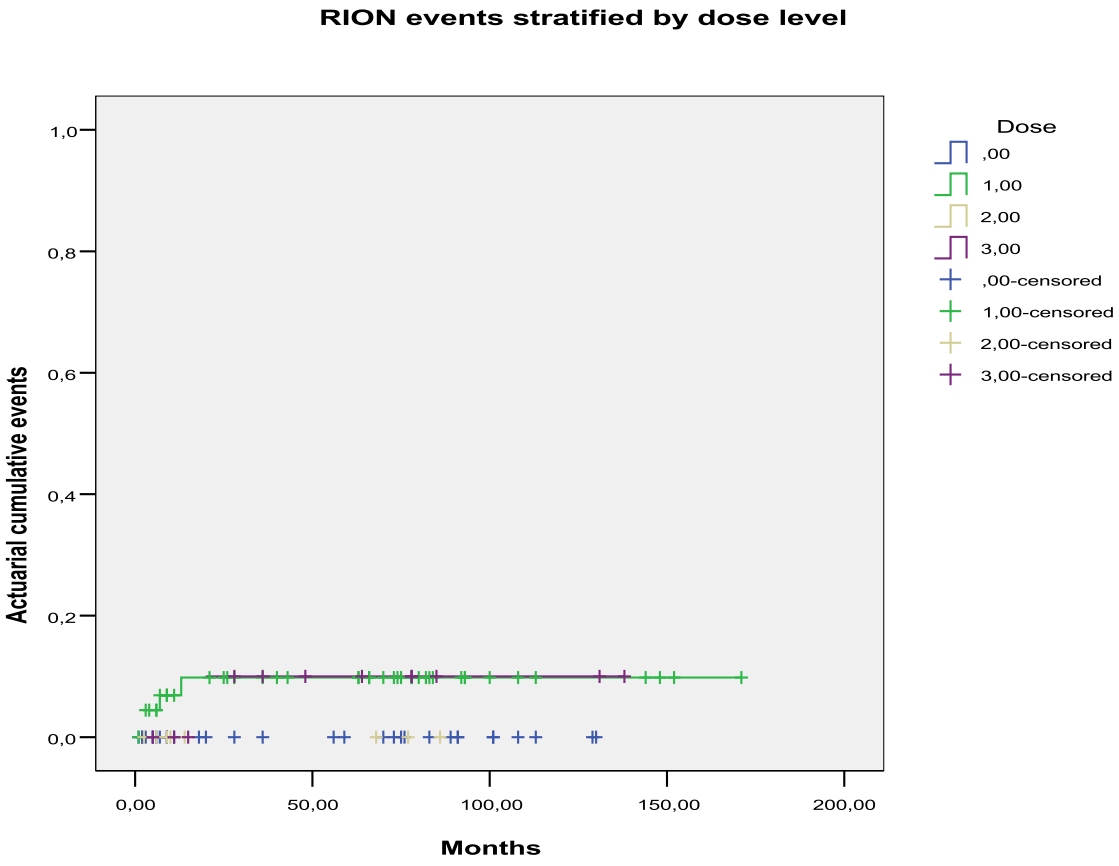
Visual field loss or reductions in visual acuity other than presbyopia-, or cataract-associated disorders occurred in 18 patients after a median time to event of 12 months (average time to event: 18.3 months, mean survival time for the cohort: 132.9 months, median not reached; see Supplementary Fig. SF-4a). Detriment of visual capacity was considered tumor-related in 7 patients (see Fig. 2a for incidence stratified by histology), unrelated to tumor and IMRT in 4 patients (Supplementary Fig. SF-4b), and likely related to radiotherapy in 7 patients (Fig. 2b). Out of these 7 patients, two had radiotherapy-associated chronic keratitis/conjunctivitis, and dry eye, respectively (grade 2, and 3). Five patients had mild-to-modest detriment (1–2 points on 5-point scale; see Table 2) in vision which was deemed possibly related to RION; crude incidence for patients with full data on visual acuity was 6.1%, actuarial incidence is shown in Fig. 3a. For VFAR-level calculations, we obtained pre/post-IMRT acuity data from 151 out of 224 VFARs. Eight showed a detriment in visual acuity or partial vision loss possibly related to radiotherapy (including two, due to keratitis/conjunctivitis and dry eye). In six VFAR-level cases, RION could not be excluded (one two-sided; see Fig. 3b). Five out of these were mild or modest, one case was severe resulting in blindness of one eye. This patient had "bad" patient-reported visual capacity at baseline (3 on the 5-point scale with 5 = equal to blindness) and developed unilateral amaurosis possibly attributable to RION. This patient had the lowest D_{max} of all possible RION cases (nominal ipsilateral D_{max}: 50.8 Gy, EQD-2 $_{[\alpha/\beta=1.6]}$ = 49.3 Gy; contralateral: 53 Gy). Details of patients with reduced visual acuity possibly attributable to RION are shown in Table 2.

Visual acuity post-IMRT improved compared to baseline in four patients mild (1 point, $n = 3$) or moderately (2 points, $n = 1$).

In patients without data on visual acuity, health records were analyzed for information on RION. In another 17 patients (30 VFAR) without post-IMRT acuity data but with available follow-up records, no evidence of RION was found. Patient-reported visual

acuity data were unavailable in these patients but it is unlikely that significant visual status deterioration occurred without being mentioned in available follow-up records. Therefore, we repeated all aforementioned RION calculations for the dataset with sufficient follow-up information, even if patient-reported visual acuity pre-/post-IMRT was unavailable. This resulted in a patient- and VFAR-level incidence of 5.1% (5/99) and 3.3% (6/181) for all cases (see Fig. 4a-b); and 1% (1/99), and 0.55% (1/181) for severe cases, respectively. Follow-up Magnetic Resonance Imaging (MRI) was available in all RION patients and could be reviewed by an expert radiologist in four out of five patients. No signs for RION [18] were observed in the possible RION cases.

We analyzed which baseline factors might be associated with RION. As already mentioned, one possibly RION-associated blindness occurred at a D_{max}-EQD-2 $_{[\alpha/\beta=1.6]}$ of 49.3 Gy, all other cases occurred at (side-specific/VFAR-level) doses above 54 Gy (54.4, 54.7, 54.1, 55.3, and 67 Gy). When dichotomized at the median D_{max}-EQD-2 $_{[\alpha/\beta=1.6]}$, detriment in visual acuity was not correlated with total dose ($p = 0.057$). Actuarial incidence stratified by dose levels is shown in Fig. 4a-b. Baseline risk factors were not associated with RION. Interestingly, all patients with possible RION were non-smokers (smoking distribution for all patients 40.8% smokers; $p = 0.11$). Smoking did not affect OS in our cohort, excluding confounding due to competitive risk of death.

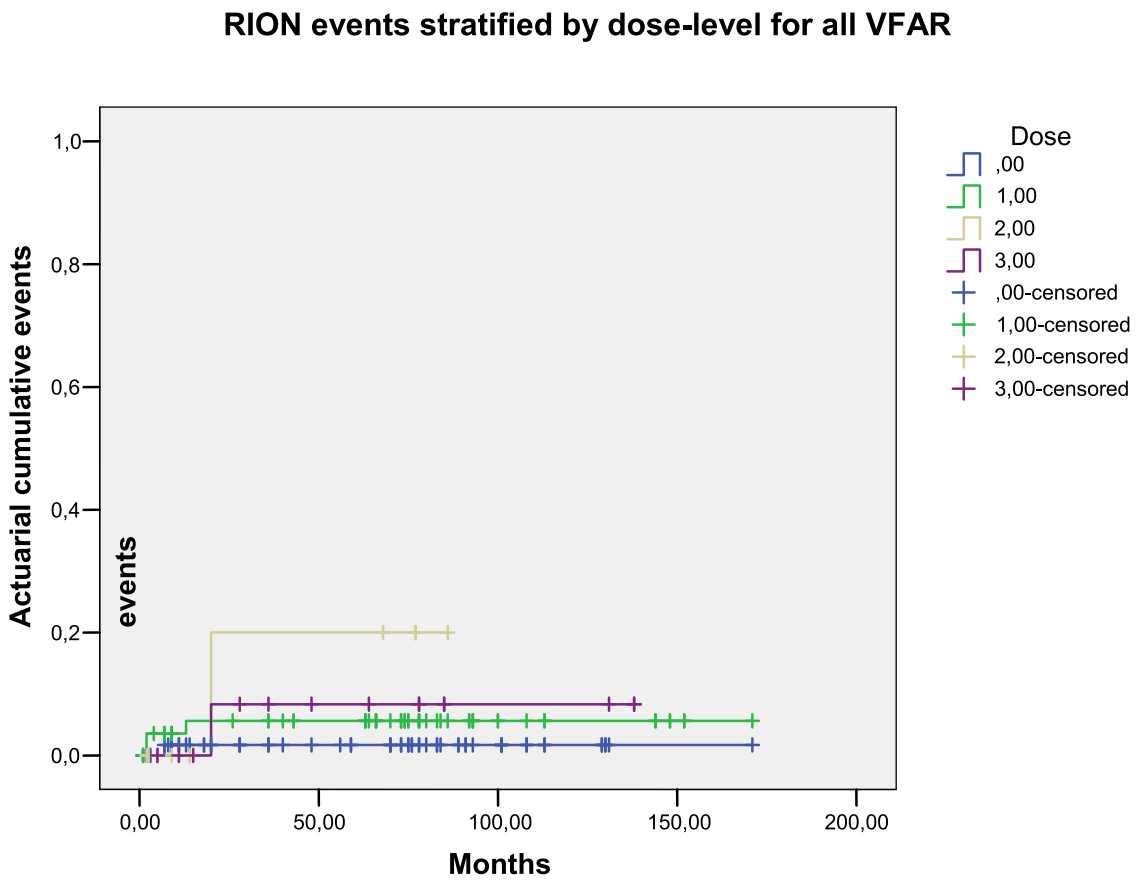


Patients at risk

	0 months	50 months	100 months	150 months	200 months
Dose <50 Gy (0)	27	15	6	0	0
Dose 50-55 Gy (1)	36	23	7	2	0
Dose 55-58 Gy (2)	6	3	0	0	0
Dose ≥58 Gy (3)	13	6	2	0	0

P=0.374 for the comparison of RION events in different dose levels.

Fig. 4. (a, b) RION incidence curves stratified by dose level with the same cohorts detailed in the legend of Fig. 3. Note that incidence levels for dose cohorts may differ between the patient-level analysis and the VFAR-level analysis due to the fact that the highest D_{max} out of all doses to AVP structures was used in the patient-level analysis while the highest dose to the respective side was used in the VFAR analysis. In some patients, the nerve receiving the higher dose was not the nerve that developed possible RION. There was no correlation of dose-levels and RION in our dataset.



VFARs at risk

	0 months	50 months	100 months	150 months	200 months
Dose <50 Gy (0)	67	37	14	1	0
Dose 50-55 Gy (1)	57	40	12	3	0
Dose 55-58 Gy (2)	12	4	0	0	0
Dose ≥58 Gy (3)	15	8	3	0	0

P=0.494 for the comparison of RION events in different dose levels.

Fig. 4 (*continued*)

Discussion

To our knowledge, we provide one of the largest series to evaluate the occurrence of impairment of visual acuity and, specifically, possible RION in patients treated with conventionally fractionated IMRT. We used either rigid frame-based immobilization with weekly portal imaging or, more recently, IGRT with cone-beam CTs, thus providing data based on treatments of high dosimetric accuracy. In our study, D_{max} was not significantly associated with occurrence of RION which, at face value is in contrast to most available data [6–10]. It has to be kept in mind, however, that in contrast to other studies, the dose range covered is smaller and the accuracy of the dosimetric information is likely higher than in earlier data, therefore the dose window studied here may still be in the plateau area of the dose–response curve. Additionally, we did not observe an association with other baseline risk factors such as diabetes or chemotherapy which were identified by analyses in Asian populations [2,3,5]. In this regard, our data are in support of another recent analysis in Western populations which did not show an association of RION with baseline risk factors [1]. In line with our data, some other authors [1] also observed a lower percentage of smokers (not significant) in the group of patients with suspected RION while others discussed smoking as a risk factor [11]. We analyzed overall survival curves for smokers in our cohort and did not find a difference ($p > 0.05$) compared to non-smokers. Hence smoking does not seem to be a competing risk factor in our cohort. Because of the inconsistent data in the literature and the non-significance of the observation, we assume that the observation may have occurred by chance.

Our study confirms the very low risk of RION in a setting with IMRT with either rigid frame-based immobilization or modern IGRT with soft immobilization. Most likely, our study even overestimates the risk; first, because patients who do not develop any side-effects might be more likely to be lost to follow-up. Second, similar to other studies [14], we could not actually *confirm* RION pathologically but we only excluded other optic lesions or local tumor growth. Nevertheless, all patients with possible RION had one or more baseline eye conditions and all of them had at least one eye condition at the time of decreased visual acuity (see Table 2). Finally, none of the RION cases showed RION-typical changes [18] in routinely performed follow-up MRI. Therefore, all RION cases in our analysis have a considerable risk of being false positive. We are aware that retrospective rating of visual acuity loss might be difficult for patients; however, we were primarily interested in the incidence of severe RION and we assumed that patients were able to recall the incidence of severe visual acuity reduction and especially blindness due to the major impact in everyday life.

Finally, we cannot completely exclude that we missed a RION case in one out of seven patients who had visual acuity loss or partial visual field loss due to tumor progression; however, due to the detailed data collected, the risk of false negative cases is most likely very low in our cohort.

Taken together, we address many of the shortcomings of the original QUANTEC dataset as discussed by the authors [10] such as

- Most series were non-IMRT datasets (and therefore most likely non-IGRT).
- Doses reported for optic structures were limited to point dose calculations (or rather estimates) with specifications that were not well defined.
- A plethora of approximations and assumptions had to be made by the authors to address shortcomings of different datasets (see Table 2 in [10]), as they had only limited access to raw data.

Our dataset provides exact doses as well as localization data. Our patients were all treated with IGRT or stereotactic localization, resulting in highly reliable dosimetric data. We show that the real-life risk of RION is very low in a cohort treated with IMRT if published dose constraints are respected and modern image-guidance and accurate positioning is applied. Occurrence of RION cases in our cohort was not different when dose-strata were compared; i.e. the risk did not increase numerically in the subgroups of evaluable patients with D_{max}-EQD-2 $_{[\alpha/\beta=1.6]}$ doses $\geq$55 Gy (n = 21, average dose: 59.9 Gy) or $\geq$ 58 Gy (n = 13, average dose: 63.2 Gy) compared to the lower cohorts of <50 Gy or 50–55 Gy. As mentioned above, the risk of false-positive results in our study is higher than the risk of false negative cases. The latter is presumably low due to the detailed clinical data on visual acuity and due to the fact that even patients without detailed visual status data are unlikely to conceal a severe toxicity such as blindness during follow-up visits. Numerically, the combined risk of tumor-related death and tumor-related deterioration of visual ability exceeds the risk of RION at all dose levels; as expected, this pattern is more pronounced in aggressive tumors such as squamous cell carcinoma.

Furthermore, only one case of severe RION resulting in blindness possibly IMRT-related was observed. This patient was in the lowest dose cohort and had severe preexisting visual acuity disorders (tumor-related nerve affection, cataract, and exophthalmos). All other patients with possibly radiation-related visual acuity deterioration had mild or modest decreases in visual acuity (1–2 points) without blindness or hemianopsia.

Assuming that our data can be reproduced in other modern series with more patients in high-dose cohorts of 55–58 Gy or more, we conclude that for selected patients, where tumor control is essential, higher maximum point doses to the AVP might be acceptable. Considering the risk of tumor recurrence in certain head-and-neck cancers, maximum point doses up to 55–58 Gy to the AVP might be associated with a more favorable long-term risk/benefit profile than doses of 50–55 Gy in selected patients with (curable) tumors close to AVP structures.

Authors' contributions

SB contacted all patients and evaluated the questionnaires and the follow-up.

JBH provided general assistance and evaluated each possible RION case.

FW provided general assistance and helped to draft the manuscript.

VS helped to create the database for patient follow-up.

FS and KS planned the radiation therapy in most patients.

JB analyzed each MRI on a case-by-case basis for signs of optical neuropathy.

FL conceived the study, provided general assistance and evaluated all possible cases with RION.

DB provided/supervised general outcome analysis, calculated all statistics and drafted the manuscript.

All authors read and approved the final manuscript.

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None.

Conflict of interest

SB, KS, FL, and JBH have nothing to disclose.

JB reports personal fees from Siemens Healthineers AG, outside the submitted work.

FS reports personal fees and travel support from Elekta, during the conduct of the study.

VS has nothing to disclose.

FW reports research grants and travel support from Elekta, during the conduct of the study.

DB reports personal fees from Siemens AG, personal fees from NB Capital ApS, personal fees from Nordic Biotech, outside the submitted work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2019.02.003.

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