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Glaucomagenesis following ionizing radiation exposure

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Abstract

Glaucoma is a group of optic neuropathies causing optic nerve damage and visual field defects, and is one of the leading causes of blindness. Nearly a century has passed since the first report of glaucoma manifested following ionizing radiation therapy of cancers. Nevertheless, associations between glaucoma and radiation exposures, a dose response relationship, and the mechanistic underpinnings remain incompletely understood. Here we review the current knowledge on manifestations and mechanisms of radiogenic glaucoma. There is some evidence that neovascular glaucoma is manifest relatively quickly, within a few years after high-dose and high dose-rate radiotherapeutic exposure, but little evidence of excess risks of glaucoma after exposure to much lower doses or dose rates. As such, glaucoma appears to have some of the characteristics of a tissue reaction effect, with a threshold of at least 5 Gy but possibly much higher.

Keywords

Glaucoma; Ionizing radiation; Radiotherapy patients; Atomic bomb survivors; US radiologic technologists; Russian Mayak workers; Radiation protection

1. Introduction

Glaucoma is a group of optic neuropathies associated with characteristic damage to the optic nerve head (ONH) and visual field abnormalities, with or without an increased intraocular pressure (IOP) [1]. Glaucoma represents one of the leading cause of vision loss, second only to cataract (Kingman, 2004), and the leading cause of irreversible blindness worldwide. Its four major types are primary open-angle glaucoma (POAG), primary angle-closure glaucoma (PACG), secondary glaucoma, and congenital glaucoma. Pooled global age-standardized prevalence of glaucoma in the population aged 40–80 years is 3.54% where POAG and PACG account for 3.05% and 0.50%, respectively [2]. POAG with IOP

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≤21 mmHg (within the normal range) and >21 mmHg is called normal- and high-tension glaucoma (NTG and HTG), respectively. Secondary glaucoma includes iatrogenic glaucoma (following medications, e.g., with steroids, sulfa, anticholinergic or adrenergic agents) [3], glaucoma in Posner-Schlossman syndrome (glaucomatocyclitic crisis) [4], exfoliation glaucoma (XFG) following exfoliation syndrome, uvitic glaucoma, pigmentary glaucoma, and neovascular glaucoma (NVG) [5]. Posterior segment ischemia that is most commonly secondary to proliferative diabetic retinopathy or central vein retinal occlusion underlies NVG in most cases [5]. The common features for all types of glaucoma are loss of retinal ganglion cells (RGCs), thinning of the retinal nerve fiber layer, and cupping of the ONH [6]. Progression usually stops if IOP is lowered by 30–50% from baseline, and thus IOP is the primary modifiable risk factor [6]. Early detection is essential, made the more difficult because chronic glaucoma is painless and symptomatic visual field defects occur late in the disease process [6].

The first four cases of glaucoma following ionizing radiation (IR) therapy of cancer (referred hereinafter to as radiotherapy) with very high dose, e.g., of 10,160 r (about 93 Gy) [7], were reported in 1924–1958 [7–10]. Since then, there has been a growing body of evidence documenting that glaucoma arises after radiotherapy. However, associations between glaucoma and IR exposures, a dose response relationship, and the underlying mechanisms are still incompletely understood. Here we review the current knowledge on manifestations and mechanisms of radiogenic glaucoma.

2. Manifestations of radiogenic glaucoma

This section overviews the current knowledge on manifestations of glaucoma in four different types of population. The first is radiotherapy patients who received tens of Gy generally fractionated to some degree (typically 2 Gy/fraction and 5 fractions/week). The second is an epidemiological cohort of Japanese atomic bomb (A-bomb) survivors who received a few Gy or less acutely (in a minute). The third is an epidemiological cohort of the United States radiologic technologists (USRT) who mostly received ≤100 mGy as highly fractionated or protracted exposures, but with some doses in excess of 1 Gy. The last is an epidemiological cohort of the Russian Mayak Production Association nuclear workers who received chronic occupational exposures (70% receiving <0.5 Sv, 17% receiving >1 Sv). We go on to discuss the possible radiation doses required to induce glaucoma.

A total of 90 papers on glaucoma in irradiated humans with information on types of tumors, dose (albeit mostly without information on dose to the optic nerve, optic disc or ciliary body), a known period of follow-up, and secondary glaucoma were selected from all 855 papers listed in PubMed (https://www.ncbi.nlm.nih.gov/pubmed) searched on 10 December 2018 with the terms “Glaucoma” and “Radiotherapy” (348 papers) and with the terms “Glaucoma” and “Radiation” (738 papers), limited to human data with abstracts; there were overlaps of 231 papers between these two searches. Of these, 88 papers were related to studies of radiotherapy patients (87 papers listed in Supplementary Table A.1, except one paper ([11]), as dealt with in section 2.1, and 2 papers [12,13] were in A-bomb survivors, as dealt with in section 2.2.

2.1. Radiotherapy patients

The most common intraocular tumors are retinoblastoma in children and uveal melanoma, both of which are often treated by external beam radiotherapy [14,15] or brachytherapy, most commonly with ^{125}I plaque [16], but ^{60}Co, ^{106}Ru and ^{192}Ir have also been used [17]. However, the eye can receive substantial radiation exposure from radiotherapy for treatment of other cancers of the head and neck [18]. Such radiotherapy of intraocular tumors is done to avoid enucleation, which is a particular complication for bilateral retinoblastoma. Cataracts and NVG are common complications following radiotherapy, and the latter occurs especially following treatment of large to extra-large intraocular tumors (e.g., uveal melanoma, iris melanoma, choroidal melanoma, orbital and retinal tumors) [19–23], in which the irradiated volume of the ciliary body appears to play a role [23–25].

A complication in interpretation of the effects of radiotherapy and subsequent NVG is the effects of tumor growth into the ocular tissue. Larger tumors, which are more likely to ingrow, are treated with higher cumulative radiation to collateral structures that likely results in greater iris microvascular injury [26], so that radiation dose is largely confounded with tumor size.

Mean radiation doses to the eye from ^{125}I brachytherapy used for treating uveal melanoma are typically about 75–85 Gy, delivered in a single fraction to the tumor apex, with dose rates of 0.4–1.2 Gy/h [27,28]. Use of proton beam therapy to treat uveal melanoma may deliver slightly less dose, 50–70 Gy, generally in 5 fractions [14], likewise other sorts of external beam therapy [15].

The prevalence of glaucoma after ^{125}I radiation treatment for uveal melanoma is very high – about 50% of patients so treated will develop glaucoma within 3 years of treatment [29]. This figure may be slightly less, ~25%, in patients treated with a proton beam [14] which is possibly a result of the slightly lower dose and its fractionated delivery. The prevalence of glaucoma is still lower, ~9%, after linear accelerator (LINAC) treatment [15], but the shorter length of follow-up (median 20 months) may be a factor here. Following carbon ion radiotherapy (57.6 or 64.0 Gy adjusted for relative biological effectiveness in 16 fractions) with the median follow-up period of 53.7 months, 9% developed glaucoma (c.f., cataract in 9% and retinopathy in 3%) [30]. The effect on NVG of even relatively modest reductions in dose are dramatic, so that if gamma knife radiosurgery is used with marginal dose reduced from 52.1 Gy to 41.5 Gy, then the prevalence of NVG is reduced to 9% (3/33) compared with 48% (15/31) in the high dose group [31]. NVG was observed in 11% of the patients with a mean onset time of 15.6 months (with a range between 11.8 and 37.1 months) following gamma knife stereotactic radiosurgery of uveal melanoma with a mean dose of 33 Gy (with a range between 27 and 35 Gy), and the volume of posterior segment receiving >20 Gy; tumor thickness and Bruch’s membrane rupture were significant prospective risk factors for such NVG [32].

Collectively, glaucoma (NVG in particular) appears to conform to what would be expected of tissue reactions (formerly termed non-stochastic or deterministic effects) with a dose threshold below which no effect is assumed to occur, as defined by the International

Commission on Radiological Protection (ICRP) [33]. Glaucoma typically develops relatively quickly, within 3 years after high dose radiotherapy [15,18].

2.2. A-bomb survivors

POAG, NTG and PACG are more frequent in Asians than in other populations (e.g., white and African) without a significant difference in IOP and with anatomical predisposition to PACG [34].

In the current Japanese adult population, glaucoma is the primary leading cause of irreversible blindness, and accounts for 21.0% of all causes of visual impairment [35]. Prevalence of glaucoma in subjects over 40 years of age is 5%, among which POAG, PACG and secondary glaucoma account for 3.9%, 0.6% and 0.5%, respectively [36,37]. 92% of such POAG are NTG, and therefore NTG accounts for >70% of all glaucoma [36].

The first substantial epidemiological study of A-bomb glaucoma was reported in 2004 [12]. In 1958–1998 (i.e., 13–53 years after exposure), glaucoma exhibited a significant negative linear dose-response relationship [relative risk at 1 Sv (RR_{1Sv}) = 0.82, 95% confidence interval (CI): 0.80, 0.97, $p = 0.025$], with no indication of a curvilinear decrease in risk at high dose. Adjustment for distal/proximal exposure status (as a surrogate for urban/rural status) resulted in a reduction in the statistical significance in the dose response ($p = 0.14$), although the RR_{1Sv} was essentially unchanged. In this study, however, glaucoma cases were ascertained based on medical history via self-report [12]. Without detailed ophthalmological examinations, glaucoma prevalence rates may be underestimated due to false negatives [38,39].

A second analysis of A-bomb glaucoma was reported in 2013, where detailed ophthalmological examinations were conducted [13]. In 2006–2008 (i.e., 61–63 years after exposure), among various types of glaucoma, only NTG was significant with the odds ratio at 1 Gy (OR_{1Gy}) of 1.31 (95% CI: 1.11, 1.53, $p = 0.001$). PACG exhibited a suggestive decrease with dose ($OR_{1Gy} = 0.54$, 95% CI: 0.29, 1.02, $p = 0.06$). However, this study had only 59% participation, and uncertainties associated with such nonparticipation therefore suggest caution in the interpretation of these results.

2.3. USRT

In the current US adult population, glaucoma is the major cause of blindness and low vision [40]. The USRT cohort is one of very few groups occupationally exposed at low doses and low dose rates and prospectively followed for glaucoma. Glaucoma and various risk factors were assessed via a series of four questionnaires administered at approximately 10 yearly intervals [41]. There were 110,373 persons responding to the relevant questionnaires, with 921,076 person years of follow-up, among whom there were 1631 newly self-reported doctor-diagnosed cases of glaucoma in aggregate; there was no subtype information elicited on any of the questionnaires. The cumulative occupational absorbed lens doses were generally very low (mean 58 mGy, mostly <50 mGy), although with cumulative doses up to 1.51 Gy in some subjects, and all incurred at low dose rate (<5 mGy/h). There were no indications of a trend in glaucoma risk with occupational radiation exposure, with an excess relative risk (ERR)/Gy of −0.57 (95% CI: −1.46, 0.60, $p = 0.304$). There was a similar

largely null risk of macular degeneration (ERR/Gy = 0.32, 95% CI: −0.32, 1.27, $p = 0.381$) [41].

A strength of the study is that adjustment was made for several factors that have been associated with glaucoma, including diabetes mellitus (DM), smoking and obesity. There was little effect of adjustment for these variables, or those for sex and birth year, on radiation risk. A weakness of the study is that all clinical disease outcome were ascertained solely by questionnaire (relating to reported physician-diagnosed glaucoma) and not validated. However, the population of radiologic technologists is medically literate, so that self-report of doctor-diagnosed glaucoma, the clinical symptoms of which are generally fairly clearcut, should be reasonably accurate. This has been demonstrated for other endpoints by the high concordance (generally above 80%) between self-diagnosed and medically confirmed malignancies, including thyroid cancer and other cancers of low mortality [42]. The technologists would also probably have had regular ocular examinations. A substantial proportion of the estimated cumulative occupational dose is derived from questionnaires [43]; however, the dosimetry has been subject to extensive validation, in particular via chromosome aberrations detected using fluorescence *in situ* hybridization (FISH) [44]. Another weakness is that, as with many occupational studies, cohort members had to survive to answer the first questionnaire. However, this degree of selection will not necessarily bias the analysis, since everyone had to survive to answer a questionnaire, and all risk was assessed conditional on that. Nonetheless, it is possible that this (presumably slightly healthier) subset of the original USRT cohort will have a somewhat variant response to these ocular variables than the parent cohort would have had, let alone a general unselected population.

2.4. Mayak workers

In the current Russian population, glaucoma is the primary leading cause of visual impairment [45]. The Mayak worker cohort received chronic occupational exposures. The principal advantages of the study are the large range of cumulative doses, long-term follow-up, available results of annual eye examinations over the entire follow-up period and detailed information on non-radiation confounders. The clinical determination of ocular endpoints is a considerable strength, compared with for example the USRT, which relied on questionnaire self-reported physician-assessed diagnoses. The Mayak cohort had 634 cases of glaucoma, among which incidence risk was not computed for PACG due to the small number of cases (15 cases), nor for secondary glaucoma (158 cases) manifested as complications accompanying an ocular or somatic pathology. Incidence of primary glaucoma (476 cases) and POAG (461 cases) was significantly associated with various non-radiation factors (sex, attained age, and cataract diagnosed prior to glaucoma) [46]. Incidence of primary glaucoma and POAG was not significantly associated with cumulative dose from external γ-rays, regardless of adjustment for neutron dose with ERR/Sv of 0.02 (95% CI: −0.10, 0.18) and 0.01 (95% CI: −0.11, 0.17) when adjusted and 0.01 (95% CI: −0.11, 0.16) and −0.003 (95% CI: −0.12, 0.15) when unadjusted, respectively [46]. Variations in dose lagging, inclusion of additional adjustments for non-radiation factors (hypertension, BMI, cataract and cataract removal surgery, DM, smoking index) did not significantly modify the observed findings: the risk estimate slightly varied but remained

not statistically significant. Sex, attained age and age at first employment at the enterprise did not significantly modify radiation risk for primary glaucoma (p >0.22, >0.37 and 0.48, respectively) and for POAG (p = 0.21, >0.5 and >0.5, respectively). The limitation of this study is the lack of information on IOP measurements among comprehensive data provided by the medical and dosimetry database 'Clinics' [47].

2.5. Possible radiation doses required to induce glaucoma

As mentioned above, the USRT study has shown no significant association between radiation exposure and self-reported doctor-diagnosed glaucoma in aggregate that does not distinguish any type of glaucoma [41]. The Mayak study has shown no significant association between radiation exposure and primary glaucoma and POAG that does not distinguish NTG and HTG [46]. As such, it remains unclear whether the USRT members and the Mayak workers exhibit a significantly increased risk for NTG as reported in A-bomb survivors [13]. Further studies on POAG in Mayak workers are ongoing to evaluate the risk separately for NTG and HTG based on the IOP data obtained from each member of the cohort.

Taken together, it is interesting to add that unlike the case for glaucoma, a significantly increased risk of cataracts has been observed in all of the afore-described three cohorts, i.e., in A-bomb survivors [48], the USRT [49], and Mayak workers [50]. For cataract removal surgery, a significantly increased risk has been observed in A-bomb survivors [51–53], but not in other exposed cohorts including the USRT [49] and Mayak workers [54]. This suggests that the dose and dose rate that can induce cataracts are much lower than those for glaucoma, although the potential differences in latency and progression of cataracts between acute exposure (A-bomb), protracted exposures (USRT), and chronic exposures (Mayak workers) remains incompletely understood.

Despite mounting evidence for glaucoma in radiotherapy patients (Table A.1), its dose response relationship remains unclear. Nevertheless, it is tempting to assess the possible minimal glaucomagenic dose; however, the limitations of the studies reviewed in Appendix A, which in most instances are case series, should be borne in mind. Following stereotactic radiotherapy, there was no difference in NVG occurrence at 60 and 70 Gy [15]. Following gamma knife radiosurgery, NVG was observed in 48% at 52.1 Gy but in 9% at 41.5 Gy [31]. Most NVG following gamma knife radiosurgery occurred at ≥50 Gy and a reduction in the prescription dose to ≤40 Gy decreased the rate of NVG [25]. Likewise, following gamma knife radiosurgery, NVG was observed in 20.8% at 50–70 Gy and in 19.7% at 45 Gy but in 8.1% at 35 Gy [55]. At similar levels of dose but with different irradiation modalities, the actuarial rate of NVG at 50 months post radiotherapy for juxtapapillary choroidal melanoma was very different: 8% after ^{125}I brachytherapy (85 Gy to tumor apex delivered at 0.5 Gy/h, 61.9 Gy to the optic disc center, 13.9 Gy to the ciliary body) vs 47% after stereotactic radiotherapy (70 Gy of 6 MV X-rays to tumor apex delivered in 5 fractions over 10 days, 69.7 Gy to the optic disc center, 10.8 Gy to the ciliary body) [56]. NVG was positively associated with the volume of posterior segment receiving >20 Gy of photons [32] and with that of lens or ciliary body receiving ≥28 Gy equivalent (GyE) of protons [23]. Three papers have reported occurrence of NVG at the level of 20 Gy [57–59], but 8 papers reported

lack of NVG after doses of 40–120 Gy [19,60–66] (see Table A.1 for more details). In the Childhood Cancer Survivor Study (14,362 survivors vs 3,901 siblings, with follow-up of 5–25 years after cancer diagnosis), risk of glaucoma was not significantly associated (albeit with indications of increased risk) with IR doses of ≤12 Gy and was not estimable at doses >12 Gy [11]. In other exposed populations, there is little evidence for excess glaucoma risk at the moderate and low doses in the A-bomb survivors (all under 5 Gy and with mean acute eye dose of 468 mGy) [13], in the USRT (mostly under 50 mGy and with a mean cumulative lens dose of 58 mGy) [41], or in Mayak workers (70% under 500 mSv and with a mean effective dose of 520 mSv) [46]. Therefore, it appears that there may be a threshold of at least 5 Gy for acute (or fractionated) radiation exposure to cause glaucoma, but the threshold dose may be as high as 30 Gy. If such a dose threshold exists and glaucoma results from radiation damage to many cells, then glaucoma is a tissue reaction rather than a stochastic effect, and so characterized by a dose response relationship with increases in risk only above a certain threshold.

To the best of our knowledge, no animal studies have thus far reported the shape of the dose response curve for glaucoma, in particular to assess the existence or otherwise of a dose threshold. However, this is outside the scope of this review, which as noted above is restricted to human glaucoma studies.

3. Mechanisms of radiogenic glaucoma

3.1. Postirradiation modification of radiogenic glaucoma

Intraocular tumors are often treated with radiotherapy to avoid enucleation, but the severest complication following such radiotherapy is NVG that often necessitates secondary enucleation. To avoid such secondary enucleation, strategies are needed. On one hand, a dose-volume histogram analysis revealed that statistically significant, independent factors for NVG following carbon ion radiotherapy of choroidal tumors were the volume irradiated at ≥50 GyE to the iris-ciliary body and the optic disk [67]. For proton therapy of iris melanoma, sector-based irradiation significantly reduced NVG and glaucoma-associated surgical interventions compared to the whole anterior segment irradiation [68]. On the other hand, histopathological and dosimetric findings showed that NVG after stereotactic radiotherapy is due to IR damage to the posterior chamber (e.g., manifested as retinal damage, retinal vascular changes of fibrinoid necrosis, and hyalinization) rather than primary IR damage to the anterior segment [16]. These warrant the continued effort to identify contributing factors and improve the physical dose conformation.

The precise mechanisms of radiation action at a tissue level, even after the high doses and dose rates that are typical of radiotherapy, are unclear. One possibility is that radiation damage to the iris–ciliary body complex can lead to NVG. An alternative mechanism is that a high dose to the central retinal vessels in the anterior part of the eye can lead to ischemic changes that ultimately result in neovascularization; the newly formed fibrovascular tissue prevents aqueous humor outflow and leads to elevated IOP and NVG. The data of Fernandes et al. [16] lend greater support to the second mechanism than to the first.

From a biological viewpoint, the toxic tumor syndrome has recently been described, and the residual tumor scar has been hypothesized to produce proinflammatory cytokines and vascular endothelial growth factor (VEGF) leading to intraocular inflammation and NVG [14]. Anti-VEGF therapy has hence been proposed for the management of NVG as radiotherapy complications [69]. In patients with NVG after photon or proton radiotherapy of intraocular tumors, repeated intravitreal injections of bevacizumab (a humanized anti-VEGF monoclonal antibody) have been shown to cause rapid regression of neovascularization [70,71]. Such intravitreal bevacizumab was effective in early phase of NVG following proton therapy, but did not reduce the overall enucleation rate despite the improved IOP level [72]. Complications following such anti-VEGF therapy of NVG include central retinal artery occlusion, especially when it is associated with ocular ischemic syndrome [73]. Other candidate modifiers (radioprotectors, mitigators, etc) may include melatonin, epigallocatechin-3-gallate (EGCG), and pituitary adenylate cyclase-activating polypeptide (PACAP) derivatives [74–76]. Hyperbaric oxygen therapy has also been discussed [77]. These show that radiogenic NVG is biologically modifiable after IR exposure, which is one of the features of some (but not all) tissue reactions [33,78].

3.2. Protein aggregation and misfolding in radiogenic glaucoma

Glaucoma and cataract share common features, both of which are major age-related ocular diseases, major complications following radiotherapy of intraocular tumors, and involve protein aggregation and misfolding. Amyloid β (Aβ) related to Alzheimer's disease (AD) is known to accumulate in the retina of glaucoma patients and in the lens epithelium of cataract patients [79,80]. Aβ accumulation has also been observed in the retina of monkeys with glaucoma [81].

Lens crystallin proteins occupy ~90% of the total water-soluble proteins, and undergo various posttranslational modifications (e.g., oxidation, deamidation, truncation and isomerization) that occur during the aging process and affect crystallin solubility and lens transparency [82]. IR produces posttranslational modifications of crystallins [83,84] that may, at least in part, underlie IR cataractogenesis.

Myocilin (MYOC), also called the trabecular meshwork-inducible glucocorticoid response (TGIR), is highly expressed in the trabecular meshwork, and is encoded by MYOC/TIGR. Gain-of-toxic-function mutations in the olfactomedin domain of myocilin cause amyloid containing myocilin aggregates, leading to POAG [85]. Ocular hypertension in glaucoma is also thought to result from overexpression of wild-type myocilin [86,87]. Myocilin is thus one of the drug targets for glaucoma [88]: for example, inhibitors of endoplasmic reticulum (ER) chaperone Grp94 (glucose regulated protein 94) promote the clearance of myocilin aggregates [89]. Myocilin responds to oxidative stress [86] and possesses anti-inflammatory activity [90]; however, its IR response is unknown. Whole exome sequencing has suggested that among POAG subtypes, whilst HTG involves aberrant responses to protein misfolding, NTG involves impaired plasma membrane homeostasis increasing susceptibility to apoptosis [91]. Further investigations are warranted to assess the impact of IR on these changes.

3.3. Different mechanisms for glaucoma at low and high doses

In 2011, ICRP listed, for the first time, circulatory disease as a health hazard from IR exposure to organs and tissues, and provisionally assigned the nominal, approximate threshold of 0.5 Gy to the heart and brain for cardio- and cerebrovascular disease (CVD and CeVD), respectively, independent of the rate of dose delivery [33]. For CVD, it has been considered that whereas microvascular changes and accelerated atherosclerosis underlie cardiovascular damage after medium to high dose to part of the heart or the whole organ, other mechanisms are responsible at much lower dose (e.g., via persistent inflammation, impaired T cell-mediated immunity, genomic instability, and monocyte killing) [33]. Although it is not clear what the mechanisms are responsible for glaucoma after different levels of IR dose, the available data suggest that there may not be much if any risk at low doses, and that risk possibly only for NTG, so that glaucoma, unlike circulatory disease, has more of the classic features of a tissue reaction rather than a stochastic effect, and so characterized by a nonlinear threshold-type dose response relationship [33].

A mechanism behind IR-associated NVG production in radiotherapy patients above about 10 Gy may be plaque formation, leading to obstruction of microcirculation, reduced ocular blood flow, and inducing neovascularization in the iris or angle leading to high IOP [13]. It remains unclear whether occupational exposure to much lower dose causes excess ocular hypertension [92,93]. In A-bomb survivors at 55 years after exposure, retinal arteriolosclerosis, retinal degeneration and diabetic retinopathy were significantly associated with IR exposure, along with a non-significant but positive change in IOP (OR_{1Gy} of 0.088, 95% CI: −0.127, 0.303) [48]. Retinal circulation disturbance via such radiogenic retinal arteriolosclerosis was therefore proposed as a possible mechanism underlying A-bomb NTG that increased with increasing dose [13]. Associated with this possibility, the Radiation Effects Research Foundation (RERF) is now investigating whether retinal arteriolosclerosis can be associated with glaucoma and with macular degeneration [94].

Garkava et al. recently reported that a group of Chernobyl clean-up workers have a significantly decreased blood circulation in the ciliary body (evaluated as the rheographic coefficient) and show an increased risk for a change in the anterior chamber angle, compared with a control group [95]. The residents of the guaranteed voluntary resettlement zone (in which internal exposure exceeds 0.3 mSv/year) were also found to show an increased risk of change in the anterior chamber angle, compared with a control group [95]. In these three groups (i.e., workers, residents and control), age at survey was 45–50 years, and workers were subjected to surveys for workers at 5–12 years after exposure. Garkava et al. considered these changes as potentially preglaucomatous [95], although there has been no epidemiologic evidence available heretofore for glaucoma following the Chernobyl accident. It is not clear how the subjects in this small study (n = 41/18/41 for the three groups) were recruited to the three groups, and details of ophthalmologic procedures are not given. There is also no dosimetry for the clean-up worker group. An oddity is that the changes in the clean-up workers were restricted to the right eye – the results for the left eyes did not differ from those in the controls. It is possible that some factor other than radiation may account for the observed changes, although it is not obvious what this might be, as most of the well

known risk factors for glaucoma (including IR) would be expected to operate equally on both eyes.

Apolipoprotein E (APOE) polymorphisms are associated with increased risk of POAG in various populations [96,97]. APOE is also associated with circulatory disease (especially atherosclerosis) and AD. In ApoE-deficient mice, radiogenic atherogenesis is accelerated [98], and several molecular targets induced by IR in hippocampus overlap with those of AD's pathology [99]. It will be interesting to test whether irradiated ApoE-deficient mice exhibit glaucomatous changes.

Cerebral microinfarcts have been proposed as an intracerebral risk factor for glaucomatous optic nerve atrophy in POAG [100]. Cerebral small-vessel ischemia has been proposed as a vascular cause of NTG [101], and NTG has been proposed as a risk factor for subsequent stroke [102]. In this regard, IR may increase the risk of stroke including cerebral infarction (e.g., after cranial or supradiaphragmatic radiotherapy for childhood cancer [103]), although data are limited. These may link IR, cerebrovascular changes, and glaucoma.

With increasing age, the axonal transport of mitochondria and lengths of transported mitochondria shorten, and RGCs become more vulnerable to stress, leading to glaucoma [104]. IR causes long-term mitochondrial dysfunction [105,106]. These may link IR, mitochondria, and glaucoma.

3.4. Ionizing radiation for treating glaucoma and for preventing postoperative scarring

The above sections have dealt with IR as a potential cause of glaucoma. We now discuss the use of IR to treat glaucoma and to prevent postoperative scar formation following glaucoma surgery. In 1954, radiotherapy of glaucoma with about 7.3 Gy given in 14–21 days was reported to alleviate the pain in 6 out of 15 patients [107]. More recently, irradiation with 7.5–10 Gy of β-rays during trabeculectomy reduced the risk of surgical failure [108,109]. Gamma knife surgery (15 or 20 Gy to the 50% isodose) for patients with advanced glaucoma also improved pains, lowered IOP and reduced neovascularization [110]. Potential mechanisms proposed for such therapeutic effects include slowing wound healing and lowering aqueous humor secretion [111,112].

Biological studies have shown that a single IR exposure (e.g., with 7.5 Gy) prevents monocyte entry into the ONH and subsequent glaucomatous damage in an inherited mouse model of glaucoma (DBA/2J strain) [113,114]. IR reduces microglial activation and improves axonal structural integrity (but without reducing IOP), leading to reduced neurodegeneration in the optic nerve and retina [115]. IR upregulates GlyCAM1 (glycosylation-dependent cell adhesion molecule 1, a proteoglycan ligand for L-selectin), and GlyCAM1 deficiency in DBA/2J mice increased radiogenic glaucomatous damage but not spontaneous glaucomatous damage [116]. This suggests a role of GlyCAM1 as a negative regulator for radiogenic glaucoma. All of these observations were obtained in DBA/2J mice, but IR exposure of adult rats (Brown Norway strain) to 10 Gy delivered in two fractions with 3 h intervals did not protect the optic nerve from injury due to elevated IOP [117].

Proliferation of Tenon's capsule fibroblasts (TCFs) and deposition of extracellular matrix (ECM) have been implicated in scarring that occurs following glaucoma filtration surgery [118]. Mitomycin C and 5-fluorouracil have been used as antiproliferative agents to prevent such postoperative scar formation, but cause complications such as hypotony and endophthalmitis [119]. Alternatively, the use of β-rays has been proposed to inhibit TCF proliferation in a p53 dependent manner [120,121].

3.5. Genetic susceptibility to glaucoma

Supplementary Table A.2 lists a series of susceptibility loci identified or suggested for glaucoma from which mechanisms suggested include cell adhesion, cytoskeleton, membrane signaling, cell cycle, mitochondria, oxidative metabolism, autophagy, DNA damage signaling, calcium signaling, protein degradation pathways, collagen metabolism, glycerol biosynthesis, glycoprotein biosynthesis, and acetylcholine signaling [6,122]. Associations between IR glaucoma and these loci have not been tested so far; nevertheless, it is tempting to speculate on the potential overlap with the known IR responses. These include IR-induced upregulation of ABCA1 and CHAT, IR-induced DNA methylation of FOXC1 modulating myocilin secretion, SIX1 involved in radiosensitivity, CDKN2B, CDKN2B-AS1/CDKN2BAS, CDC7, TBK1, SIX6 and RBMS3 related to cell cycle arrest and senescence, CACNA1A involved in IR-induced adaptive response, ABCA1 related to IR-induced dermatitis, TXNRD2 related to IR-induced subcutaneous fibrosis, CYP1B1 related to IR cancer risk in USRT, AFAP1, ABS10, TGFBR3, CDKN2B and LOXL1 for IR-inducible cytokine signaling (TGFβ, TNFα, IL1α), CAV1 and CAV2 for IR-inducible lipid raft signaling, TMCO1 and CACNA1A for IR-inducible calcium signaling, ATXN2 and TXNRD2 related to redox homeostasis and mitochondrial signaling, TBK1 and POMP related to NF-κB signaling, oxidative stress-induced upregulation of LOXL1, TBK1 regulating IR-induced EMT, FERMT2 involved in photosensitivity, UV-induced upregulation of CYP1B1, TXNRD2 and LOXL1, MAP3K1 linked with ocular development and involved in IR-induced apoptotic signaling, and HMGA2 delaying the clearance of IR-induced foci of phosphorylated histone H2AX (see Table A.2, and references therein). These warrant molecular studies to investigate the mechanisms of IR glaucoma.

Glaucoma and cataract share some common features. Both are major age-related ocular diseases, major normal tissue complications following radiotherapy and involve protein aggregation and misfolding, as discussed in section 3.2. Although also involving different mechanisms (e.g., NVG involving neovascularization, and cataracts, particularly posterior subcapsular cataracts, involving abnormal differentiation and proliferation of lens epithelial cells), NVG and cataracts occur with similar frequency following radiotherapy. Neovascularization in the eye occurs when the homeostatic balance is perturbed through increased pro-angiogenic and/or decreased anti-angiogenic factors/events [123]. NVG is more prevalent following the treatment of larger tumors [19–26] as described in section 2.1, suggesting that larger tumor tissue may produce pro-angiogenic factors that increase not only preexisting neovascularization prior to radiotherapy but may also produce increases in neovascularization in irradiated tissue, sustaining the onset of NVG following radiotherapy. VEGF is a representative pro-angiogenic factor involved in NVG production, and potential pro-angiogenic initiating factors include TGF-β1, TGF-β2, basic fibroblast growth factor,

IL6, and endothelin-1 [123], which have been implicated in IR response of lens and other tissues [124,125]. TGF-β1 is also linked to several susceptibility loci listed in Table A.2 (e.g., AFAP1, CDC7-TGFBR3, CDKN2B and LOXL1).

4. Conclusions

ICRP has not listed glaucoma as a health hazard from IR exposure to organs and tissues, even after high dose exposure [33]. We have adduced some evidence that glaucoma may be associated with high dose exposure, for example after certain sorts of radiotherapy of the head and neck. There is much less evidence of glaucoma after lower dose exposure. Continued studies on glaucoma are critical both from the viewpoints of radiotherapy and radiation protection. This also follows the recent recommendation by the US National Council on Radiation Protection and Measurements that the overall radiation effects to the eye be comprehensively evaluated, because ocular impacts except for cataracts remain almost entirely uncharacterized especially at low dose and low dose rate [126,127].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

ABC	ATP binding cassette
ABCA1	ATP binding cassette subfamily A member 1
A-bomb	atomic bomb
AD	Alzheimer’s disease
AFAP1	actin filament associated protein 1
AGPAT1	1-acylglycerol-3-phosphate *O*-acyltransferase 1
ANKRD55	ankyrin repeat domain 55
APOE	apolipoprotein E
ARHGEF12	Rho guanine nucleotide exchange factor 12
ASB10	ankyrin repeat and SOCS box containing 10
ATOH7/MATH5	atonal bHLH transcription factor 7
ATP	adenosine triphosphate
ATXN2	ataxin 2

Aβ	amyloid β
bHLH	basic helix loop helix
CACNA1A	a P/Q type voltage dependent calcium channel subunit α1A
CACNA2D1	an L type calcium voltage-gated channel auxiliary subunit α2δ 1
CAV1/2	caveolin 1/2
CDC7	cell division cycle 7
CDKN2A/B	cyclin dependent kinase inhibitor 2A/B
CDKN2B-AS1/CDKN2BAS	CDKN2B antisense RNA 1
CeVD	cerebrovascular disease
CHAT	choline acetyltransferase
CI	confidence interval
CIP1B1	cytochrome P450 family 1 subfamily B member 1
COL11A1	collagen type XI α1 chain
CTGF/CCN2	connective tissue growth factor
CVD	cardiovascular disease
DLG2	discs large MAGUK scaffold protein 2
ECM	extracellular matrix
EFEMP1	EGF containing fibulin-like extracellular matrix protein 1
EGCG	epigallocatechin-3-gallate
EGF	epidermal growth factor
EMT	epithelial-mesenchymal transition
EPDR1	ependymin related 1
ER	endoplasmic reticulum
ERR	excess relative risk
FAD104	factor for adipocyte differentiation 104
FERMT2	fermitin family member 2
FISH	fluorescence *in situ* hybridization
FNDC3B	fibronectin type III domain containing 3B

FOXC1	forkhead box C1
GAS7	growth arrest specific 7
GDP	guanosine diphosphate
GLIS3	GLI-similar 3
Glycam1	glycosylation-dependent cell adhesion molecule 1
GMDS	GDP-mannose 4,6-dehydratase
Grp94	glucose regulated protein 94
GyE	Gy equivalent
HMGA2	high mobility group AT-hook 2
HTG	high-tension glaucoma
ICRP	International Commission on Radiological Protection
IκB	inhibitor of NF-κB
IL1α/6	interleukin 1α/6
INK4A/B	inhibitor of kinase 4A/B
IOP	intraocular pressure
IR	ionizing radiation
LHPP	phospholysine phosphohistidine inorganic pyrophosphate phosphatase
LIM	lin-11, Isl-1 and mec-3
LINAC	linear accelerator
LMX1B	LIM homeobox transcription factor 1β
LOXL1	lysyl oxidase like 1
MAGUK	membrane-associated guanylate kinase
MAP3K1	mitogen-activated protein kinase kinase kinase 1
MEIS2	Meis homeobox 2
mTOR	mammalian target of rapamycin
MYOC	myocilin
NF-κB	nuclear factor κB
NTG	normal-tension glaucoma

NVG	neovascular glaucoma
ONH	optic nerve head
OPTN	optineurin
OR_{1Gy}	odds ratio at 1 Gy
PACAP	pituitary adenylate cyclase-activating polypeptide
PACG	primary angle-closure glaucoma
PCMTD1	protein-L-isoaspartate (D-aspartate) *O*-methyltransferase domain containing 1
PLEKHA7	pleckstrin homology domain containing A7
PMM2	phosphomannomutase 2
POAG	primary open-angle glaucoma
POMP	proteasome maturation protein
RBMS3	RNA binding motif single stranded interacting protein 3
RERF	Radiation Effects Research Foundation
RGC	retinal ganglion cell
ROS	reactive oxygen species
RR_{1Sv}	relative risk at 1 Sv
SALL1	spalt like transcription factor 1
SEMA6A	semaphorin 6A
SIX1/6	Sine oculis homeobox 1/6
SOCS	suppressor of cytokine signaling
ST18	suppression of tumorigenicity 18
TANK	TRAF-associated NF-κB activator
TBK1	TANK-binding kinase 1
TCF	Tenon's capsule fibroblast
TGFBR3/TβRIII	transforming growth factor β receptor 3, TGF-β1/2, transforming growth factor β1/2
TIGR	trabecular meshwork-inducible glucocorticoid response
TMCO1	transmembrane and coiled-coil domains 1
TMEM136	transmembrane protein 136

TNFα	tumor necrosis factor α
TRAF	tumor necrosis factor receptor associated factor
TXNRD2/TrxR2	thioredoxin reductase 2
USRT	United States radiologic technologist
UV	ultraviolet light
VEGF	vascular endothelial growth factor
WD	Trp-Asp
WDR36	WD repeat domain 36
XFG	exfoliation glaucoma

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