Radiation-induced lens opacities: Epidemiological, clinical and experimental evidence, methodological issues, research gaps and strategy

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ABSTRACT

In 2011, the International Commission on Radiological Protection (ICRP) recommended reducing the occupational equivalent dose limit for the lens of the eye from 150 mSv/year to 20 mSv/year, averaged over five years, with no single year exceeding 50 mSv. With this recommendation, several important assumptions were made, such as lack of dose rate effect, classification of cataracts as a tissue reaction with a dose threshold at 0.5 Gy, and progression of minor opacities into vision-impairing cataracts.

However, although new dose thresholds and occupational dose limits have been set for radiation-induced cataract, ICRP clearly states that the recommendations are chiefly based on epidemiological evidence because there are a very small number of studies that provide explicit biological and mechanistic evidence at doses under 2 Gy.

Since the release of the 2011 ICRP statement, the Multidisciplinary European Low Dose Initiative (MELODI) supported in April 2019 a scientific workshop that aimed to review epidemiological, clinical and biological evidence for radiation-induced cataracts.

The purpose of this article is to present and discuss recent related epidemiological and clinical studies, ophthalmic examination techniques, biological and mechanistic knowledge, and to identify research gaps, towards the implementation of a research strategy for future studies on radiation-induced lens opacities.

The authors recommend particularly to study the effect of ionizing radiation on the lens in the context of the wider, systemic effects, including in the retina, brain and other organs, and as such cataract is recommended to be studied as part of larger scale programs focused on multiple radiation health effects.

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1. Introduction

Cataracts are the most frequent cause of blindness worldwide. Apart from ageing, genetics (congenital cataracts), ultraviolet radiation exposure, diabetes, high body mass index, smoking, alcohol intake, persistent use of corticosteroids and ocular trauma, ionizing radiation exposure to the lens of the eye is a known risk factor for the development of eye lens opacities in human.

The International Commission on Radiological Protection (ICRP) recommended dose limits for the lens of the eye in 1954, and gradually revised them in 1977 in its Publication 26 (ICRP, 1977), in 1980 in Publication 41 (ICRP, 1984), in 1990 in Publication 60 (ICRP, 1991), and in 2007 in Publication 103 (ICRP, 2007). Between 1980 and 2011, the ICRP lifetime limitation of equivalent dose[2] to the lens of the eye varied between 15 Sv[3] in 1977; 5 Sv for a single acute exposure or 8 Sv for fractionated or protracted exposures in 1984; and 2 Sv for a single acute exposure or 5 Sv for fractionated or protracted exposures since 2007. Annual occupational dose limits to the eye were set at 300 mSv in 1977 and were decreased at 150 mSv since 1984.

Because recent epidemiological and experimental studies on radiation-induced cataracts suggested that the dose threshold for cataracts could be lower than previously considered or that there may be no dose threshold at all, the ICRP recommended in a statement on tissue reactions approved in April 2011, a threshold in absorbed dose to the lens of the eye of 0.5 Gy. For occupational exposure in planned exposure situations, the ICRP now recommends an equivalent dose limit for the lens of the eye of 20 mSv in a year, averaged over defined periods of 5 years, with no single year exceeding 50 mSv (ICRP, 2012). However, although new dose thresholds and occupational dose limits have been set for radiation-induced cataract, ICRP clearly states that the recommendations are chiefly based on epidemiological evidence because there are a very small number of studies that provide explicit biological and mechanistic evidence at doses under 2 Gy.

Shore (2016) reviewed new epidemiological data reported since 2012, when ICRP Publication 118 was issued (ICRP, 2012). The author concluded that most available epidemiological data suggest there is a dose threshold somewhere between several hundred mGy and one Gy for lens opacities and highlighted that new studies of medical and occupational exposures that have evaluated groups with low doses tend to confirm there is little or no excess risk at doses under 100 mGy, while new studies of interventional cardiologist personnel who often have substantial doses to the lens of the eye (estimated mean dose varying from 0.42 to 6.0 Gy) have shown elevated opacity risks (estimated relative risk at 1 Gy ranging from 1.4 to 7.7).

Thome et al. (2018) also summarized in a review paper all of the human epidemiological data on ionizing radiation exposure to the lens of the eye published since 1956, including Japanese atomic bomb (A-bomb) survivors, Chernobyl "liquidators" (or clean-up workers), medical workers, and radiotherapy patients. The authors stated that the evidence of an increase in cataract formation at dose below 0.5 Gy was inconclusive, because very few publications have formally calculated a threshold dose, and only a limited number of studies directly relate to occupational exposure scenarios.

Concerning biological and mechanistic studies, Ainsbury et al. (2016) recently reviewed published information regarding mechanisms of ionizing radiation cataract initiation and development, publication in which the authors provide also future research perspectives. *In vitro* and *in vivo* studies reviewed in this publication have yielded information on a number of pathways induced by ionizing radiation in human lens epithelial cells. These include the role of DNA damage and repair/mis-repair processes, damage to the extracellular matrix, proteins or membrane lipids, change in gene and protein expression leading to altered protein functions and morphological changes in lens epithelial cells and protein fibres, the role of oxidation throughout and the role of non-targeted effects and intercellular communication of factors including glucose transport and Ca^{2+} signalling. The authors concluded that despite the recent advances in understanding the mechanisms involved in radiation-induced lens opacities, further study of the role of low dose of ionizing radiation in cataractogenesis is clearly needed. The authors also recommended that particular attention should be given to mechanisms of cataract induction by low dose of ionizing radiation, the potential of dose rate effect, and further development of accurate dosimetry techniques.

In the light of a scientific workshop held in April 2019 under the auspices of the Multidisciplinary European Low Dose Initiative (MELODI) association and the EC-funded CONCERT (European Joint Programme for the Integration of Radiation Protection Research), this article aims to summarize the state of the art in terms of epidemiological evidence, clinical studies, ophthalmological techniques, mechanistic information, and to identify research gaps towards the implementation of a research strategy for future studies on radiation-induced lens opacities. It should be noticed that this 2019 workshop followed a previous one held in December 2011 in the frame of the European Commission (EC)-funded DoReMi project. Lessons learnt from this 2011 workshop were taken into consideration for the preparation of this paper.

2. Emerging epidemiological evidence and its implications for radiation protection

In 2011, ICRP recommended reducing the occupational equivalent dose limit for the lens of the eye from 150 mSv/year to 20 mSv/year, averaged over five years, with no single year exceeding 50 mSv. With this recommendation, several important assumptions were made, such as lack of dose rate effect, classification of cataracts as a tissue reaction with a dose threshold at 0.5 Gy, and progression of minor opacities into vision-impairing cataracts (VICs) (ICRP, 2012). Shore reviewed the epidemiological studies reported from 2012 through early 2016 and evaluated the impact on the ICRP judgments (Shore, 2016). The following subsections provide a brief overview of the main epidemiological studies published since mid-2016, with particular focus on the studies following exposures at low doses (500 mGy and below) as well as studies addressing the influence of dose rate.

2.1. Evidence for radiation-induced cataracts

Over the last few years, several reports have become available from two large occupational cohorts (i.e. adulthood exposures only): firstly, the cohort of workers of the Russian Mayak Production Association (one of the biggest nuclear facilities in the Russian Federation, founded in 1948), who received chronic radiation exposure; and secondly, that of US medical radiologic technologists (USRT), who received protracted radiation exposure. The rough number of eligible participants for eye studies is 21,000 in the Mayak workers (Azizova et al., 2016, 2018) and 70,000 in the USRT (Little et al., 2018a, 2020a, 2020b): see Table 2 in Hamada et al., 2020, for more information on these cohorts. In addition, information has been published relating to cataract risk in those living in high natural background areas, who also received protracted radiation exposure (Wang et al., 2015).

Among the Mayak workers, the risk for cataracts increased linearly with chronic cumulative effective dose from external γ-rays at ≥0.25 Sv, with an excess relative risk per unit effective dose (ERR/Sv) of 0.28 (95% CI: 0.20, 0.37) for cataracts in aggregate, 0.91 (95% CI: 0.67, 1.20) for posterior subcapsular (PSC), 0.63 (95% CI: 0.49, 0.76) for cortical,

[2] Absorbed dose in Gray (Gy) is a physical dose quantity, energy deposited to unit mass. Effective dose in Sievert (Sv) is a dose quantity considering cancer and heritable effects arising in the major sites. Eye dose is not included in effective dose. Equivalent dose for the lens in Sv is an absorbed dose in the lens considering different effects of various radiation qualities.

[3] In this article, authors used Gy or Sv according to the original publications.

and 0.47 (95% CI: 0.35, 0.60) for nuclear cataracts (Azizova et al., 2016, 2018). This indicates that radiosensitivity was highest for PSC, and progressively lower for cortical and nuclear cataracts. The risk for each cataract type was significantly higher in females than in males (ERR/Sv being 3.8-fold higher in females for PSC, 2.5-fold for cortical, and 1.9-fold for nuclear cataracts). This study was the first large study to suggest a significant gender difference in radiation cataracts (PSC cataracts in particular), and a significantly increased radiation risk for nuclear cataracts, in contrast to null results from other large studies (Hamada and Fujimichi, 2014).

In the USRT cohort, the risk for self-reported cataracts in aggregate significantly increased linearly with protracted cumulative 5 year-lagged lens absorbed dose over the full dose range: the excess hazard ratio per unit lens absorbed dose (EHR/Gy) and the excess absolute (additive) risk per 10^4 person-year (PY) unit lens absorbed dose (EAR/10^4 PY Gy) were 0.69 (95% CI: 0.27, 1.16) and 94 (95% CI: 47, 143), respectively (Little et al., 2018a, 2020a). The risk estimates were statistically significantly elevated at doses <0.1 Gy with no dose-response curvature (i.e. a linear dose–response); but were no longer-significant below 0.05 Gy (Little et al., 2018a, 2020a). Radiation risk was much higher in those with diabetes (EAR/10^4 PY Gy of 1725, 95% CI: 1227, 2270) than those with no or unknown diabetes (EAR/10^4 PY Gy of 110, 95% CI: 64, 158) (Little et al., 2020a). This study was the first to suggest that radiation exposure at low dose (<0.1 Gy) and low dose rate (typically < 0.005 Gy/h) causes cataract. A significantly increased risk for cataracts was also observed among a USRT subcohort performing nuclear medicine procedures (63.3% of the entire USRT cohort) with HR of 1.08 (95% CI: 1.03, 1.14) compared to those not performing such procedures, and among its subcohort ever assisting with fluoroscopically guided interventional procedures (53.2% of the entire USRT cohort) with RR of 1.18 (95% CI: 1.11, 1.25) compared with those never assisting with such procedures (Bernier et al., 2018; Velazquez-Kronen et al., 2019).

In interventional cardiologists, a meta-analysis of eight studies found a significantly increased risk for PSC opacities (RR of 3.21, 95% CI: 2.14, 4.83) compared with unexposed controls, with a non-significantly decreased risk for cortical (RR of 0.69, 95% CI: 0.46, 1.06) and nuclear (RR of 0.85, 95% CI: 0.71, 1.02) opacities (Elmaraezy et al., 2017). A cross-sectional study (not included in the meta-analysis) also reported a significantly increased risk for cataract prevalence with an odds ratio (OR) of 6.07 (95% CI: 1.38, 43.45) compared with unexposed controls (Karatasakis et al., 2018).

There have also been several recent reports from chronically exposed, non-occupational cohorts (i.e., populations with childhood and/or adulthood exposures). In the high natural background radiation area of Yangjiang, Guangdong, China, residents aged ≥45 years had a significantly increased risk for PSC opacities – OR of 4.05 (95% CI: 1.56, 10.46) compared to those living in control areas (Enping), a marginally significantly increased risk for cortical opacities (OR of 1.45, 95% CI: 0.99, 2.11), a non-significantly decreased risk of nuclear opacities (OR of 0.82, 95% CI: 0.60, 1.14) and a non-significant risk for all types of opacities in aggregate (OR of 0.99, 95% CI: 0.72, 1.37) (Wang et al., 2015); the lifetime chronic lens dose in this area is estimated to be below a few hundred mSv (vs less than one hundred mSv in control area). However, this study did not provide the dose response data. In 1949–1956, liquid radioactive waste was released from the Russian Mayak Production Association into the Techa River, leading to long term exposures of the residents in the Techa riverside villages. Residents in such villages showed a non-significantly increased risk for cataracts with ERR/Gy of 0.40 (95% CI: −0.43, 1.47), although the study group accounted only 21.7% of the cohort members, among whom only 11.1% received >0.1 Gy (Mikryukova and Akleyev, 2017).

Accordingly, the epidemiological evidence available from various cohorts as mentioned above tends to support lack of a clear dose rate effect, although we do not yet have enough evidence to make a decision on dose rate dependence. The lens capsule ensures the lens cells stay inside the lens throughout life, and lens fibre cells possess no cellular organelles. Mechanistically, lens cells and their components (e.g., proteins and lipids) undergo little if any turnover (Uwineza et al., 2019), which might be interpreted as indicating that a dose rate effect is biologically implausible. However, biological studies with animal models have shown either conventional sparing dose rate effects (a decrease in biological effectiveness per unit dose with a decrease in dose rate), no dose rate effect, or inverse dose rate effects (Hamada, 2017, Barnard et al., 2019), although the "low dose rates" used in some experiments are not low from radiation protection viewpoints. It is clear that more studies are needed.

Medical exposures of patients consist of diagnostic and therapeutic exposures. The dose limit legislation documents do not generally cover patients, as protection of patients is always subject to justification due to clinical need weighed against risk. However, patients form an interesting group for the study of cataracts, as doses to the patients are often well characterized and can be high. Little information is available regarding cataract risk from diagnostic exposures. One study (Yuan et al., 2013) suggested that head and neck computed tomography (CT) increased cataract risk, particularly with ≥5 CT examinations (HR of 2.12, 95% CI: 1.09, 4.14). 1–2 CT examinations also increased cataract risk, albeit non-significantly, with HR of 1.61 (95% CI: 0.90, 2.88). There may be a selection bias, because a putative 61% excess risk of cataract was estimated after one CT examination (Shore, 2016). Neurointerventional procedures for patients with an aneurysm were also reported to significantly increase cataract incidence in exposed patients compared to non-exposed or propensity score matched controls (Cheng et al., 2018). For therapeutic exposures, clinical studies on ocular complications in radiotherapy patients are described separately in Section 3.

Further to the presentation of the epidemiological evidence above, dose rate has only been studied in a very limited way to date. In epidemiological terms, very few studies have considered chronic exposure in the true sense – one notable exception being the chronic exposure to low-dose-rate gamma irradiation which occurred following the accidental incorporation of radiocontaminated steel into residential and civilian buildings in Taiwan in the 1980s. Chen et al. (2007) examined the occurrence of opacities in 114 members of the exposed population. Doses were calculated by age group and were of the order of 0–8 mSv. A dose dependent statistically significant increase in minor focal lens defects (those not likely to impair visual acuity) was recorded for those subjects aged 3–20 years old (P = 0.027). Dose dependence was also observed for the other age groups (20–40 years and 42–65 years), but the results were not statistically significant, suggesting that chronic low-dose irradiation is an independent risk factor for minor lenticular changes, especially in young people. Importantly, the data also indicate that protraction of the exposure over long periods does not substantially increase the threshold dose. This is in-line with the findings of Chodick et al. (2008), who found an increased risk of 'cataract' of 15% per year for a cohort of over 35,000 US radiologic technologists exposed to low doses over an average period of 19.2 years (albeit with a non-significant dose response), and recent studies in similar populations with much improved dosimetry, longer follow up and a significant dose response (e.g. Little et al., 2018a, 2020a, 2020b).

As for the existence of dose threshold, only limited studies (Little et al., 2018a; Nakashima et al., 2006, 2013; Neriishi et al., 2007, 2012; Worgul et al., 2007) investigated this issue, with inconsistent results. Among atomic bomb survivors who received single, acute childhood or adulthood exposure, the estimated threshold dose was significant at 41–60 years after exposure (0.5 Gy, 95% CI: 0.10, 1.05 Gy for cataract surgery) (Neriishi et al., 2012), but not at 55–57 years after exposure (0.7 Sv, 90% CI: <0.0, 2.8 Sv for PSC cataract and 0.6 Sv, 90% CI: <0.0, 1.2 Sv for cortical cataract, and 0.1 Gy, 95% CI: <0.0, 0.8 Gy for cataract surgery) (Nakashima et al., 2006; Neriishi et al., 2007). In Chernobyl clean-up workers who received protracted, adulthood exposure, a significant threshold dose was found for PSC and cortical cataracts (Worgul et al., 2007). However, these significant thresholds were not

systematically compatible with a curvature departure of the linear non-threshold dose-response relationship, and there may be some methodological issues in the dose-threshold statistical inference mainly based on the likelihood ratio test (Little et al., 2018a). So, the existence of a dose threshold for cataracts remains unclear.

2.2. Evidence for cataract surgery as a surrogate for VICs

The dose limits for the ocular lens recommended by ICRP and the US National Council on Radiation Protection and Measurements (NCRP) aim to prevent occurrence of VICs, but not minor opacities (ICRP, 2012; NCRP, 2016). VICs affect quality of life in general and at work, and some patients with VICs undergo cataract surgery. Therefore, cataract surgery is sometimes used as a surrogate for VICs in epidemiological studies.

The most important evidence underlying the ICRP assumption that minor opacities progress into VICs (ICRP, 2012) was that in atomic bomb survivors at 55–57 years after exposure, the risk for prevalence of cataract surgery (OR at 1 Sv of 1.39, 95% CI: 1.24, 1.55) was similar to that of cataracts (e.g., OR/Sv of 1.44, 95% CI: 1.19, 1.73 for PSC opacity) (Nakashima et al., 2006; Neriishi et al., 2007). In contrast, there was no significant increased risk for cataract surgery in Mayak workers (ERR/Gy of 0.09, 95% CI: –0.02, 0.22) (Azizova et al., 2019) and for self-reported cataract surgery in the USRT cohort (EHR/Gy of 0.34, 95% CI: –0.19, 0.97; EAR/10^4 PY Gy of 13, 95% CI: <0, 57) (Little et al., 2018a, 2020a) and subcohort (Velazquez-Kronen et al., 2019). There was, however, an association between radiation dose and cataracts in these two cohorts, as mentioned in Section 2.1. This was also the case in ^{131}I-treated thyroid cancer patients, but with a short mean follow-up of 5.9 years (Lin et al., 2016), compared to mean follow-ups of ≥60 years in atomic bomb survivors, >30 years in Mayak workers, and >10 years in USRT. Despite the huge sample size, there was no overall positive relationship between the number of head CT scans and the risk of cataract surgery in Ontario, Canada (Gaudreau et al., 2020). A significantly increased risk of cataract surgery as a function of radiation dose has hitherto been reported only in atomic bomb survivors. Although it remains unclear whether difference in dose rate, progression rate, age at exposure, nationality or follow-up period explains the differences in results between studies of cataracts and those of operated cataracts, the results need to be interpreted with caution. First, some VICs need surgical intervention, but the likelihood of surgery depends on various factors, such as the size and location of the cataract, socioeconomic, medical-cost and health consciousness factors, visual acuity in the opposite eye, nature of work or avocational activities affecting the need for visual acuity, and amount of ultraviolet exposure (Shore, 2016). Thus, there is no reason to suppose that cataract surgery prevalence is simply proportional to cataract prevalence. As a surrogate for VICs, cataract surgery is imperfect, it may underestimate the prevalence of VICs and is more subjective than high-grade opacities, but is better than low-grade opacities that many radiation epidemiological studies have used as an endpoint (Hamada et al., 2020). This is because low-grade opacities do not often impair vision and its development (progression) into high-grade opacities is not clear, e.g., regression (diminishment) of lenticular changes with time following radiation exposure has also been reported in atomic bomb survivors (e.g., ~9% and ~30% respectively at 6 and 21 years after exposure) (Hamada et al., 2014) and also in Fukushima nuclear workers (Yokoyama et al., 2017, 2019). Altogether, to gain more insights from future epidemiological studies for radiation protection purposes, evaluation of temporal changes during cataract development and use of high-grade cataracts (VICs) as an endpoint will be important. Such studies may provide insights into an open question as to whether minor opacities induced by low dose and/or low dose rate radiation progress much slower than those induced by acute higher dose (e.g., in atomic bomb survivors).

3. Information collected through clinical studies assessing eye lens opacities in irradiated patients

Radiotherapy is used in most patients with cancer. Owing to the radiosensitivity of the lens, radiation-induced cataract is expected to be very common. Any type of irradiation involving the head may result in radiation-induced cataracts. Thus, orbito-ocular/central nervous system (CNS)/head and neck radiotherapy (in particular external beam radiotherapy treatment (EBRT)) are particularly likely to induce cataract (Thariat et al., 2016b). However, ocular non-cancer effects include acute transient effects or late effects that are more clinically meaningful than cataract, such as optic neuropathy and retinopathy, which are often irreversible (Boldt et al., 2020). In contrast, it is important to note that cataracts can significantly impair the vision but can usually be treated with relatively minor procedures (phacoemulsification, a modality of mini-morbid surgery) (Chen and Gragoudas, 2002; Gragoudas et al., 1992). Surgery is usually without complication and allows visual restoration when vision loss is cataract-related. Accordingly, lens opacities and VICs are inconsistently reported in clinical cancer studies because of their relatively limited impact on visual function compared to other more clinically significant iatrogenic effects, and low importance compared to the cancer prognosis. In contrast to epidemiological studies, clinical studies often deal with much larger doses to the lens, and various fractionation regimens. This section deals with therapeutic doses given to the patients (not the medical staff/workers (considered above).

3.1. Assessment of cataract in irradiated patients/clinical follow-up

The common toxicity criteria classification of adverse events, now in its fifth version (CTCVAE v5), is broadly used in the oncology community but has been used rarely for cataract assessment (Table 1, see below) because severity assessment is based on vision loss, which is often due to other ocular toxicities. In many cancers however, there are several confounding factors for vision loss, such as maculopathy, optic neuropathy or dry eye syndrome. Additionally, thorough clinical/paraclinical examination is always possible to distinguish between the various causes of vision loss but is seldom performed for tumours in the head and neck area. Moreover, the CTCVAE v5 does not report lens opacities.

Consequently, the CTCVAE classification is used rarely. Clinical assessment of cataracts often relies on a discretized, non-standardized scale in routine practice (Thariat et al., 2017). The standardized use of a slit lamp may limit interobserver variability and subjective assessment of cataracts by demonstrating phenotypic changes of the lenses that could be related to therapeutic irradiation. This, however, requires that a baseline examination should be performed before irradiation. Moreover, it does exclude the possibility that a *de novo* cataract is related to aging, to traumatism (such as fiducial placement for ocular proton therapy) or to topical or systemic steroids (Mathis et al., 2019; Thariat et al., 2017). “Cataractogenic load” represents radiation-induced acceleration of cataracts that would otherwise be seen in old age (Uwineza et al., 2019). Lens effects of radiation have not been well studied in cases of uveal melanomas because irreversible optic toxicities that can make people blind are more likely related to maculopathy or optic neuropathy, than cataract.

The Lens Opacities Classification System III (LOCS III) (Chylack et al., 1993) has been used in 2019 in a prospective, interventional case series of fifty-two consecutive ocular melanomas patients with cataract following proton therapy (Mathis et al., 2019). This classification requires training and has a learning curve. Inter-observer variability has not been quantified. Scheimpflug imaging is seldom used in radiation therapy (Eter et al., 2000). Identification of mild toxicities, in addition to clinically relevant/severe toxicities, may be very informative to understand the mechanisms of low dose radiation therapy and radiation damage by subsite of the lens. Finally, standardized assessment of lens

Table 1
Classification of cataract according to the Common Toxicity Criteria scale of Adverse Events (Version 5).

Cataract	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline); glare symptoms affecting instrumental ADL	Symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or>3 lines of decreased vision from known baseline, up to 20/200); limiting self-care ADL	Best corrected visual acuity of 20/200 or worse in the affected eye	–

Definition: A disorder characterized by partial or complete opacity of the crystalline lens of one or both eyes. This results in a decrease in visual acuity and eventual blindness.

opacities is slowly moving toward less subjective assessment of lens opacities. As a perspective, data banks of slit lamp or Scheimpflug images might be captured to allow automatic machine learning approaches in a near future. This could eliminate the tedious task of grading cataracts manually and might reduce inter observer variability.

3.2. Latency and probability of lens opacities in treated patients

Latency of radiation induced lens opacities has been related to dose per fraction, dose rate and total dose in clinical studies (Belkacemi et al., 2001). In a study of radiation cataracts in patients with ocular adnexal mucosa-associated lymphoid tissue (MALT) lymphoma, 8 of 16 patients (11 eyes: 52.3%) required cataract surgery after radiotherapy, and the mean latency between radiotherapy and surgery was 43 months (Fukutsu et al., 2018). With median follow-up of 51.8 months, sixty-one retinoblastoma patients (94 eyes) who were treated with whole-eye radiotherapy (WERT) or lens-sparing radiotherapy (LSRT) had cataract in 71.1% versus 35.3% of respectively (Nguyen et al., 2019) ($P < 0.01$). A mean lens dose of 7 Gy was projected to lead to a 5-year cataract incidence of 20%-25%. High-dose rate irradiation is associated with short latency (Collaborative Ocular Melanoma Study, 2007; Gragoudas et al., 1992; Thariat et al., 2017). The US Childhood Cancer Survivors Study (CCSS) five year prevalence of 3.8%, 2.4%, 1.3%, and 0.9% in children with soft tissue sarcoma, leukaemia, neuroblastoma, or CNS malignancies, respectively (Chodick et al., 2016). A European study observed a long-term incidence rate of cataracts of 2.3% in children with a former primary CNS tumour who received radiotherapy (Allodji et al., 2016). Moreover, in children who received 6–12 Gy total body irradiation (TBI), during 1980–1999, 50–90% had evidence of cataracts within 10 years. Reduced rates were reported after shielding was introduced to protect the lens (van Kempen-Harteveld et al., 2002, 2003). The probability of staying cataract-free for at least five years was 0.77 with, and 0.33 without shielding. The relative risk of developing a cataract without shielding vs with shielding was three (95% CI; 1.5, 5.9). Moreover, other factors may influence latency time of a cataract. After high-dose-rate TBI (in one or two fractions), steroids for graft versus host disease (GVHD) influence latency time and are of great importance for the severity the cataract finally attains (van Kempen-Harteveld et al., 2000). However, patterns of cataract risk among adult childhood cancer survivors remain unclear (ICRP, 2012), since most studies involved <10 years follow-up time (van Kempen-Harteveld et al., 2002, 2003), or non-shielded patients (Chodick et al., 2009; Horwitz et al., 2015).

After hypofractionated ocular proton therapy using a few high-dose fractions, 15% and 9% of patients had cataracts and VICs within median times of 19 and 28 months, respectively (Thariat et al., 2017). However, for radiotherapy modalities that deliver lower total doses with conventional fractionation, lens opacities may appear 5 or 10 years after irradiation, and even later. The longer the latency, the more difficult the determination of causality due to additional and complex confounding factors.

Overall, the estimates of risk here may be appreciably too low, because of the very short follow-up period of times.

3.3. Impact on life quality (assessment via questionnaire)

Longitudinal studies are necessary to assess quality of life (QOL). Vision oriented QOL questionnaires (Braithwaite et al., 2019), when given to patients treated for ocular treatments, cannot accurately distinguish between different causes of vision loss. QOL was assessed in 130 childhood leukaemia survivors using SF-36 questionnaires, in who received hematopoietic cell transplantation after BU (busulfan) or TBI (Bernard et al., 2014) but omitted cataracts.

Patient reported outcomes (PRO) can be obtained using the following instruments: the Visual Disability Assessment, The Rasch-scaled VDA which measures mobility and activity limitation, the Quality of Vision Questionnaire (with scales of Frequency, Severity and Bothersome), the Catquest 9SF test, or the Visual Functioning Questionnaire – 25 (VFQ-25) of the US National Eye Institute. Although these questionnaires could provide important information, it should be noticed that patient compliance to PRO reproducibly declines over time. Repeat incitation by the medical/paramedical team requires staff resources.

3.4. Effect of different radiation qualities (radiation therapy with or without image guidance, nuclear medicine, diagnostic radiology, etc.)

Compared to doses obtained in epidemiological studies of other types of radiation exposure, therapeutic dose distribution assessment and time-related factors can be expected to be better documented in external beam radiotherapy because there is no need for (complex) dose reconstruction (Jeffery et al., 2015). The delivered doses are usually documented using dedicated radiotherapy software (treatment planning systems (TPS)). At worst, there is a need for a posteriori definition of ocular regions of interest on planning CT images if they have not been delineated and documented as three-dimensional (3D) dose distributions and dose volume histograms during external beam radiotherapy.

Common radiotherapy schemes vary from 20 Gy (hypofractionated) to 70 Gy in 5 to 35 fractions using conformal photon-based irradiation or conformal intensity modulated radiotherapy to 60 Gy in 3 fractions with stereotactic (hypofractionated) photon-based irradiation. Hypofractionation is defined by the use of doses per fraction higher than 2.5 Gy per fraction, standard fractionation delivering 1.8–2 Gy per fraction in 30 daily fractions. Particle therapy is increasingly used. Dose rate may also influence clinical effects (4 Gy/min by intensity modulated X-ray radiotherapy (IMXRT) to 75 Gy/min by ocular proton therapy at some dedicated installations). Lens shielding or sparing are usually inefficient in delivering doses below the ICRP threshold of 0.5 Gy for VICs (ICRP, 2012).

Non-ocular particle therapy with protons or carbon ions results in better ocular dose sparing, owing to the physical properties of charged particles. For accurate estimates of the dose to the lens, contributions from machine related stray radiation, planning CT, setup imaging and follow-up imaging modalities should be accounted for. Therapeutic out-of-field extra-doses are potential confounding factors in the assessment of non - ocular treatment effects, especially with respect to low doses. For example, in proton therapy of CNS, head and neck tumours, the larger field of view used for setup imaging than for the therapeutic

beams may contribute to some dose to ocular structures using 2D (with orthogonal kV images) (Fig. 1) or 3D with kV or MV cone beam CT. Low doses from setup imaging prior to therapeutic dose might have relevant biological effects. So it might be relevant to calculate this low dose to the estimation of the absorbed dose to the organs at risk, in every treatment plan of a patient.

Brachytherapy of the head is seldom performed except for ocular plaques in uveal melanomas. Several radioelements (mostly 3) can be used and brachytherapy plaques do not require ionizing radiation setup imaging as plaque placement can be assessed using ultrasound. The doses delivered to the eye lens during ocular brachytherapy by far exceed the ICRP threshold ß in general (Ebrahimi-Khankook and Vejdani-Noghreiyan, 2018).

At the lower dose end of the scale, diagnostic (ionizing) radiology procedures include systematic dose reporting with no specific reporting for the lenses. Doses are much lower than after therapeutic irradiation. Little is known about radiology procedures and risk on PSC cataract. In a study on 4926 adults who had a brain CT scan, the odds ratio of developing PSC cataract was examined (Kleineidam et al., 1993). The mean age at eye examination was 43–84 years. ORs of 1.45 (95% CI: 1.08, 1.95) was found for PSC and 1.28 (95% CI: 1.02, 1.61) for nuclear cataract in relation to having a brain CT scan. A study by Harbron et al. (2019) in over 280,000 patients with 440,000 head and neck CT examinations, showed that the majority of young people received cumulative lens doses well below 500 mGy – with about 1% having 10 CTs or more and doses above 500 mGy.

The radionuclides in radiopharmaceuticals currently used in nuclear medicine do not concentrate in the tissues of the healthy human eye, with the possible exception of iodoamphetamine used in the synthesis of melanin (ICRP, 2015), and therefore the lens doses are likely to be quite low.

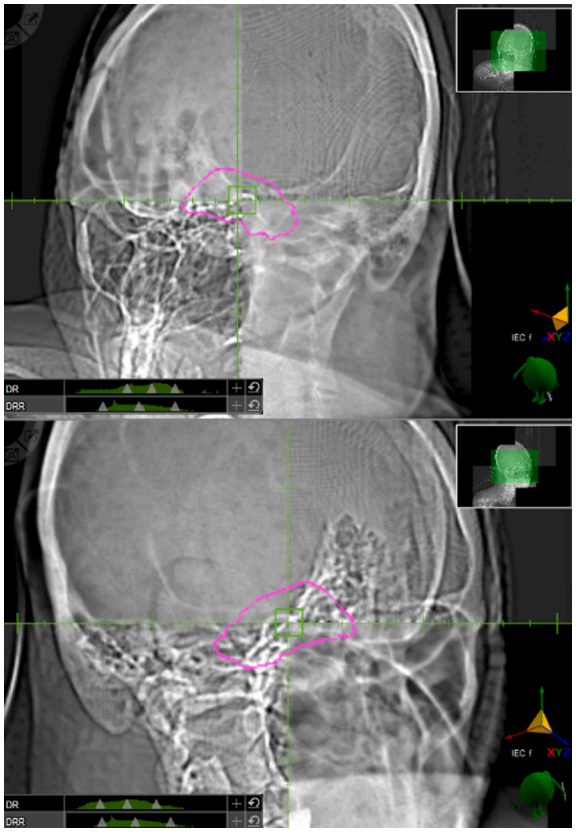

Fig. 1. 2D setup imaging, much larger than tumour area (in pink). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3.5. Dose ranges in clinical studies of external beam radiotherapy or brachytherapy plaques

Clinical threshold doses were 10 Gy and 18 Gy for VICs requiring surgery in respectively 5% and 50% of cases at 5 years after irradiation based on pivotal dose-effect meta-analyses, which are reference works for radiotherapy (Emami et al., 1991; Henk et al., 1993). The ICRP threshold of 0.5 Gy is much lower (ICRP, 2012; Kleiman, 2012). In radiotherapy, the lens dose is usually minimized according to the ALARA (as low as reasonably achievable) principle. Due to the large dose spread with conventional radiation therapy (using photons), sparing such a small organ as the eye lens is difficult. Partial lens irradiation can be achieved with particle therapy (Thariat et al., 2016a). Using hypofractionated ocular proton therapy, no significant excess risk of radiation-induced cataracts was observed for doses below 0.5 Gy if less than 5% of the lens was irradiated with a median follow up of 48 months. The risk for VICs only increased significantly in the 5–10 Gy range if no more than 2% of the lens was irradiated (Thariat et al., 2017). Above that minimal threshold, the dose-volume profiles suggested a linear relationship (Allodji et al., 2016; Henk et al., 1993; Neriishi et al., 2012; Thariat et al., 2017). In another study of irradiated 42 patients with lens irradiation, the extent of PSC significantly correlated with the dose to the lens, the dose to the lens periphery and the dose to the ciliary body, which received 10, 26, and 47 Gy, respectively (Mathis et al., 2019). Proton dose also correlated with the occurrence of PSC and nuclear colour cataracts as defined by LOCS III grading (Mathis et al., 2019).

In brachytherapy studies, dose to the lens was associated with cataract risk with a hazard ratio of 1.15 for each 10-Gy increase ($p = 0.002$) (Puusaari et al., 2004). Lens near-maximum dose, i.e. the dose given to 2% of the volume of the lens (Lens D2%) had the largest impact on the risk of cataract along with older age and the largest base dimension (Espensen et al., 2019). Finally, cataract incidence at 5 years reaches up to 83% after ^{125}I brachytherapy, with a need for surgery in 12% of cases (Finger, 2000; Finger et al., 2011).

4. Biological and mechanistic knowledge relating to the initiation and development of eye lens opacities, from animal models

4.1. Ophthalmic examination techniques used in mice

Nowadays we have precise examination tools in ophthalmology that can detect and document minor changes in the ocular lens and other structures of the eye. However, the important question for the affected individual is the level of vision impairment. According to Pei et al. (2008) reduced visual acuity caused by clouding of the lens is correlated with a peak lens density in Scheimpflug imaging of about 14% and higher.

Historically, mechanistic studies of the effects of ionizing radiation in the lens have been carried out in mouse, rat, rabbit and even frog models (reviewed in Ainsbury et al., 2016). Mice are a valuable model organism in radiation studies and for ophthalmic investigations, even if some differences exist between murine and human eyes. The eyeball of a mouse is much smaller than a human eye; on the other hand, the murine lens is relatively larger and nearly fills the vitreous. Compared to the human retina the mouse retina has no macula but possesses a higher photoreceptor cell density in the central area (Volland et al., 2015). The examination methods of the visual system in mice are similar to those used in humans. Usually the exploration of the murine visual system starts with an examination for gross eye abnormalities of the eyelids, eyeballs, cornea and iris/pupil. For more detailed analyses different ophthalmic examination techniques and devices are used that are often the same for mice and humans.

Slit lamp biomicroscopy gives a magnified view to almost all parts of the mouse eye. Nevertheless, it is particularly suitable for the

examination of the anterior parts of the eye, namely the cornea and the crystalline lens (Favor, 1983). Various grading system have been used over the time for classification and documentation of lens opacities in different species. The most common system used in many studies is LOCS III adapted to mice (Molnar et al., 2019). This qualitative grading is somehow subjective and not well reproducible and can cause difficulties in follow-up studies. Since several decades ago, the slit lamp has been regularly used in ophthalmological research in mouse models and grading systems were adapted to mice or new ones were defined with the problem that studies on cataracts are rarely comparable (Eaton et al., 2017).

Scheimpflug imaging is used for anterior eye examinations of the cornea, anterior chamber angle and the lens. Corneal thickness and curvature can be determined and the opacity of the lens and the cornea may be quantified as percentage of density. Compared to slit lamp biomicroscopy the objective assessment of the lens densities can be easily used for statistics. The peak lens density measured by Scheimpflug imaging has a linear correlation with the LOCS III grading system used to analyse slit lamp examinations and reduced visual acuity is correlated with a peak lens density measured by Scheimpflug imaging of about 14% and higher (Pei et al., 2008). On the other hand, the image resolution, compared to anterior segment optical coherence tomography (OCT) is not very high and some details are poorly visible when using Scheimpflug. A difficulty for investigation of the lens density can be an opaque cornea that will limit the accuracy of the Scheimpflug imaging.

Ophthalmoscopy, also known as *funduscopy,* is used for examinations of the posterior eye, especially the retinal fundus, blood vessels and optic disc. Hawes et al. (1999) presented different phenotypes of normal and mutant mouse fundus images. The fundus pictures or the aberrations documented therein give a good indication for retinal lesions, but are hardly quantifiable and there is no established system available to record the severity of the lesions. Therefore, the description of the phenotype is subjective and hard to compare between different studies. A recent study on retinal degeneration 8 (rd8) mutation of crumbs homolog 1 (CRB1) gene (*CRB1*^{rd8} mutation) and its influence on age-related macular degeneration (AMD)-like retinal alterations tries to correlate the fundus phenotype with OCT images and angiography (Richert et al., 2020). In mouse models the *CRB1*^{rd8} mutation is present in different mouse strain backgrounds and leads to retinal degeneration.

Optical coherence tomography (OCT) uses the reflection of infrared light passing through all parts of the eye. Therefore, nearly the whole eye can be investigated, from the anterior segments to the posterior eye, namely the retina and the optic disc. Serial images can be acquired and three-dimensional images may provide a better understanding of histopathological changes *in vivo*, allowing evaluation of progression or regression of a lesion. OCT allows to quantify the total thickness of the retina and the retinal nerve fibre layers. In contrast to Scheimpflug imaging, the spectral domain OCT (SD-OCT) is not only feasible to analyse anterior segments, but has been shown to be a suitable method to investigate PSC in mouse models (Pawliczek et al., 2020). An important feature since PSC is the predominant type of cataract developed after radiation exposure in humans.

Electroretinography (ERG) is a sensitive test for the retinal function. Like the techniques described before, it is a non-invasive method for quantification of the electrical response of the neural retina to a light stimulus. Differences in wave formation were investigated in various mouse strains and have been described (Dalke et al., 2004; Pinto et al., 2007). Suitable protocols to address different retinal cell types by ERG measurement in mice are published, including a description how to interpret the resulting waves (Benchorin et al., 2017; Tanimoto et al., 2015).

The *optokinetic drum* is a visual acuity testing method for laboratory animals such as mice or fish. During the examination the mouse is placed in the centre of a moving stripe pattern provoking the optokinetic reflex/optomotor response that is detectable by eye and head movements of the mouse tracking the stripes (Prusky et al., 2004; Puk et al., 2008). Efforts have been made to automate the system to speed up the measurements and to get better comparable, less subjective results (Benkner et al., 2013; Kretschmer et al., 2015; Shi et al., 2018).

Increased *intraocular pressure (IOP)* is typically correlated with glaucoma, a progressive loss of retinal ganglion cells. For the use of animal models in glaucoma research devices for mice are established (Prusky et al., 2004; Tao et al., 2019).

Laser Interference Biometry (LIB) is an appropriate method to investigate different eye size parameters, including axial length, lens thickness, and anterior chamber depth (Schmucker and Schaeffel, 2004; Puk et al., 2006; Park et al., 2012).

4.2. Mechanisms

Since mechanistic evidence for the involvement of low-linear energy transfer (LET[4]) ionizing radiation in cataractogenesis was reviewed in detail in Ainsbury et al. (2016) there have been a small number of explicit studies in animal and *in vitro* models, mostly looking at one specific step in the hypothesized 'chain of radiation action' of radiation in the lens.

The largest study using mice as mammalian animal model exposed the mice to a single dose of 0; 0.063; 0.125 and 0.5 Gy at 10 weeks of age. Dalke et al. (2018) determined lens opacities for up to 2 years and compared it with overall survival, cytogenetic alterations and cancer development, to assess the relative radiosensitivity of the lens and other tissues, and in order to survey the global effects of radiation exposure in this new strain of *Ercc2*$^{+/-}$ heterozygotes hypothesised to be radiation sensitive. The highest dose was significantly associated with increased body weight and reduced survival rate. Chromosomal aberrations in bone marrow cells showed a dose-dependent increase 12 months after irradiation. Pathological screening indicated a dose-dependent risk for several types of cancers, including ovary tumours and pituitary adenomas. Scheimpflug imaging of the lens revealed a small significant dose-dependent effect of lens opacity. Comparison of different biological end points demonstrated long-term effects of low-dose irradiation for a number of endpoints including chromosomal aberrations in mutant mice at 18 months post irradiation together with a non-significant dose dependent decrease in telomere length (Dalke et al., 2018).

Barnard et al. (2019) identified an intriguing result in terms of early DNA damage responses in lens epithelial cells irradiated *in vivo*. P53-binding protein 1 (53BP1) foci in cells exposed to 0–2 Gy of gamma rays indicated that DNA damage was repaired faster at higher dose rates, in direct contrast to data obtained in lymphocytes and the expected response based on the paradigm of dose protraction reducing the impact of radiation exposure. As the link between DNA damage and cataractogenesis remains a hypothesis, the consequences of these results remain to be seen, however, the authors hypothesize that lens cells thus behave differently to other tissues. This clearly requires further investigation.

The effects of ionizing radiation exposure on telomere length and oxidative stress in human lens epithelial cells were assessed by Bains et al. (2019). Although the results were not conclusive, telomere length was observed to increase with dose, and this was matched by a corresponding decrease in telomerase activity. Further work in this area is clearly needed.

The concept of the 'cataractogenic load' was introduced by Uwineza et al. (2018), as the 'combined lifestyle, genetic and environmental processes that increase biomolecular damage to lens macromolecules

[4] Linear energy transfer (LET) indicates the amount of the initial energy of a particle given up per unit length of its path through material as a result of ionizations and other interactions. High-LET radiations include alpha particles and neutrons. Beta and gamma radiations and X-rays are low-LET radiations. Its relevance to eye is neutrons (in nuclear power plants and in space) and heavy ions (in aircrew, space, cancer therapy).

leading to cataract formation'. This idea is discussed in detail in the light of current scientific evidence; the authors conclude that exposure to ionizing radiation increases the cataractogenic load through formation of radicals and oxidative stress which lead to a variety of downstream processes resulting in apparent advancement of the aging process. If, as the literature suggest, cataractogenesis is viewed in this context, then studies of the involvement of radiation going forward should focus on development of comprehensive understanding of the full adverse outcome pathways (AOP), from the initiating event to the outcome of a clinically relevant VIC.

4.3. Experimental designs and models

As access to human lens material *in vivo* is more or less impossible and *ex vivo* samples bring their own challenges, the majority of the additional information since 2016 has come from targeted *in vitro* models.

Barnard et al. (2018) demonstrated the differential response of a variety of strains of mouse model in terms of DNA damage responses assessed by 53BP1 staining of DNA double strand breaks. The level of DNA damage as well as the inter-individual variability varied widely between strains, again indicating the importance of genetic background. The contribution of genetic background to cataract risk in general has also only been studied in a minor way. However, the ataxia telangiectasia mutated (ATM), RAD9 and BRCA1 genes are known to be critical to pathways controlling DNA damage response signalling, repair or apoptosis. There is human evidence that those with heterozygous mutations of these genes are at increased risk of certain health effects; for instance, they have elevated tissue responses to ionizing radiation and are more susceptible to cancers. Heterozygosity of the ATM gene, for example, is estimated to occur in 0.5–1% of the Western population (Ahmed and Rahman, 2006), and inadvertent irradiation of ATM homozygous humans ionizing radiation exposure can be fatal. Worgul et al. (2002) investigated the sensitivity of Atm-deficient mice exposed to 0.5 to 4 Gy of X rays. Cataract development was strongly dependent on radiation dose. Opacities were observed earliest in Atm homozygotes, but cataracts also developed earlier in heterozygotes compared to wild-type mice for all doses. The severity and latent period were directly related to the number of genomically damaged cells attempting differentiation. Because Atm is involved in cell cycle control and pathways to apoptosis, this would indicate that cataracts may be due to defective control of these pathways in response to DNA damage. These results indicate genetic predisposition to cataract development for Atm heterozygotes.

In addition to the individual factors, although the ICRP note the need for further work in this area, in the current radiation protection regulations for cataract (ICRP, 2012), no effect of quality of the radiation (LET or RBE, relative biological effect[5]) is considered, nor is any effect of dose rate – rather the assumed threshold and dose limit (BSS, 2014) are for any type of radiation delivered in an acute or protracted manner (IAEA, 2014; ICRP, 2012).

In 2017, the evidence for dose rate specifically was reviewed by Hamada (2017). The author concludes that the only clear conclusions that can yet be drawn are that lens cells are not radiosensitive to cell killing, rather the radiosensitivity of the lens is driven by alternative mechanisms including mis- or slow repair of DNA double strand breaks, abnormal differentiation or proliferation, telomeric effects and/or senescence and morphological changes to the lens crystallin itself. Taken together with the data from Barnard et al. (2019), discussed above, the mechanisms are still highly uncertain, but the existence of a genuine dose rate effect could have clear implications for radiation protection.

In the limited data from animal models thus far, the radiation quality effect is clear (Hamada and Sato, 2016). Worgul et al. (1996) found that rats exposed to neutrons exhibited significantly higher rates and severity of opacification compared to those exposed to X-rays at doses between 2 and 250 mGy. In 2019, Chauhan and colleagues exposed HLE cells to 0–5 Gy of X-rays at two different dose rates in order to explore transcriptional responses (Chauhan et al., 2019). The authors found that pathways were activated below approximately 0.6 Gy, and that above 2 Gy the response was non-linear with a clear dependence on dose rate (with the albeit limited data provided).

5. Discussion

Here we have provided an overview of recent developments in epidemiological, clinical and biological studies on radiogenic cataracts. Although several projects have in recent years (e.g. LDLensRad, 2020) focused on development of understanding of the involvement of ionizing radiation in mechanisms of cataract development, a number of gaps remain.

The biological effectiveness greatly differs with increasing LET of ionizing radiation, and it is well known that high-LET radiation (e.g., neutrons and heavy ions) has generally higher RBE compared to low-LET radiation (e.g., photons and protons) (Hamada, 2009; Hamada et al., 2010). The high dose mechanistic evidence is clear in that lens has much higher RBE than other tissues, and cataract is a unique effect for which a significant increase in radiation risk has been known in astronauts who encounter high-LET radiation exposure in space (Hamada and Sato, 2016). Given that new epidemiological studies in astronauts are no longer being conducted or planned, epidemiological studies in people on Earth (particularly for low-LET radiation) and biological studies with animal and cell culture models (particularly for high-LET radiation) play more important roles than ever. Such studies for high-LET radiation should also lead to a better understanding of ocular complications following heavy ion therapy. Reassessment of RBE for radiation protection on Earth is also important: this is not only because the US NCRP now recommends an absorbed dose limit for the lens with the use of RBE for high-LET radiation, instead of an equivalent dose limit for the lens with the use of a radiation weighting factor (w_R) (NCRP, 2016), but also because ICRP has had similar discussions recently (Harrison et al., 2016).

The animal studies and human studies on congenital cataracts, for example, illustrate that genetic and other factors strongly influence cataract development, thus suggesting that the ionizing radiation response of the lens will differ among genetically diverse human individuals. The most important of these factors would appear to be sex, age at exposure, attained age, genetics and epigenetics (Hamada and Fujimichi, 2015; Ainsbury et al., 2016), but there is little knowledge available on what this all means for humans in practice. Dalke et al. (2018) found only a very small increase in cataracts associated with ionizing radiation exposure in their animal model; however, research carried out since then (LDLensRad, 2020) suggests the major involvement of genetic background as well as sex, dose and dose rate influencing cataract risk. The impact of such individual factors, together with dose rate (plus consideration of protraction) and radiation quality, are of high priority for future studies. A deeper understanding of such potential individual differences will be important for personalized radiation protection of radiotherapy patients, radiation emergency workers, and astronauts (Foray et al., 2016; Hamada et al., 2018; Seibold et al., 2020).

From the point of view of dose estimation, the eye lens is very special in a number of respects.

[5] For a specified radiation, RBE is the ratio of the (a) absorbed dose of a reference radiation required to produce a specific level of a response in a biological system to the (b) absorbed dose of the specified radiation required to produce an equal response, with all physical and biological variables, except radiation quality, being held as constant as possible. The reference radiation with a defined RBE of unity normally is gamma rays (often those from ^{60}Co) or X-rays (most commonly 180–250 kVp X-rays). RBE generally depends on dose, dose per fraction (if the dose is fractionated), dose rate, and biological end point.

First, considering occupationally exposed cohorts, eye lens doses were historically never monitored as a target organ, though safety regulations included eye lens dose limits. Before reduction of the dose limit from 150 to 20 mSv y^{-1}, which is now mandatory regulated by European Basic Safety Standards (Euratom, 2014), there was a consensus that in case if whole body (effective) and skin doses are below respective limits, the eye lens dose was also controlled. However, the reduction of the eye dose limit necessitates direct monitoring of $H_p(3)$, the operational quantity representing eye lens exposure (ICRU, 1998). This technically and methodologically challenging problem is not yet entirely solved (Behrens, 2017), meaning that all the historical, and the majority of the current, monitoring data (for example, records in the national dose registries) does not contain information on occupational exposure of eye lenses of workers.

Second, due to the anatomy of the eye and the eye lens location, the lens is covered by a relatively thin layer of tissue, so not only photons (including low energy X-rays), but also electrons (beta-particles) may reach sensitive volume of the eye lens and deposit substantial dose there. This is, in particular, the situation with Chernobyl liquidators or clean-up workers (Chumak et al., 2007), whose lenses were exposed to a mixture of gamma- and beta-emitting sources. It is assumed that the depth of sensitive volume of eye lens is 3 mm, however, in real life this depth is different and may vary between subjects. These deviations from 'standard' depth may cause a large difference in dose in case of weakly penetrating radiation like beta-particles or low energy photons.

Third, as mentioned before, the eye and eye lens are rarely target organs for therapeutic exposure and, therefore doses to lenses are not usually evaluated or recorded in routine practice. At the same time radiation scattered in a patient's body may contribute substantially high doses to eye lens, though this tissue is located out of incident radiation field (e.g. Harbron et al., 2019).

All the aforementioned factors lead to the situation that there are virtually no ready-to-use dose estimates good for establishing dose-effect relationship for cataracts or other endpoints attributed to eye lens. In practical terms it means that prior or during any epidemiological or clinical study the eye lens doses need to be estimated using the most appropriate means, in most cases using dosimetry calculations, instead of measured dose.

Indeed, as discussed widely in the literature, the quality of the dose-response relationship modelling is closely related to the quality of the estimation and reconstruction of lens dose (Ainsbury et al., 2016), and that of the outcome assessment (see below). According to the context (e.g., accidental vs medical, protracted exposure), this dosimetry mobilizes various methodologies based on metrological dose assessment, physical equation for particle transport, beam scattering, intake and biokinetics of nuclides which are combined with a person specific data collected such as on medical and/or career history. The complex designs inevitably include uncertainties which should be identified and quantified in order to provide adequate health risk estimations: are they classical errors, Berkson errors or shared errors? (Carroll et al., 2006). This leads to a paradigm shift in the risk estimation where the dose in past studies tended to be considered as a single point estimate ignoring the associated uncertainties. In the medical staff context, for example, the European EURALOC project developed a methodology combining self-reported data regarding work practice and available procedure-specific eye lens dose values to produce an individual distribution of possible cumulative lens doses for each eye (Covens et al., 2018; Struelens et al., 2018). Statistical methods dealing with uncertainties in risk estimation already exist (Kwon et al., 2016; Schafer and Gilbert, 2006) and have successfully been applied in some radiation epidemiological studies (Little et al., 2015, 2020b, 2020c). The dissemination of such approaches is encouraged. As mentioned above, a special effort in a statistical dose threshold inference is also needed regarding its implications for dose limit recommendations. As always, appropriate calibration and optimization of the techniques will remain key to ensuring the quality and reliability of the results. Further, as programs will need to incorporate expertise from a range of fields (radiation biology, biochemistry, physics and dosimetry), balanced and multidisciplinary projects are highly recommended.

Integration of epidemiology and biology has long been discussed for cancer and circulatory disease (NCRP, 2015, 2020), and is indeed indispensable also for cataracts (Dauer, 2018). To this end, risk-predictive biomathematical modelling (Sakashita et al., 2019) and the adverse outcome pathways (AOP) approach (Chauhan et al., 2019) will be crucial. The dose limit recommended for the lens aims to prevent occurrence of high-grade opacities that impairs vision and impact daily life. However, in regards to the accumulated evidence of radiogenic low-grade opacities, it is crucial to study the biological mechanisms, i.e., whether minor opacities develop to severe ones, and the associated modifying factors. Preclinical studies will be certainly helpful to address this issue. In this regard, most studies to date have focused on effects *in vitro* rather than *in vivo* – the challenges clear are here; however, it would be of use to establish a system for this going forward regarding which endpoints can be realistically assessed using at each study level – *in vitro*, animal models *in* and *ex vivo*. Prioritization of use of the limited amount of human material will also be of high importance.

In terms of endpoints, as there are still many open questions, it is recommended to focus research now particularly on elucidation of the effects of dose, dose rate and LET in the areas of oxidation and intracellular communication, DNA damage in the context of cell cycle, damage to the extracellular matrix, proteomic, lipidomic and epigenomic responses (particularly as technologies in these three areas further develop), altered fibre cell proliferation and differentiation, morphological and post translational changes, as well as the potential impact of non-targeted effects such as the bystander effect (Ainsbury et al., 2016; Hamada et al., 2011) and the exosomes as its potential mediator (Dismuke et al., 2015). Importantly, it is recommended to carry out all studies in the context of the age, sex, genetic specific responses, i.e. to directly compare or to actively control these factors in all cases. Such studies should also ideally be in the context of wider tissues such as the brain, to further investigate the relative radiosensitivities across the whole body (LDLensRad, 2020).

As access to human lens material *in vivo* is more or less impossible, it is recommended to use a combination of relevant animal models to identify and further develop the potential mechanisms explored in the literature and appropriate *in vitro* models to support these findings. For animal studies, the effects of animal husbandry need to be better controlled and considered, e.g. Forssell-Aronsson and Quinlan (2017).

If *ex vivo* human lens material is available, then this will likely most usefully be used for validation of mechanisms identified in animal and/or *in vitro* studies. However, in most cases, as the latency period for low dose cataract is long, it is unlikely that high quality, reliable, individual dosimetry (with appropriate uncertainties) will be available to allow formal conclusions regarding the effect of dose and other factors. Exceptions include the Mayak worker studies, where the dosimetry systems are well validated (Azizova et al., 2018 and related studies) – these studies should be prioritized for exploring access to such material for future work.

It should also be noted that within this field there is currently a lack of mathematical models with a genuine biological basis. One recent exception was published by Sakashita et al. (2019), which uses data regarding human lens growth based on stem and progenitor cell proliferation as well as epithelial fibre cell differentiation to explore the relationship between dose and cataract onset at various ages and thus to estimate cataract incidence following chronic lifetime exposure. However, the authors recognize this is a simple model and further work is needed here.

In addition, radiation mitigators should be further considered going forward. The current status of this topic was reviewed in brief in Ainsbury et al. (2016) – with the main conclusions being that there are some good candidate protective agents proposed in the literature, however, a huge amount of additional work is needed here. Only a very small

number of studies of direct relevance to ionizing radiation exposure have been published in recent years; one example is Karimi et al. (2017) who identified an antioxidant effect of hesperidin against 15 Gy gamma radiation in rat lenses. Research on agents protective against lens exposure to low doses is still at a relatively early stage, however, if effective agents were identified, this could be of benefit for example to support personalized radiation protection for those exposed to medical radiation or indeed for radiation workers.

Clinically, the dose ranges considered to be responsible for lens opacities following the detailed literature review of the ICRP are much lower than those given in orbito-ocular/CNS/head and neck cancer patients in general. The data also suggest that the frequency and severity of radiation induced cataracts increases with dose, dose per fraction, and dose rate, in a manner influenced by genetics, age and sex. More subjects and clinically relevant cohorts, with more subjects with low to moderate doses (below 5 Gy), are needed to study the relationship between latency and dose, (Kleiman, 2012). Thus, a more clinically relevant notion than lens opacities, given the prognosis of cancer, is that of VIC. However, it remains tedious to provide accurate retrospective clinical dosimetry data in the clinics in the low dose range and in the long term. Clinical studies could, however, be conducted in the low dose range to assess dose lens effects in humans prospectively. Imaging of patients receiving proton therapy beams sparing the lenses (i.e. for CNS or head and neck tumours), for example, together with prospective longitudinal follow up using standardized slit lamp (LOCS III) or Scheimpflug images as well as quality of life questionnaires and accurate lens doses could be correlated with clinical outcomes to improve our understanding of radiation-induced cataracts. However, in terms of the open research questions, the priority for research to underpin effective radiation protection remains to understand the effects of LET and RBE, and the interaction of dose and dose rate with the other individual factors including genetic background, age and sex.

Data collection in routine clinical practice is not yet systematically archived for future use. Data collection for research requires constrained regulatory works and patient consents. It usually relies on retrospective initiatives, with loss of data quality and missing data issues (multiple imputation FDA (US Food and Drug Administration)-approved methods). The advantage of retrospective studies is that they allow for long-term follow-up (modelling). Prospective studies provide shorter term outcomes usually with less missing and better data quality, but may omit late toxicities, which are more likely irreversible and compromise quality of life. Dose-volume effects from clinical studies delivering higher doses to organs at risk of serial architecture or irradiate large volumes of organs at risk of parallel architecture are intensively investigated. Low dose effects and effects that have less significant impact on quality of life or can be surgically repaired (using lens implants) are less documented.

Future epidemiological studies of cataracts should obtain standardized systematic slit lamp (LOCS III) or Scheimpflug images of all study participants, with additional blinded independent review. This is particularly critical for studies based on different geographic localities (e.g., in some natural high background radiation studies) or dose-related different sources of examinees, where the blinding of the ophthalmologist performing the examination as to dose is not feasible, where different dose groups were examined at different times, or where there are changes in observers over time.

Better characterization of cataracts with the LOCS III after irradiation in human populations and in experimental animals may help to further fill gaps in the understanding radiation induced cataracts and the mechanisms of radiation-induced cataracts. More studies are needed to inform guideline-based recommendations for long-term follow-up for radiogenic cataract, combined with registered dose and volume data for the lens and the eye from the treatment planning system. Long-term observation of patients who received radiotherapy for orbito-ocular/CNS/head and neck will also be needed to prospectively collect data in radiogenic cataract.

It would also be relevant to take into account in future research different types of studies. To investigate the influence on development of tissues and organs in children treated with radiotherapy (retrospectively and prospectively) for cancer, to elucidate the developmental changes of the lens in children compared to the lens of the eyes of adults (probably differences in latency times will come across and also differences of total doses in protocols of children and adults of CNS tumours). Accuracy of calculating low doses in TPS (particularly when the target area is more distant from the lens) and consideration of low doses of radiology procedures in children and adults also seem to be important fields of investigations.

Classifications of radiation effects either into tissue reactions or stochastic effects are pragmatic categories for radiation protection purposes and are not necessarily able to fully reflect the biological complexities (Hamada and Fujimichi, 2014, Cléro et al., 2019). ICRP and NCRP have both classified radiation cataracts as a tissue reaction, but also discussed the potential stochastic nature of cataractogenesis (ICRP, 2012; NCRP, 2016; Dauer et al., 2017). Currently, ICRP recommends a threshold of 0.5 Gy independent of dose rate, but NCRP does not recommend any dose threshold because of uncertainty in epidemiological studies (ICRP, 2012; NCRP, 2016; Dauer et al., 2017). Epidemiological studies tend to show that a dose threshold becomes less evident with longer follow-up, e.g., “early onset” cataracts (e.g., those manifested within a decade after radiation exposure) with threshold vs “late onset” cataracts (e.g., those manifested decades after radiation exposure) without threshold (Hamada and Fujimichi, 2015; Hamada et al., 2020). There is also emerging evidence for the involvement of tumour-related factors in cataractogenesis (Hamada and Fujimichi, 2015; Hamada et al., 2020). These suggest the stochastic nature of cataractogenesis. To help inform whether cataract is a tissue reaction, a stochastic effect or both, more mechanistic studies are clearly needed, e.g., to test whether an irradiated single lens stem cell can form a cloudy lentoid body (Hamada, 2014).

The ICRP 2011 Statement and subsequent Publication 118 (ICRP, 2012) stimulated interest in radiation cataracts, leading to an increase in the body of epidemiological and biological evidence. Upon radiation exposure of the lens of the eye, other ocular structures also receive radiation. It is therefore important to assess the risk not only for cataracts, but also for other major causes of visual impairments, such as glaucoma and diabetic retinopathy (Hamada et al., 2020). Secondary glaucoma following radiation therapy at fractionated, high dose (e.g., >40 Gy) has long been recognized (Hamada et al., 2019), but a significantly increased radiation risk has recently been found in atomic bomb survivors for normal-tension glaucoma (a subtype of primary open-angle glaucoma), but not for other types of primary glaucoma (Kiuchi et al., 2013, 2019). Risk of primary glaucoma and primary open-angle glaucoma was not significant in Mayak workers (Bragin et al., 2019), neither was radiation risk of self-reported glaucoma in aggregate in the USRT cohort (Little et al., 2018b). Risk of normal-tension glaucoma has thus far been evaluated only in atomic bomb survivors, and this is also the case for diabetic retinopathy (Minamoto et al., 2004). These warrant more extensive studies for confirmation in various exposed cohorts, and such studies will be useful not only for radiation protection, but also for a deeper understanding of ocular complications following radiation therapy.

The effect of ionizing radiation on the lens also needs to be studied in the context of the wider, systemic effects, including in the retina, brain and other organs (LDLensRad, 2020) and as such cataract is recommended to be studied as part of larger scale programs focused on multiple radiation health effects.

6. Conclusion

The 2011 ICRP statement on tissue reactions (ICRP, 2012) stimulated the resurgence of interest in radiogenic cataracts. This led to recent developments in epidemiological, clinical and biological studies as

reviewed here. Nevertheless, gaps remain and continued studies are clearly needed, contributing better knowledge for radiation protection of workers and public, also for estimating and managing ocular complications in radiotherapy patients.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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