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EPTN consensus

Radiation dose constraints for organs at risk in neuro-oncology; the European Particle Therapy Network consensus



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Purpose: For unbiased comparison of different radiation modalities and techniques, consensus on delin-eation of radiation sensitive organs at risk (OARs) and on their dose constraints is warranted. Following the publication of a digital, online atlas for OAR delineation in neuro-oncology by the same group, we assessed the brain OAR-dose constraints in a follow-up study.

Methods: We performed a comprehensive search to identify the current papers on OAR dose constraints for normofractionated photon and particle therapy in PubMed, Ovid Medline, Cochrane Library, Embase and Web of Science. Moreover, the included articles’ reference lists were cross-checked for potential studies that met the inclusion criteria. Consensus was reached among 20 radiation oncology experts in the field of neuro-oncology.

Results: For the OARs published in the neuro-oncology literature, we summarized the available literature and recommended dose constraints associated with certain levels of normal tissue complication proba-bility (NTCP) according to the recent ICRU recommendations. For those OARs with lacking or insufficient NTCP data, a proposal for effective and efficient data collection is given.

Conclusion: The use of the European Particle Therapy Network-consensus OAR dose constraints summa-rized in this article is recommended for the model-based approach comparing photon and proton beam irradiation as well as for prospective clinical trials including novel radiation techniques and/or modalities.

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The field of radiotherapy is rapidly evolving with new tech-niques, e.g., MR-linac, and beam modalities, i.e., protons and carbon ions, entering the scene of image-guided high precision treatment. These innovations aim at increasing the tumour control probability

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| M. Lambrecht et al. / Radiotherapy and Oncology 128 (2018) 26–36 | 27 |

(TCP) while maintaining or reducing the normal tissue complica-tion probability (NTCP). For comparison of the latter, ideally, con-sensus on (1) the delineation of the organs at risk (OARs), on (2) the tolerable radiation dose to be administered to the OARs, and on (3) the outcome reporting measure, i.e., uniform follow-up tim-ing, patient questionnaires and content of the follow-up, should exist.

Regarding the first pre-requisite, Eekers et al. [[1,2]](#page9) recently published a digital, online atlas for OAR delineation in neuro-oncology on behalf of the task group ‘‘European Particle Therapy Network” (EPTN) of ESTRO. Addressing the second required condi-tion, it has been a while since the recommendations by Emami et al. [[3]](#page9) and the QUANTEC series [[4–7]](#page9) were published. In an attempt to reach the ideal conditions for comparison, we therefore summarize the OAR’s distinct radiation induced toxicities and the recommended dose constraints for conventionally fractionated radiotherapy.

Moreover, we identified gaps of knowledge that need to be filled, preferably in a prospective multi-centre effort, to fully exploit the potential of highly conformal radiotherapy. Of note, this summary of the literature does not explicitly cover hypofraction-ated / ablative regimens, carbon ion radiotherapy, re-irradiation, or paediatric data.

Material and methods

For each of the OAR described in the EPTN delineation consen-sus paper a dose constraint was sought for and the available data summarized [[1]](#page9). Published manuscripts were identified through a PubMed search using combinations of (‘‘radiotherapy” or ‘‘radia-tion therapy” or ‘‘radiation-induced”) and ‘‘xerophthalmia”; ‘‘dry eye syndrome”; ‘‘keratoconjunctivitis”; ‘‘retinopathy”; ‘‘cataracts”; ‘‘optic neuropathy”; ‘‘vision loss”; ‘‘hemianopsia”; ‘‘hearing loss”; ‘‘tinnitus”; ‘‘vertigo”; ‘‘hypopituitarism”; ‘‘neurocognition”; ‘‘ra-dionecrosis”; ‘‘Temporal lobe necrosis”; ‘‘brain stem toxicity”; ‘‘hippocampus”; ‘‘cerebellum”; ‘‘alopecia”. Those manuscripts available in English or French, containing data on adult patients obtained from primary conventionally fractionated photon and proton radiotherapy, and describing a dose–toxicity relationship were included in this recommendation. Papers on re-irradiation, hypofractionation, carbon ion therapy and stereotactic ablative radiotherapy were omitted.

Relevant papers were summarized and put into [Supplementary](#page9) [Tables (I-X)](#page9).

The relevant quantitative analyses of normal tissue effect in the clinic (QUANTEC) papers were used for reference when applicable as was the paper by Emami et al. [[3–7]](#page9).

Table 1

The literature was then reviewed by 20 Radiation Oncology experts in the field of neuro oncology and a consensus was reached as depicted in [Table 1](#page9) (see [Fig. 1](#page9)). The units of all dose constraints are given in Gy regardless of the reported unit in the analysed data. Doses were recalculated to equivalent dose in 2 Gy-fractions (EQD2) using the formula:

EQD2 ¼ Dðd þ a=bÞ with D : the total dose and d : the dose per fraction

ð2 þ a=bÞ

Results

Orbital structures

Radiotherapy of central nervous system (CNS) tumours often results in intentional or incidental irradiation of the different orbi-tal structures. This gives rise to a wide variety of acute and late tox-icities ranging from transient erythema of the peri-orbital skin to permanent blindness. The complex anatomy and physiology of the eye make it a challenging task to give a full and detailed description of all toxicities, and literature on many of them is scarce.

Lacrimal gland

The lacrimal gland system includes the main lacrimal gland, accessory lacrimal glands and the lacrimal duct system. This sys-tem is crucial for the production of tears, however, other struc-tures, such as Meibomian glands or the conjunctival goblet cells also contribute to the production of an adequate tear film. Radia-tion injury to any of these structures might result in xerophthalmia or the so-called dry eye syndrome (DES) and the exact contribution of the individual components is difficult to establish [[8–10]](#page9). DES typically develops between 1 month and 3 years after irradiation, depending on the total dose and fractionation [[9,11]](#page9).

In the common terminology criteria for adverse events (CTCAE) version 4.0 three grades of xerophthalmia are identified ranging from mild symptoms up to a decrease in visual acuity (<20/40); limiting self-care activities of daily life (ADL) [[12]](#page9). DES can lead to damage of the conjunctival and corneal epithelium (keratocon-junctivitis sicca), which causes pain, foreign body sensation, photo-phobia, corneal ulceration, and even perforation [[13]](#page9).

Several retrospective series have demonstrated that the risk of atrophy and fibrosis of the lacrimal gland increases sharply with the delivered dose ([Supplementary Table I](#page9)) [[9,11,14–16]](#page9). Although the exact clinical endpoints in these series are not always clearly defined, they agree on a sigmoidal dose–response curve for DES with a negligible risk at absolute maximum doses (Dmax) < 30 Gy,

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|  |  |  |  |  |
| Organ | a/b (Gy) | Dose constraint EQD2 | Toxicity |  |
| Brain [[7,86–89]](#page9) | 2 | V60 Gy 3 cc | Symptomatic brain necrosis |  |
| Brainstem [[52,92–100]](#page9) | 2 | Surface D0.03 cc 60 Gy | Permanent cranial neuropathy or necrosis |  |
|  |  | Interior D0.03 cc 54 Gy |  |  |
| Chiasm & Optic nerve [[23,48–54]](#page9) | 2 | D0.03 cc 55 Gy | Optic neuropathy |  |
| Cochlea [[57–60,64–66]](#page9) | 3 | Dmean 45 Gy | Hearing loss |  |
| Cornea [[13,21]](#page9) | 3 | Dmean 32 Gy | Tinnitus |  |
| D0.03 cc 50 Gy | Erosion/ulceration |  |
| Hippocampus [[107,108]](#page9) | 2 | D40% 7.3 Gy | Memory loss |  |
| Lacrimal gland [[9,11,14–16]](#page9) | 3 | Dmean 25 Gy | Keratoconjunctivitis sicca |  |
| Lens [[36,37]](#page9) | 1 | D0.03 cc 10 Gy | Cataract |  |
| Pituitary [[66,76,79,80]](#page9) | 2 | Dmean 45 Gy | Panhypopituitarism |  |
| Retina [[13,23,26,31]](#page9) | 3 | Dmean 20 Gy | Growth hormone deficiency |  |
| D0.03 cc 45 Gy | Loss of vision |  |
| Skin [[113]](#page9) | 2 | D0.03 cc 25 Gy | Permanent alopecia |  |

Abbreviations: EQD2 = equivalent dose in 2 Gy per fraction; D3 cc = dose to 3 cc of structure/organ; D0.03 cc = near maximum dose to 0.3 cc of structure/organ; Dmean = mean dose; D40% = mean dose to 40% of the volume of both hippocampi.

28 Neuro-Oncology organs at risk dose constraints

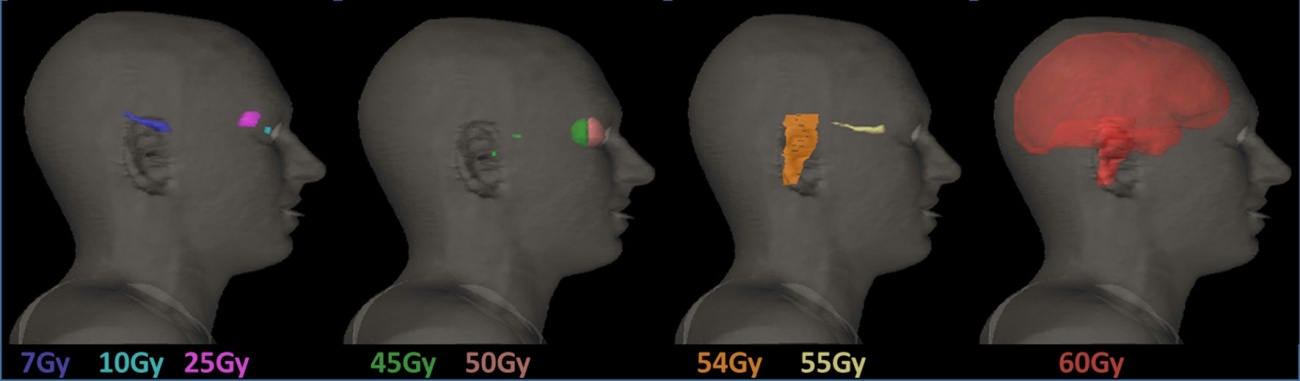


Fig. 1. A 3D representation of the OARs and the recommended corresponding dose constraints [[1]](#page9): hippocampus (purple), lenses (light blue), lacrima gland (magenta), pituitary (green), cochlea (green), cornea (pink), brainstem interior (orange), chiasm (yellow), optic nerve (yellow), brainstem surface (red), brian (red). All doses are given as maximum dose to 0.03 cc of the OAR volume (D0.03cc), except for the dose to hippocampus, which is the D40%, and the pituitary gland and cochlea, which are mean doses

(Dmean).

with a steeply increasing risk >40 Gy and a 100% rate of severe dry eye with Dmax > 57–60 Gy [[17,18]](#page9).

The EPTN consensus group therefore proposes that if possible, the mean dose (Dmean) to the lacrimal gland should not exceed 25 Gy for a risk for DES (>grade 1) less than 5%. No data were found on an a/b ratio for the lacrimal gland and late dry eye syndrome, therefore we suggest to assume an a/b ratio of 3 Gy for late toxicity similar to that of the parotid gland [[19]](#page9).

Cornea

The cornea’s main functions are refraction of the light and pro-tection, and even slight alterations of its shape can result in decreased visual acuity. Corneal complications may arise sec-ondary to the loss of the tear film (keratitis sicca) or resulting from direct injury to the corneal surface epithelium and the deeper lay-ers of the cornea. Direct radiation induced changes originate from the disruption of the mitotic activity in these layers and do not arise from the avascular cornea.

In CTCAE v4.0 keratitis is defined as a disorder characterized by an inflammation of the cornea with severity ranging from mild inflammation to perforation and complete blindness [[12]](#page9).

Even though accurate dose–volume parameters are scarce, a dose–toxicity relationship has been described in several retrospec-tive series [[13,18,20,21]](#page9). In one retrospective analysis corneal com-plications were evaluated after orbital radiotherapy for lacrimal gland malignancies [[21]](#page9). In this series patients were treated up to cumulative doses of 50–60 Gy to the entire orbit. All patients developed an acute radiation keratoconjunctivitis, 54% of the patients had chronic corneal epithelial defects and 13% developed a corneal perforation. These perforations generally occurred within 3 years of radiotherapy. While there are several limitations to this analysis, it confirms that high dose radiotherapy can have serious consequences on the ocular surface (see [Supplementary Table II](#page9)). We therefore propose D0.03 cc to the cornea not to exceed 50 Gy if the orbit is not part of the target volume. Again, we propose an a/b ratio of 3 Gy for late toxicity in absence of solid data.

Retina

The retina is the third and inner coating of the eye and is essen-tial in visual perception. In embryogenesis both the retina and the optic nerve originate from the diencephalon and should therefore be considered as part of the central nervous system.

Retinopathy is characterized by slowly progressive microangio-pathic decompensation with a focal loss of capillary endothelial cells and pericytes [[18]](#page9). Clinically, radiation retinopathy includes microaneurysms, cotton wool pots, capillary dilation, telangiec-tasia and capillary closure, all histopathologically resembling dia-betic retinopathy [[22,23]](#page9). The latency period is typically between

6 months and 3 years, although longer periods have been described [[18,24–26]](#page9). The CTCAE v4.0 defines retinopathy using 4 grades ranging from asymptomatic up to grade 4 blindness (20/200 or worse) in the affected eye [[12]](#page9). The pathogenesis of radiation induced retinopathy is dependent on the total dose, the fraction size, number of fractions, concurrent chemotherapy and coexisting morbidity, e.g., diabetes, hypertension [[23,27–29]](#page9). A selected number of studies reported on the dose–toxicity relation-ship for retinopathy and are depicted in [Supplementary Table III](#page9) [[13,26,30,31]](#page9).

The risk of retinopathy increases steeply with Dmax exceeding 45–50 Gy in 5 weeks. Emami et al. [[3]](#page9) estimated the 5% severe complication rate in 5 years (TD5/5) of the retina, i.e., visual loss, to be 45 Gy and the 50% severe complication rate at 5 years (TD50/5) to be 65 Gy.

We therefore propose the D0.03 cc to the retina to be kept below 45 Gy. Again, we propose an a/b ratio of 3 Gy for late toxicity in absence of solid data [[19]](#page9).

Lens of the eye

The lens is a biconvex structure in the eye that helps to refract light. Any stimulus causing posterior migration and proliferation of the lens epithelial cells reduces the lens clarity, causing a cataract, and often results in some degree of visual loss [[32]](#page9). The CTCAE v4.0 distinguishes 4 grades of cataract based on visual acuity ranging from asymptomatic (grade 1) to complete blindness (20/200 or worse) in the affected eye (grade 4) [[12]](#page9).

Irradiating the lens can lead to cataract formation. The initial insult consists of damage to the germinative zone of the lens epithelium, which leads to extensive cell death, compensatory mitosis, and the generation of the so-called ‘Wedl’ cells [[18,27,32–35]](#page9). The severity and delay until onset of radiation-induced cataracts is dose-dependent, however, the accurate threshold is poorly understood. Several retrospective studies have investigated the occurrence of cataract after irradiation [[36,37]](#page9) ([Supplementary Table IV](#page9)).

While Emami et al. [[3]](#page9) estimated the TD5/5 of the lens to be 10 Gy and the TD50/5 to be 18 Gy, other series have demonstrated that even lower doses can result in the occurrence of cataract [[38,39]](#page9). Recently, the International Commission on Radiological Protection (ICRP) defined 0.5 Gy as the new threshold dose for lens opacities, which is based on the data from population based stud-ies in diagnostic imaging and occupational exposure [[40,41]](#page9).

Based on these data, the EPTN consensus panel suggests the dose to the lens to be kept as low as reasonably achievable (ALARA) and should not surpass D0.03 cc of 10 Gy. Conversely, as replace-ment of a damaged lens is a relatively harmless procedure nowa-days, target volume coverage should not be compromised in an

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| M. Lambrecht et al. / Radiotherapy and Oncology 128 (2018) 26–36 | 29 |

attempt to spare the lenses. Since the limited data on an a/b ratio for the lens suggests values of 0.76–1.2 Gy, we propose to use an a/ b ratio of 1 Gy for late toxicity [[19,42,43]](#page9).

Optic nerve

First described in 1956, radiation induced optic neuropathy (RION) is a rare yet disabling condition with a potentially devastat-ing impact on the vision of the affected eye [[44]](#page9). The pathogenesis of RION is not fully understood, but it is often considered to be delayed radionecrosis in the CNS and thus the effect of radiation on the optic nerve appears to be both vascular and neuropathic in nature [[23,32,45,46]](#page9). It usually presents with painless, rapid visual loss and can occur between 3 months and 8 years after treat-ment, with a peak between 1 and 1.5 years [[45,47]](#page9). It is graded according to the CTCAE v4.0 as grade 1 being asymptomatic, grade 2 limiting vision of the affected eye (20/40 or better), grade 3 lim-iting vision in the affected eye (worse than 20/40) but better than 20/200 or grade 4, blindness which is 20/200 or worse in the affected eye [[12]](#page9).

Complication data for RION have been reported for photons and protons, and following irradiation for several indications. A selected group of studies is depicted in [Supplementary Table V](#page9) [[23,48–54]](#page9). Emami et al. [[3]](#page9) suggested a TD5/5 of 50 Gy and a TD50/5 of 65 Gy. However, in the QUANTEC analysis this was deemed inaccurate after review of the literature concluding that the incidence of RION was unusual for a Dmax < 55 Gy using con-ventional fractionation [[5]](#page9). The incidence of RION increased between 55 and 60 Gy (3–7%) and was substantial (>7–20%) for Dmax > 60 Gy, although it should be noted that in some studies even at these high doses no clinically significant RION was observed. For particles most investigators also confirmed that the incidence of RION was low for a Dmax < 54 Gy (RBE).

Within the EPTN group we therefore support the use of D0.03 55 Gy for the optic nerve and suggest to use an a/b ratio of 2 Gy for late toxicity [[19]](#page9).

Optic chiasm

In the optic chiasm, the optic nerve fibres from the nasal sides of each retina cross to the opposite side of the brain. Toxicity of the optic chiasm is graded similarly as in RION. However, instead of unilateral visual loss, it typically presents as a bitemporal hemi-anopsia or even total blindness. As pathophysiology is similar to RION, the same principles apply, and we suggest to use the same constraint, i.e., D0.03 cc 55 Gy and a/b ratio of 2 Gy [[19]](#page9). Specific caution should be taken in patients, in whom the optic chiasm has been manipulated, e.g., during neurosurgery.

Inner ear

The inner ear, also called labyrinth of the ear, is that part of the ear that contains the organs responsible for hearing (cochlea) and balance (vestibule and semi-circular canal). The bony labyrinth is divided into three sections: the vestibule, the semi-circular canals and the cochlea. Each section of the bony labyrinth contains peri-lymph and a part of the membranous labyrinth. The vestibule con-tains the utriculus and sacculus, the semi-circular canals contain a semi-circular duct, and the cochlea contains the cochlear duct.

Cochlea

Sensorineural hearing loss (SNHL) is the most important radiotherapy-induced complication of the inner ear, with up to 44% of patients reporting hearing loss after radiotherapy when one of the radiation beams passes the inner ear [[55,56]](#page9). Consis-tently throughout the literature, the high frequencies appear to be more affected than lower frequencies, and this is dose-dependent [[56–60]](#page9).

Hearing loss can be graded according to the CTCAE v4.0 [[12]](#page9). While early hearing loss during conventionally fractionated radio-therapy is usually transient and commonly due to serous otitis media, true SNHL classically occurs with a latency period of 1.5– 5 years after radiotherapy and is irreversible [[55,57,61,62]](#page9). Histopathologically it results from loss of cochlear primary sensory cells and/or damage to the spiral ganglion or cochlear nerve [[63]](#page9).

The relationship between the dose to the cochlea and SNHL has been extensively investigated. Emami et al. [[3]](#page9) identified a TD 5/5 of 60 Gy and TD 50/5 of 70 Gy for sensorineural or vestibular dam-age. However, based on more recent dose–volume data the QUAN-TEC consensus paper suggested the Dmean to the cochlea 45 Gy or even more conservatively 35 Gy [[57–60,64,65]](#page9).

The recent publication by De Marzi et al. [[66]](#page9), who investigated 140 patients treated with photon and proton therapy for base of skull tumours, reported on a dose–response model for the inner ear. After qualitative correlation of Dmean with auditory toxicity (scored as grade 1–2 hearing loss, based on CTCAE v4.0), no signif-icant cut-off value could be determined. Considering the size of the organ, they calculated the generalized equivalent uniform dose and found it to be a predictive factor for late complications. For the cochlea and inner ear, a tolerance uniform dose delivered to the whole organ for 50% complication rate (TD 50) of 56 Gy (95%CI 53.6–58.5) and 53.6 Gy (95%CI 51.8–55.4 Gy) was reported with slope of the response curve at TD50 (c50) of 2.8 for both and an a-value of 1.2 and 0.1, respectively. These values are in the same range as the QUANTEC data.

The EPTN consensus panel proposes the Dmean to the cochlea to be kept to 45 Gy. Since, there is no clear threshold dose for hear-ing loss after radiotherapy, the ALARA principle applies. Again, we propose an a/b ratio of 3 Gy for late toxicity in absence of solid data.

Besides SNHL, tinnitus is also a potential side effect from ioniz-ing radiotherapy. CTCAE v4.0 defines tinnitus as a disorder charac-terized by a perception of noise or ringing in the ears, and has 3 grades, based on the impact of the tinnitus on the activities of daily life [[12]](#page9). Limited data are available on the effect of dose on the occurrence of tinnitus and it is probably under-reported. As a result, there is no QUANTEC guideline for the cochlea to avoid tin-nitus. Lee et al. [[67]](#page9) investigated the incidence of tinnitus after intensity modulated radiation therapy (IMRT) for head and neck cancer patients and noticed that 11.6% of developed grade >2 tin-nitus, consistent with other reports in the literature [[68,69]](#page9). Based on a logistic and Lyman–Kutcher NTCP model derived from their results, Dmean to the cochlea should be kept <32 Gy in order to keep the incidence of grade >2 tinnitus <20% using IMRT [[67]](#page9). External validation of this model is thus far lacking. In the absence of data, we suggest to use a traditional a/b ratio of 3 Gy for late toxicity [[19]](#page9).

Vestibulum and semi-circular canal

Vestibular toxicity can be graded according to the CTCAE v4.0 as vertigo or more generally as a vestibular disorder [[12]](#page9), even though occasionally acute nausea following radiotherapy is reported instead.

There is very little data concerning vestibular toxicity related to radiotherapy. Gabriele et al. [[70]](#page9) investigated the vestibular func-tion in 25 head and neck cancer patients. Eleven of these patients showed vestibular abnormalities on electronystagmography, but only three reported vertigo. More recently Lee et al. [[71]](#page9) analysed 49 consecutive nasopharyngeal carcinoma patients treated with radiotherapy alone, of whom six reported nausea and no patient dizziness or vertigo. Using multivariate analysis, the authors iden-tified a correlation between the volume of the vestibules receiving 40 Gy (V40 Gy) and incidence of nausea. Again, external validation is awaited. Prospective collection of dose–volume data and accurate