Radiation dose constraints for organs at risk in neuro-oncology

Radiotherapy and Oncology 128 (2018) 26–36

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

EPTN consensus

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

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ARTICLE INFO

Article history:
Received 7 February 2018
Received in revised form 16 April 2018
Accepted 1 May 2018
Available online 17 May 2018

Keywords:
Dose constraints
Organs at risk
Particle therapy
European Particle Therapy Network

ABSTRACT

Purpose: For unbiased comparison of different radiation modalities and techniques, consensus on delineation 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 probability (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 summarized 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.

The field of radiotherapy is rapidly evolving with new techniques, *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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https://doi.org/10.1016/j.radonc.2018.05.001
0167-8140/

(TCP) while maintaining or reducing the normal tissue complication probability (NTCP). For comparison of the latter, ideally, consensus 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 timing, patient questionnaires and content of the follow-up, should exist.

Regarding the first pre-requisite, Eekers et al. [1,2] 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 condition, it has been a while since the recommendations by Emami et al. [3] and the QUANTEC series [4–7] 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 hypofractionated / ablative regimens, carbon ion radiotherapy, re-irradiation, or paediatric data.

Material and methods

For each of the OAR described in the EPTN delineation consensus paper a dose constraint was sought for and the available data summarized [1]. Published manuscripts were identified through a PubMed search using combinations of ("radiotherapy" or "radiation therapy" or "radiation-induced") and "xerophthalmia"; "dry eye syndrome"; "keratoconjunctivitis"; "retinopathy"; "cataracts"; "optic neuropathy"; "vision loss"; "hemianopsia"; "hearing loss"; "tinnitus"; "vertigo"; "hypopituitarism"; "neurocognition"; "radionecrosis"; "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 Tables (I-X).

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].

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 (see Fig. 1). 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:

$$EQD2 = \frac{D(d+\alpha/\beta)}{(2+\alpha/\beta)} \text{ with D : the total dose and d : the dose per fraction}$$

Results

Orbital structures

Radiotherapy of central nervous system (CNS) tumours often results in intentional or incidental irradiation of the different orbital structures. This gives rise to a wide variety of acute and late toxicities 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 system is crucial for the production of tears, however, other structures, such as Meibomian glands or the conjunctival goblet cells also contribute to the production of an adequate tear film. Radiation 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]. DES typically develops between 1 month and 3 years after irradiation, depending on the total dose and fractionation [9,11].

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]. DES can lead to damage of the conjunctival and corneal epithelium (*keratoconjunctivitis sicca*), which causes pain, foreign body sensation, photophobia, corneal ulceration, and even perforation [13].

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) [9,11,14–16]. 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 (D_{max}) < 30 Gy,

Table 1

Organ	α/β (Gy)	Dose constraint EQD2	Toxicity
Brain [7,86–89]	2	$V_{60\ Gy} \leq 3$ cc	Symptomatic brain necrosis
Brainstem [52,92–100]	2	Surface $D_{0.03\ cc} \leq 60$ Gy Interior $D_{0.03\ cc} \leq 54$ Gy	Permanent cranial neuropathy or necrosis
Chiasm & Optic nerve [23,48–54]	2	$D_{0.03\ cc} \leq 55$ Gy	Optic neuropathy
Cochlea [57–60,64–66]	3	$D_{mean} \leq 45$ Gy $D_{mean} \leq 32$ Gy	Hearing loss Tinnitus
Cornea [13,21]	3	$D_{0.03\ cc} \leq 50$ Gy	Erosion/ulceration
Hippocampus [107,108]	2	$D_{40\%} \leq 7.3$ Gy	Memory loss
Lacrimal gland [9,11,14–16]	3	$D_{mean} \leq 25$ Gy	Keratoconjunctivitis sicca
Lens [36,37]	1	$D_{0.03\ cc} \leq 10$ Gy	Cataract
Pituitary [66,76,79,80]	2	$D_{mean} \leq 45$ Gy $D_{mean} \leq 20$ Gy	Panhypopituitarism Growth hormone deficiency
Retina [13,23,26,31]	3	$D_{0.03\ cc} \leq 45$ Gy	Loss of vision
Skin [113]	2	$D_{0.03\ cc} \leq 25$ Gy	Permanent alopecia

Abbreviations: EQD2 = equivalent dose in 2 Gy per fraction; $D_{3\ cc}$ = dose to 3 cc of structure/organ; $D_{0.03\ cc}$ = near maximum dose to 0.3 cc of structure/organ; D_{mean} = mean dose; $D_{40\%}$ = mean dose to 40% of the volume of both hippocampi.

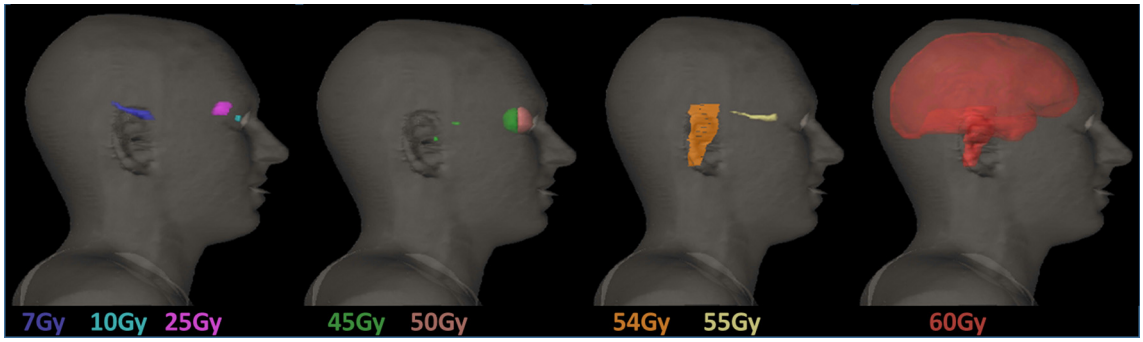

Fig. 1. A 3D representation of the OARs and the recommended corresponding dose constraints [1]: hippocampus (purple), lenses (light blue), lacrima gland (magenta), pituitary (green), cochlea (green), cornea (pink), brainstem interior (orange), chiasm (yellow), optic nerve (yellow), brainstem surface (red), brian (red). All doses are given as maximum dose to 0.03 cc of the OAR volume ($D_{0.03cc}$), except for the dose to hippocampus, which is the $D_{40\%}$, and the pituitary gland and cochlea, which are mean doses (D_{mean}).

with a steeply increasing risk >40 Gy and a 100% rate of severe dry eye with D_{max} > 57–60 Gy [17,18].

The EPTN consensus group therefore proposes that if possible, the mean dose (D_{mean}) 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 α/β ratio for the lacrimal gland and late dry eye syndrome, therefore we suggest to assume an α/β ratio of 3 Gy for late toxicity similar to that of the parotid gland [19].

Cornea

The cornea's main functions are refraction of the light and protection, and even slight alterations of its shape can result in decreased visual acuity. Corneal complications may arise secondary to the loss of the tear film (*keratitis sicca*) or resulting from direct injury to the corneal surface epithelium and the deeper layers 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].

Even though accurate dose–volume parameters are scarce, a dose–toxicity relationship has been described in several retrospective series [13,18,20,21]. In one retrospective analysis corneal complications were evaluated after orbital radiotherapy for lacrimal gland malignancies [21]. 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). We therefore propose $D_{0.03\ cc}$ to the cornea not to exceed 50 Gy if the orbit is not part of the target volume. Again, we propose an α/β 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 essential 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 microangiopathic decompensation with a focal loss of capillary endothelial cells and pericytes [18]. Clinically, radiation retinopathy includes microaneurysms, cotton wool pots, capillary dilation, telangiectasia and capillary closure, all histopathologically resembling diabetic retinopathy [22,23]. The latency period is typically between 6 months and 3 years, although longer periods have been described [18,24–26]. 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]. 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]. A selected number of studies reported on the dose–toxicity relationship for retinopathy and are depicted in Supplementary Table III [13,26,30,31].

The risk of retinopathy increases steeply with D_{max} exceeding 45–50 Gy in 5 weeks. Emami et al. [3] 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 $D_{0.03\ cc}$ to the retina to be kept below 45 Gy. Again, we propose an α/β ratio of 3 Gy for late toxicity in absence of solid data [19].

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]. 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].

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]. 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] (Supplementary Table IV).

While Emami et al. [3] 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]. 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 studies in diagnostic imaging and occupational exposure [40,41].

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 $D_{0.03\ cc}$ of 10 Gy. Conversely, as replacement of a damaged lens is a relatively harmless procedure nowadays, target volume coverage should not be compromised in an

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

Optic nerve

First described in 1956, radiation induced optic neuropathy (RION) is a rare yet disabling condition with a potentially devastating impact on the vision of the affected eye [44]. 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]. It usually presents with painless, rapid visual loss and can occur between 3 months and 8 years after treatment, with a peak between 1 and 1.5 years [45,47]. 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 limiting 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].

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 [23,48–54]. Emami et al. [3] 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 D_{max} < 55 Gy using conventional fractionation [5]. The incidence of RION increased between 55 and 60 Gy (3–7%) and was substantial (>7–20%) for D_{max} > 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 D_{max} < 54 Gy (RBE).

Within the EPTN group we therefore support the use of $D_{0.03} \leq$ 55 Gy for the optic nerve and suggest to use an α/β ratio of 2 Gy for late toxicity [19].

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 hemianopsia or even total blindness. As pathophysiology is similar to RION, the same principles apply, and we suggest to use the same constraint, *i.e.*, $D_{0.03\ cc} \leq 55$ Gy and α/β ratio of 2 Gy [19]. 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 perilymph and a part of the membranous labyrinth. The vestibule contains 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]. Consistently throughout the literature, the high frequencies appear to be more affected than lower frequencies, and this is dose-dependent [56–60].

Hearing loss can be graded according to the CTCAE v4.0 [12]. While early hearing loss during conventionally fractionated radiotherapy 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]. Histopathologically it results from loss of cochlear primary sensory cells and/or damage to the spiral ganglion or cochlear nerve [63].

The relationship between the dose to the cochlea and SNHL has been extensively investigated. Emami et al. [3] identified a TD 5/5 of 60 Gy and TD 50/5 of 70 Gy for sensorineural or vestibular damage. However, based on more recent dose–volume data the QUANTEC consensus paper suggested the D_{mean} to the cochlea $\leq$45 Gy or even more conservatively $\leq$35 Gy [57–60,64,65].

The recent publication by De Marzi et al. [66], 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 D_{mean} with auditory toxicity (scored as grade 1–2 hearing loss, based on CTCAE v4.0), no significant 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 (γ50) 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 D_{mean} to the cochlea to be kept to $\leq$45 Gy. Since, there is no clear threshold dose for hearing loss after radiotherapy, the ALARA principle applies. Again, we propose an α/β ratio of 3 Gy for late toxicity in absence of solid data.

Besides SNHL, tinnitus is also a potential side effect from ionizing radiotherapy. CTCAE v4.0 defines tinnitus as a disorder characterized 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]. 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 tinnitus. Lee et al. [67] 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 tinnitus, consistent with other reports in the literature [68,69]. Based on a logistic and Lyman–Kutcher NTCP model derived from their results, D_{mean} to the cochlea should be kept <32 Gy in order to keep the incidence of grade >2 tinnitus <20% using IMRT [67]. External validation of this model is thus far lacking. In the absence of data, we suggest to use a traditional α/β ratio of 3 Gy for late toxicity [19].

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], 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] investigated the vestibular function 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] 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 identified a correlation between the volume of the vestibules receiving 40 Gy ($V_{40\ Gy}$) and incidence of nausea. Again, external validation is awaited. Prospective collection of dose–volume data and accurate

toxicity scoring is mandatory to identify dose–volume parameters in the nearby future. As such, EPTN cannot recommend any dose-constraint threshold for this OAR.

Pituitary gland/hypothalamus

The pituitary gland is an endocrine gland essential for the regulation of many physiological processes including growth, thyroid gland function, reproduction, and lactation. It is closely linked to the hypothalamus through the pituitary stalk. Dysfunction of this hypothalamic–pituitary axis is a common problem after radiotherapy of both brain and head and neck tumours and is associated with significant morbidity and even mortality [72–76]. Adequate management of radiation induced hypopituitarism is essential to optimize outcomes and improve quality of life in these patients [77]. The CTCAE v4.0 identifies several endocrine disorders, which may be associated with hypopituitarism, although clinically it can present with a large variety of non-specific symptoms and should always be in the differential diagnosis in the follow-up of patients treated with radiotherapy for head and neck or brain tumours [12]. Despite its high incidence, little information on the correlation between dose and dysfunction of the hypothalamic pituitary axis is available [74,78]. Relevant studies are depicted in Supplementary Table VI [66,76,79,80].

In children, Merchant et al. [81] described the decline in growth hormone (GH) levels after cranial radiotherapy by an exponential equation dependent on the radiation dose to the hypothalamus and the follow-up time interval, which was confirmed by Agha et al. [76] in an adult population. GH deficiency may occur after low doses (D_{mean} < 40 Gy) especially in patients whose hypothalamopituitary axis (HPA) was impaired by the presence of a tumour and/or previous surgery [78,82,83]. Deficiency of all anterior-pituitary hormones occurs mainly after high dose irradiation (D_{mean} > 60 Gy) in nasopharyngeal carcinoma or base of skull tumour patients (see Supplementary Table VI) [79,80,84]. There is a steep increase in the incidence of endocrinopathy at a D_{mean} or minimum dose (D_{min}) of 40–50 Gy. Only one study attempted to model the NTCP for the pituitary gland using the equivalent uniform dose and found a TD50 of approx. 60.5 Gy (95%CI: 59.1–62 Gy)[66].

Some preclinical studies suggest there may be a differential radiosensitivity between the hypothalamus and the pituitary gland [85]. One study by Pai et al. [80] found that doses below 20 Gy (RBE) to the hypothalamus were associated with endocrinopathies, while this association was only found for a D_{min} above 50 Gy (RBE) for the pituitary gland. Noteworthy, target volumes of most patients included in this analysis were located in the clivus and strict dose constraints were imposed on the optic chiasm resulting in a steep dose gradient between pituitary gland and hypothalamus. Larger dose variation and patient populations will be necessary to distinguish the individual contribution of each of these structures to HPA dysfunction. Until further data are available we propose to use the same dose constraint to both these structures.

The EPTN consensus panel proposes a $D_{mean} \leq 45$ Gy to the pituitary gland in the prevention of panhypopituitarism. Of course, if clinical context demands, higher doses may be justified. However, even at low doses deficiency of one of the hormonal axes might occur and a rigid endocrinological follow-up needs to be put in place, as adequate hormone replacement therapy is available and needs to be prescribed. Specific care is to be taken in patients treated for pituitary tumours or after surgery to this area, in which cases, lower tolerance doses should be employed [77,78]. There is currently no valuable data on the tolerance doses of the hypothalamus. As such, EPTN cannot recommend any dose-constraint threshold for the hypothalamus at this stage. Prospective and standardized reporting of dose and toxicity might help us to overcome this. In addition, there are no clear data on the α/β ratio of the pituitary gland or hypothalamus for the endpoint hypopituitarism, therefore we suggest to use an α/β ratio of 2 Gy for late toxicity.

Brain

Damage to the CNS is of considerable concern in the radiation treatment of brain tumours. However, evaluating cerebral toxicity is extremely difficult as we only begin to understand the intricate interplay between the different substructures in physiological conditions, let alone in pathological conditions. In this review two main long-term adverse effects will be evaluated mainly radionecrosis and neurocognition.

Brain

Despite its complexity, dose constraints to the brain and cerebrum are uniformly applied to the entire cerebral parenchyma without distinction between cortex, white matter and nuclei. Concerning radionecrosis, Emami et al. [3] reported a TD5/5 of 60 Gy, 50 Gy and 45 Gy and a TD50/5 of 75 Gy, 65 Gy and 60 Gy if 1/3, 2/3 or the entire brain, respectively, was irradiated up to that dose. These values appear to be too conservative in the 3D era, as the QUANTEC project found a dose–response relationship in the brain: the incidence of radionecrosis increases from 3% with a D_{max} < 60 Gy, to 5% at D_{max} = 72 Gy, and to 10% when D_{max} = 90 Gy, using an α/β = 3 Gy [4,7]. Following the QUANTEC data, several papers reported on the dose–volume relationship for temporal lobe necrosis using both photons and protons [86–89]. They all highlight the importance of the volume receiving a certain dose in the occurrence of brain necrosis. The results are depicted in Supplementary Table VII.

Based on these data, the EPTN consensus panel proposes to $V_{60\ Gy} \leq 3$ cc in $EQD2_2$. The α/β ratio for brain tissue is 2 Gy for radionecrosis [19].

Aside from radionecrosis, radiation induced white matter damage can also cause serious neurocognitive disturbances [90]. However, to our knowledge there is no clear dose–volume data available allowing us to selectively spare a specific part of the supratentorial brain. As such we cannot recommend any dose constraint threshold for brain and neurocognition, and thus the ALARA principle applies.

Brainstem

The brainstem consists of the medulla oblongata, pons and midbrain. It plays a crucial role as a relay between the body, the cerebellum and cerebrum, it gives rise to nine pairs of cranial nerves and plays an important role in the regulation of many vital functions. Damage to the brainstem is therefore a severe and potentially lethal complication and can present as a wide spectrum of clinical features depending on the location and the extent of the damage [91]. This of course has important implications for the dose constraints; unlike for several other OARs, no long-term toxicity should occur at the level of the brain stem. There are several recommendations based on the available literature and there seems to be a clear distinction between the dose constraints used for photons and protons [6,91]. An overview of some selected reports on planning constraints and toxicity are depicted in Supplementary Table VIII [52,92–100].

Historically, Emami et al. [3] defined the TD5/5 for necrosis of the brainstem as 50 Gy, 53 Gy and 60 Gy to the entire, 2/3 and 1/3 of the volume of the brainstem, respectively, and the TD50/5 of the entire brainstem was estimated at 65 Gy [101]. However, these values appear to be overly conservative considering the data available from recent retrospective analysis. It appears that the entire brainstem may be treated to 54 Gy using conventional

fractionation with limited risk of severe or permanent neurological effects, while small volumes of the brainstem may even be irradiated to D_{max} = 59 Gy. The risk appears to increase markedly for D_{max} > 64 Gy [6,102].

The consensus panel therefore suggests $D_{0.03\ cc} \leq 54$ Gy in $EQD2_2$, in particular to the interior to the brainstem. Whenever institutions opt to use higher doses, we propose that $D_{0.03\ cc}$ of the brainstem surface should be kept ≤60 Gy $EQD2_2$, which correlates with the absolute dose of 64 Gy RBE used in the proton literature for base of skull [96–100]. For both, the brain and brainstem, we assume an α/β ratio of 2 Gy for late CNS toxicity [19].

Hippocampus

One of the most elusive long-term toxicities related to radiotherapy of the brain is neurocognitive decline and memory impairment. It has become exceedingly important in the debate surrounding the use of more complex and expensive radiotherapy techniques, even though the exact pathophysiology is complex and poorly understood [103–105]. In the time of the QUANTEC project there was insufficient evidence to support the claim that partial brain radiotherapy in 2 Gy fractions causes neurocognitive decline [7]. This was partly due to insufficient outcome measurements as well as the lack of detailed brain dose–volume data. However, over the last decade there is a growing insight into the mechanisms behind neurocognitive disability after radiotherapy, particularly in respect to the hippocampi, which are instrumental in learning, memory and neurogenesis [103,106]. The seminal article by Gondi et al. [107] compared a control group with a historical group of patients treated for benign tumours or low grade gliomas. They found that if the $D_{40\%}$ of the bilateral hippocampi exceeded 7.3 Gy this was associated with a decrease in the WMS-WL delayed recall test at 18 months. Many studies are currently underway, investigating hippocampal avoidance in several clinical settings, however, we are still awaiting results. Imaging studies have revealed that doses exceeding 40 Gy resulted in a significant atrophy of the hippocampus (see Supplementary Table VIII) [108].

Based on these data it is somewhat preliminary to propose dose constraints to the hippocampus. If possible, the dose to the hippocampi should be kept ALARA and preferably the $D_{40\%}$ of both hippocampi combined should be kept below 7.3 Gy. Again, an α/β ratio of 2 Gy for late CNS toxicity.

Cerebellum

Classically, the cerebellum is known for its role in the regulation and coordination of movement posture and balance. Radionecrosis could thus have an important influence on these factors. For this outcome there is currently no data suggesting a different radiosensitivity of the cerebellar cortex or white matter, and thus the same constraints as those used in the brain are proposed.

Interestingly there is more and more evidence that the cerebellum is also involved in cognitive functions [109]. In paediatric patients with infratentorial ependymoma one report found a correlation between the infratentorial radiation dose and neurocognitive decline [110]. However, in adults this evidence is lacking and so to date no clear dose constraints can be defined for the anterior and posterior cerebellum.

Skin

Radiation to the scalp can give rise to several toxicities. Since the skin itself is rarely part of the target volume in primary brain tumours, temporary and permanent alopecia is the most important late toxicity after radiotherapy. Temporary alopecia can occur after very low doses, while permanent alopecia requires relatively higher doses to the skin [111,112]. Lawenda et al. [113] performed an depth dose–response analysis on permanent alopecia at >12 months in patients treated with photons for a primary CNS tumour. After multivariate analysis, only the follicle dose was significantly correlated to permanent alopecia. In the dose–response relationship the TD_{50} was estimated at 43 Gy EQD2 (95%CI 33–52) with a $\gamma 50$ slope of 0.9 (95% CI 0.3–1.4). Using this dose–response relationship, a follicle dose of 25 Gy is associated with <20% risk of permanent alopecia grade ≥3. In order to avoid this side effect a reduction of the dose to the hair follicles should be attempted.

The EPTN therefore suggests the $D_{0.03\ cc}$ of the skin should be kept ≤25 Gy to avoid permanent focal alopecia and consequently the $V_{25\ Gy}$ to the skin should be kept ALARA. The suggested α/β ratio for the skin is 2 Gy [19,113].

Discussion

Despite the increasing number of patients treated with radiotherapy for brain tumours, scarce precise information is available on the relationship between dose and toxicity of the central nervous system. In the past several efforts have already been undertaken to try and summarize the available evidence on the tolerance of normal tissues [3,4,101]. However, several relevant OARs, such as the lacrimal gland, the cornea, the vestibulum and semi-circular canals, the HPA, hippocampus, cerebellum and skin were not discussed in these papers. In addition, the increasing availability of highly conformal photon and proton therapy, the widespread use of image-guided and adaptive radiotherapy enable the radiotherapy community to deliver high doses to the target volume and selectively spare certain organs at risk. While dosimetrically these techniques might produce 'better' treatment plans, they do not always translate into clinical reality. In order to justify the use of these expensive treatments and make an accurate estimation of the benefit of one technique over the other, an objective estimation of the normal tissue complication rate is crucial [114,115]. Such a model-based approach allows us to compare different treatment strategies and select patients who will most likely benefit from a certain technique based on the difference in NTCP models between two techniques. These NTCP models need to incorporate both dosimetric and clinical factors and provide us with objective data on the superiority of one technique over the other [4,101,116]. However, the construction of these models requires a large amount of uniformly scored patient data. Consequently, for all OAR and toxicities described in the manuscript, such a multifactorial NTCP model is not available.

Therefore, one of the key goals of the EPTN is to try and set-up a framework for international cooperation within the radiotherapy community, which allows the introduction of a uniform, consensus-based means for data collection. In a first consensus paper, relevant OARs in neuro-oncology were selected and delineation guidelines were given [1]. This manuscript aimed to review the available evidence on the dose–toxicity relationship for the previously defined OAR. While we succeeded in producing a consensus table on dose constraints (see Table 1), there are several shortcomings of the data presented here.

First, as is clear from this review, the vast majority of dose constraints rely on the reports from retrospective, single centre studies. Furthermore, in most of the cases no accurate dose–volume analysis could be done as the majority of patients within each series is treated for a variety of primary tumours with a variety of doses and fractionation schedules, using old radiotherapy techniques, and without uniform contouring of the OARs. We can therefore only estimate the dose delivered to a certain OAR. Also, in the majority of cases absolute doses are reported, with little to no information on the exact fractionation, making it impossible to recalculate the doses to EQD2. For the consensus table we aimed to define all D_{max} constraints in EQD2, using the linear quadratic

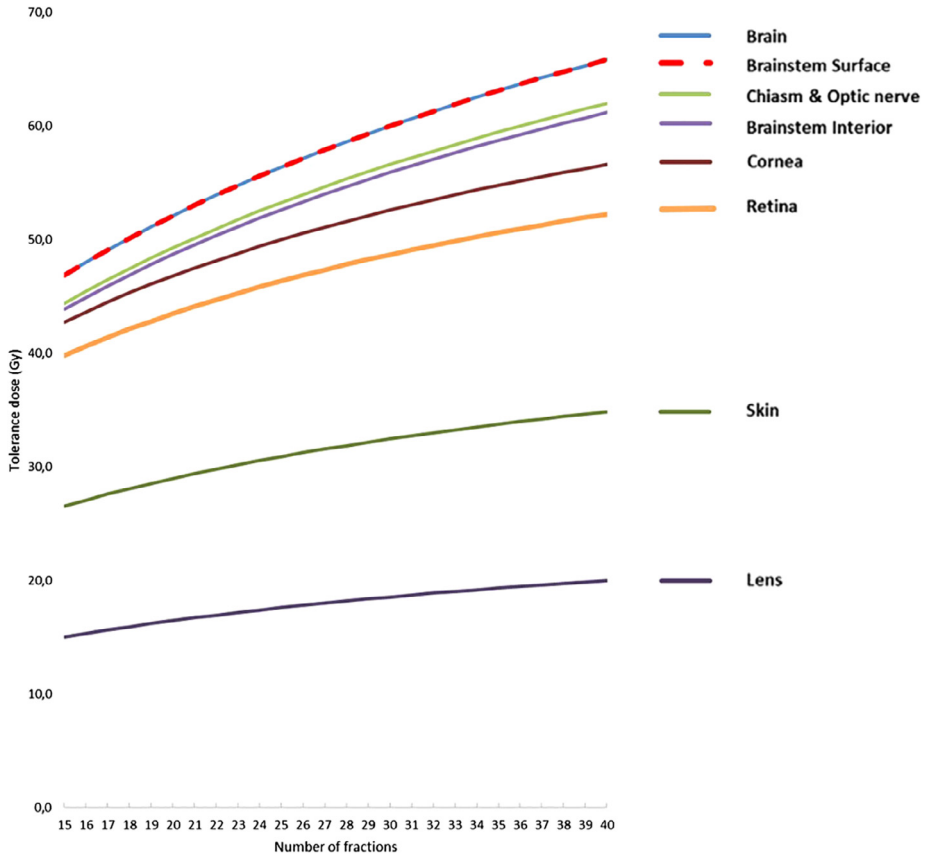

Fig. 2. Tolerance dose *versus* total number of fractions. The Tolerance dose is calculated using the EPTN consensus dose constraints and α/β *versus* the total number of fractions. On the X-axis the total number of fractions is given and on the Y-axis the corresponding physical tolerance dose (Gy); for all OAR the $D_{0.03\ cc}$ (= dose to 0.03 cc of the organ/structure) except for the brain (D_{3cc} = dose to 3 cc of the brain).

formula, this allows us to recalculate the dose depending on the number of fractions (Fig. 2) [117]. Of note, this conversion using the linear quadratic formula does not apply to D_{mean} dose constraints. Instead, the mean dose to the OAR and its standard deviation is required for this conversion, and therefore, we cannot provide these technique-dependent values [118,119]. In keeping with the ICRU 83 and 91 reports we avoided using the maximum absorbed dose at a single calculation point (D_{max}) for the constraint table [120,121]. However, for larger OARs such as the brain and brainstem, the classical $D_{2\%}$ might result in a relatively large volume exceeding the tolerance dose. We therefore opted to use the $D_{0.03\ cc}$ as this approximates the D_{max} used in the majority of the literature, since this depends less on the treatment planning system and scanner parameters used, and thus provides a more realistic calculation of the delivered dose. Only dose parameters related with specific toxicities were included in the consensus table, however, for planning purposes it is obvious that more than one dose–volume parameter should be included in the optimization process (as objectives or constraints) to ensure the optimal plan is generated.

Second, when setting dose constraints we assume a dose–volume effect for the structures, and set a threshold below which the odds of a certain toxicity are reasonable. The outcome of this exercise depends highly on the severity of the toxicity and at what cost the dose is pushed below a certain threshold. Conversely, it is obvious that RT related toxicity is a more complex and multifactorial process where genetic disposition, co-morbidities, dosimetric and clinical factors all play an important role in explaining why some patients experience excess toxicity at low doses and others can be treated up to high doses without any toxicity [116]. This interplay is impossible to grasp in a single parameter and, again, requires more complex models, which incorporate clinical, genetic, and dosimetric factors into a multifactorial NTCP model, which allows for an individual patient-based risk assessment.

Third, toxicity was not uniformly scored in all series. In the review several toxicity scoring mechanisms have been used, with the RTOG/EORTC Late Effects Normal Tissue Task Force subjective, objective, management, and analytic (LENT/SOMA) score and CTCAE being the most prominently used [12,122]. Uniform scoring of toxicity is of utmost importance when constructing a prospective database. Throughout the manuscript, we promote the use of the CTCAE scoring system as it is widely accepted and applicable and allows for a more detailed scoring of the severity of toxicity compared to the LENT/SOMA evaluation. Aside from the physician scored toxicity, patient reported outcome (PRO) scoring systems should also be implemented, in the prospective data collection as several studies have demonstrated that there is severe discrepancy between patients and physician reported toxicities and that generally physicians tend to underreport the presence and severity of treatment related toxicities [123,124].

Fourth, it is very important to realize that there is an interplay between different structures when looking at toxicity. For example, while DES and corneal damage are described separately, in reality they are very closely interlinked. This interplay, however, is not taken into account when proposing a single dose constraint for the lacrimal gland. The problem becomes even more complex when looking at a toxicity which is multifactorial in principle such as neurocognition [107,109,125]. While the hippocampus was

among the first structures to be related to neurocognitive decline, and is instrumental in learning and memory, it is not the only structure responsible for good cognitive functioning. The prefrontal cortex, the cerebellum and the hypothalamus all play an important role in the higher cognitive function of the brain [105,109,125,126]. To what extent radiation induced damage to these structures impairs their function is far less understood. With increasing practice to spare the hippocampus, the relative importance of these or other structures will become increasingly important.

Therefore, it is important that the summary constraint table in this manuscript is not to be considered as an endpoint. As radiation techniques evolve, treatment changes and survival improves, relevant toxicities will also evolve. While some toxicities were initially of great importance and dose limiting, they can become less frequent and other toxicities gain the upper hand. An example for this is optic neuropathy. While frequently reported in older papers, there have been no relevant papers on this toxicity using conventionally fractionated radiotherapy since the QUANTEC report [5]. This can partly be explained by the combination of clear dose constraints with the ability to effectively reduce the dose to the optic nerve using conformal radiotherapy techniques.

The true value of this manuscript lies in the fact that it provides a consensus on the dose constraints for relevant OARs in the treatment of brain tumours among experts in the field. Of note, it is only a consensus, with all the shortcomings described above. Together with the delineation guidelines by Eekers et al. [1], however, it is a starting point for uniform OAR delineation and dose prescription. If we succeed in setting up a standardized follow-up with prospective scoring of toxicity it provides a basic framework within which a large number of patients are treated and followed uniformly and thus can be used to develop and validate multifactorial NTCP models.

Fifth, all constraints in Table 1 are reported in EQD2 unless otherwise reported. To facilitate conversion we suggested an α/β ratio based on the best available evidence found, while it should be noted that there is considerable uncertainty regarding these ratios [19,127]. In principle, the dose constraints are useful for both photon and proton radiotherapy provided that a conversion factor of 1.1 for conventional fractionation is used to account for the difference in RBE [128]. However, at the very distal edge of the Bragg peak, the linear energy transfer is higher, resulting in an increased RBE [129]. This is of concern as the distal edge of the Bragg peak is often very close or even overlapping with the dose-limiting OAR and might result in unexpectedly high toxicity or abnormal imaging changes [130–132]. Therefore, close observation of all these patients remains crucial.

Finally, the set of dose constraints aims to provide assistance to the physician and physicist/dosimetrist in the difficult task of coming up with the optimal plan for each patient, balancing out tumour control and potential toxicity with regard to the age, comorbidities and life expectancy of the patient. From this review it should be obvious that they are not absolute values and the risks and benefits of each treatment should be thoroughly discussed with the patient.

Acknowledgement

NGB is supported by the National Institute for Health Research Cambridge Biomedical Research Centre.

Disclosure of Conflicts of Interest

Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.radonc.2018.05.001.

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