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Review

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

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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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(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.

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