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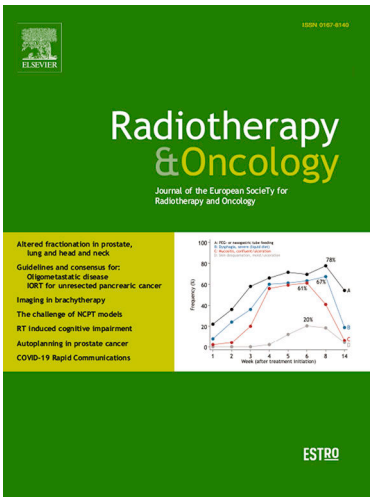

Review Article

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Laurien De Roeck, Hiska L. van der Weide, Daniëlle B.P. Eekers, Miranda C. Kramer, Claire Alapetite, Malin Blomstrand, Neil G. Burnet, Valentin Calugaru, Ida E.M. Coremans, Dario Di Perri, Semi Harrabi, Alberto Iannalfi, Yvonne L.B. Klaver, Johannes A. Langendijk, Alejandra Méndez Romero, Frank Paulsen, Erik Roelofs, Dirk de Ruysscher, Beate Timmermann, Pavel Vitek, Damien C. Weber, Gillian A. Whitfield, Petra Witt Nyström, Jaap Zindler, Esther G.C. Troost, Maarten Lambrecht, on behalf of work package 1 of the taskforce "European Particle Therapy Network" of ESTRO,

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Title

The European Particle Therapy Network (EPTN) consensus on the follow-up of adult patients with brain and skull base tumours treated with photon or proton irradiation

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Abstract

Purpose: Treatment-related toxicity after irradiation of brain tumours has been underreported in the literature. Furthermore, there is considerable heterogeneity on how and when toxicity is evaluated. The aim of this European Particle Network (EPTN) collaborative project is to develop recommendations for uniform follow-up and toxicity scoring of adult brain tumour patients treated with radiotherapy.

Methods: A Delphi method-based consensus was reached among 24 international radiation-oncology experts in the field of neuro-oncology concerning the toxicity endpoints, evaluation methods and time points.

Results: In this paper, we present a basic framework for consistent toxicity scoring and follow-up, using multiple levels of recommendation. Level I includes all recommendations that are considered minimum of care, whereas level II and III are optional evaluations in the advanced clinical or research setting, respectively. Per outcome domain, the clinical endpoints and evaluation methods per level are listed. Where relevant the organ at risk threshold doses for recommended referral to specific organ specialists are defined.

Conclusion: These consensus-based recommendations for follow-up will enable the collection of uniform toxicity data of brain tumour patients treated with radiotherapy. This will facilitate collaboration and further propel the research field of radiation-induced toxicities relevant for these patients. An online tool to implement this guideline in clinical practice is provided at www.cancerdata.org.

Introduction

Brain and base of skull tumours comprise very diverse and rare entities. Aside from tumour diversity, various patient characteristics, symptoms, radiation target volumes, techniques, doses, prognoses and radiation-induced toxicities exist. Moreover, radiation-induced toxicities relevant for adult brain tumour patients have been under-reported. The current knowledge of central nervous system (CNS) toxicity after radiotherapy is therefore very limited.

With high volume and high-quality datasets, dose-volume metrics and clinical data can be used to design Normal Tissue Complication Probability (NTCP) models. NTCP models are an important driver

for radiotherapy technique development and selection. With the rapid increase in technical options for brain tumour patients, there is an unmet need for data of the different toxicities these patients may encounter [1]. In order to obtain large datasets of toxicity outcome of adult brain tumour patients that enable NTCP model development and validation, multicentre collaborative efforts are essential. Aligning the follow-up programmes in multiple centres in which patients are systematically and consistently evaluated in a prospective manner, will allow for collection of large and reproducible datasets.

Previous efforts have already resulted in consensus on (1) the delineation of organs at risk (OARs) [2-4], and on (2) the dose constraints to the OARs [5]. The aim of this project is to formulate consensus-based recommendations for uniform follow-up, with regard to method and timing of evaluations of adult patients treated with fractionated radiotherapy (RT) for brain tumours and to develop an interactive tool to facilitate implementation. In this paper, the recommendations and the implementation tool are presented.

Methods

This consensus paper is written on behalf of the ‘‘European Particle Therapy Network” (EPTN) task group of ESTRO. Multiple steps were taken to formulate the consensus-based recommendations. In September 2018, the general idea, principles and outcome domains were discussed in the EPTN group (first comments-round). In November 2018, the outcome domains and levels of recommendation were further defined and discussed. Moreover, assessments and tools for scoring were assessed. Where relevant, domains were worked out in detail in collaboration with field-specific professionals (e.g. neurologist, radiologist, ophthalmologist, neuropsychologist, ear, nose & throat specialist (ENT) and endocrinologist) and all included a summary of relevant OARs and current NTCP model knowledge. In December 2018, a second comments-round of the EPTN group took place. To redefine the relevance of the outcome domains, the time points of evaluation and threshold doses for referral to the organ specialists, anonymous surveys were set-up according to the Delphi method and distributed among the experts in May 2021 [6]. This round was therefore considered as the final consensus-round. This consensus was reached among 24 radiation oncology experts from 20 centres (10 countries) in the field of neuro-oncology. The final draft of the paper was completed in September 2021. To summarise these recommendations and facilitate the data collection, a comprehensible and easy-to-use interactive spreadsheet is made available at www.cancerdata.org.

Results: recommendations for follow-up

Clinically relevant time points for long-term toxicity scoring were established: baseline and after 1, 2.5 and 5 years. When feasible, we also recommend collecting data at 10 and 15 years after RT. We classified these recommendations into different levels of recommendation ranging from level I - III (Table 1).

We advise to assess all level I evaluations in all adult brain tumour patients treated with radiotherapy. Level II and III evaluations are optional but can provide us with deeper insights or more sensitive evaluation methods. In this paper, we suggest some level III evaluations of particular interest; however it is beyond the scope of this paper to provide extended recommendations for research settings. Recommendations are given when it is considered useful to give some directions on endpoints that are particularly interesting for future data-merging or validation of data. Each centre can determine which items and at which level they are able or willing to monitor outcome in their patients. However, if we aim to develop NTCP models on CNS toxicity, uniform big datasets are urgently needed.

The follow-up recommendations are categorized into one radiological outcome domain and eight clinical domains (general, hair, neurological, neurocognitive, endocrine, visual, ocular and auditory). For each domain, a set of recommended evaluations for specific time points is proposed to evaluate the patients’ outcomes. Moreover, OARs’ threshold doses for referral to organ specialists for specific follow-up were defined (Table 2). These threshold doses are on the safe side and set below the OARs’ dose constraint levels, since patients in whom little or no toxicity is expected, also need to be included in order to develop highly performing NTCP models.

To facilitate this toxicity scoring and follow-up in clinical practice, we provided an extensive spreadsheet to guide clinicians in this process [7]. This instrument can be adapted according to the feasibility and needs of each centre and will be updated whenever needed. The outcome domains are further elaborated below.

1. General

Introduction: Under this heading, we have included some of the most important outcomes in cancer care, i.e. performance status, (instrumental) activities of daily living (ADL & iADL), psychological status, stamina, wellbeing, fatigue, sleep, medication use [antiepileptic drugs (AED)/steroids], comorbidities, associated events (e.g. stroke) and patient-reported outcome measures (PROMs) such as quality of life (QoL). Despite the importance of QoL in brain tumour patients, few clinical trials have focused on QoL as a primary outcome [8,9]. To date, the effect of irradiation of the brain and its impact on patients' wellbeing is not fully understood. PROMs are instruments for reporting the patient's perspective on health care outcomes, using different types of questionnaires. In recent years, the widespread use and feasibility of these questionnaires have led to a large amount of data. Since our goal, apart from better overall survival, is to improve our patients' QoL, these data are of utmost importance.

Recommendation: The EPTN recommends assessing these evaluations at baseline and after 1, 2.5, 5, 10 and 15 years of follow-up as a minimum. Data acquisition (level I) should consist of patient's performance status, employment, education, driving license, medication use (steroids, AED), major events/comorbidities and QoL/ADL (short: EUROQOL-5D-5L questionnaire). Other optional (level II), however clinically relevant, assessments are iADL and QoL [EORTC QLQ-C30 (cancer-specific)/ EORTC QLQ-BN20 (brain-specific)].

2. Hair

Introduction: Alopecia is a side-effect characterised by decreased hair density compared to normal for a given age and individual. Temporary and permanent alopecia are common toxicities of cranial radiotherapy, which can have a severe psychosocial impact on the patient [10]. Radiation dose to the hair follicles of the skin is responsible for this outcome. The availability and quality of NTCP data are limited and different radiotherapy techniques [opposing fields, Volumetric Modulated Arc Therapy (VMAT)] already have been studied for better hair sparing outcomes [11,12]. The interobserver variability is an issue in the existing alopecia grading scales [EORTC BN20 questionnaire, the Severity of Alopecia Tool (SALT Score)].

OAR and constraint: To avoid permanent alopecia, the dose to 0.03 cc ($D_{0.03\ cc}$) of the hair follicles [located in epidermis and dermis (skin defined as body-5mm)] should be ≤ 25 Gy equivalent dose in 2 Gy fractions (EQD2), and the volume receiving 25 Gy EQD2 (V_{25Gy}) should be limited as much as possible [5]. A recent experience using VMAT identified the V_{40Gy} ≥ 5.4 cc and V_{43Gy} ≥ 2.2 cc as the strongest predictors of chronic G2-alopecia risk [13]. The NTCP model of Dutz et al. [11] found the dose to 2% of the hair follicles ($D_{2\%}$) as a prognostic parameter for alopecia G≥1 in primary brain tumour patients treated with proton beam therapy (PBT).

Recommendation: The EPTN recommends assessing alopecia grading at baseline and at 2.5 years post-RT. As a minimum, alopecia should be graded (level I) according to the common terminology criteria for adverse events version 5.0 (CTCAE v5.0) [14]. In level II, we suggest a more detailed mapping of the region of alopecia to the actual skin dose distribution. Herein we depict the alopecia areas for a more detailed visual representation of the dose-toxicity relationship (Figure 1). Dermatological photographs can depict the amount and distribution of hair follicles in more detail (level III).

3. Neurological function

Introduction: The neurological domain includes both focal neurological deficits and epilepsy, which can be influenced by cranial radiotherapy, both positively and negatively [15]. These outcomes significantly impact the patient's daily functioning and are particularly important to monitor when the dose-volume

constraints of the supratentorial brain, cerebellum and brainstem are approached [5]. Medication used for symptom control (steroids and AEDs) should be taken into account, because they can modify the symptomatic neurological outcomes.

Despite AEDs, 15%–35% of patients still experience seizures [16,17]. Uncontrolled seizures may result in high morbidity and negatively impact QoL [18]. Apart from the tumour itself, radiation-induced brain damage such as oedema, radionecrosis (RN) and intracranial hypertension can cause epilepsy. Radiation-induced focal neurological deficits arise from damage to the brain cells, usually referred to as RN. Neurological deficits include gait impairment, dysphasia and cranial nerve disorders, amongst others.

OAR and constraint: To minimise RN with secondary focal neurological deficits and epilepsy, the total brain volume receiving a specific dose should be kept as low as reasonably achievable (ALARA). We propose the volume of the brain receiving a dose of 60 Gy EQD2 ($V_{60\ Gy}$) to be ≤ 3 cc and the $D_{0.03cc}$ to be kept below 54 Gy EQD2 (in particular the interior part) for the brainstem [5]. However, adequate PTV coverage should always be considered. No correlations of dose–volume parameters of the brain were found for headache [11].

Recommendation: The EPTN recommends obtaining data at baseline and after 1, 2.5, 5, 10 and 15 years of follow-up as a minimum. In level I, CTCAE v5.0 [14] is used to objectify epilepsy, headache, gait impairment and dysphasia. In level II, overall neurological function impairment can be investigated in depth using the NANO scale [19], an objective clinician-reported scoring tool with a high inter-observer agreement. Additionally, the outcome of more specific cranial nerves can also be scored using CTCAE v5.0 [14] in level II.

4. Neurocognitive function

Introduction: One of the main clinical benefits of more complex RT (e.g. particle therapy) techniques in brain tumour patients is expected to improve neurocognitive outcomes. Various attempts have been made to better preserve cognitive function after RT, e.g. hippocampal avoidance and concomitant use of memantine [20,21]. Even though the pathophysiology is complex [22] and the evaluation of neurocognitive function in daily practice is challenging, there is a significant need for high-quality neurocognitive data. Unfortunately, there is no international consensus to date on the optimal neurocognitive assessment battery for adult brain tumour patients. In non-CNS patients, Hopkins Verbal Learning Test-Revised (HVLT-R), Trail Making Test (TMT) and Controlled Oral Word Association Test (COWA) are recommended as core tests assessments by the International Cancer and Cognition Task Force (ICCTF) [23].

OAR and constraint: Based on the currently available data, the supratentorial brain, cerebellum, corpus callosum, thalamus, periventricular space and hippocampus (anterior and posterior) are considered the most important OARs for neurocognitive function as a clinical endpoint [3,24-26]. For instance, dosimetric findings in frontal lobes were associated with executive functioning [26]. Poorer verbal delayed recall was correlated with the volume receiving at least 60 Gy (V_{60Gy}) of the left temporal lobe and left hippocampus, while poorer verbal immediate recall was correlated to the V_{40Gy} of the left temporal lobe [24,27]. Cognitive impairment may also be driven by damage to specific fibre tracts, which can be modelled based on diffusion-weighted Magnetic Resonance (MR) tractography [28]. The relation between hippocampal dosimetry and memory decline is still under debate [24,29]. We recommend the dose to both hippocampi to be kept ALARA, and preferably the $D_{40\%}$ in both hippocampi combined to be kept below 7.3 Gy EQD2 [5]. There are currently no other defined dose-volume constraint recommendations for these OARs and brain volumes than the ALARA principle. The

exact anatomical substrate of cognitive functioning is however still unclear, underlining the need for externally validated models on this matter.

Recommendation: The EPTN recommends scoring cognitive disturbance, concentration and memory impairment using the CTCAE v5.0 criteria [14] at baseline and after 1, 2.5, 5, 10 and 15 years of follow-up (level I). More specific neurocognitive tests (level II) can be used, as recommended by the ICCTF, to assess verbal learning and memory (HVLT-R), processing speed and executive functioning (TMT part A/B) and verbal fluency (COWA). All evaluations should be performed at all time points and carried out by certified personnel. Since neurocognitive functioning is such a crucial outcome after RT, we would encourage implementing neurocognitive evaluation in each centre at the highest level reasonably achievable.

5. Endocrine function

Introduction: Radiation to the hypothalamic-pituitary axis can lead to significant neuroendocrine dysfunction, which is a common problem after RT of brain tumours. There seems to be a dose-dependency, of both severity and delay of onset with growth hormone (GH) being the first to be affected, followed by the gonadotrophins [follicle stimulating hormone (FSH)/luteinizing hormone (LH)], adrenocorticotropic hormone (ACTH) and thyroid-stimulating hormone (TSH) [30]. Clinical presentation of these deficiencies varies from vague symptoms such as fatigue, anorexia, muscle weakness, and lethargy to specific complaints such as infertility (gonadotrophins), hypotension (ACTH) and weight gain (TSH). Dysfunction of this hypothalamic–pituitary axis is thus associated with significant morbidity and mortality [31]. Some patients already have hormone deficiencies before RT, primarily driven by prior surgery, tumour location and histology. Baseline screening is therefore recommended.

OAR and constraint: Relevant OARs are the hypothalamus and pituitary gland. In a recent retrospective study of 58 glioma survivors, clinically relevant growth hormone-, gonadotropin-, ACTH- and TSH deficiency occurred above threshold doses to the hypothalamic-pituitary axis of 10, 30, 32 and 40 Gy, respectively [32]. The EPTN consensus panel proposes a D_{mean} ≤45 Gy EQD2 to the pituitary gland to prevent panhypopituitarism [5]. There are currently no valuable data on the hypothalamus' tolerance doses and thus no constraint can be defined.

Recommendation: Clinical presentation of hypopituitarism can be very non-specific, so defining an exhaustive set of clinical toxicities to be scored is nearly impossible. The consequences of hypopituitarism also cause downstream hormonal changes, which again will result in a variety of clinical symptoms. We propose clinical follow-up for all patients documenting the presence of endocrine disorders and replacement therapy (yes/no) (level I). 'Hypopituitarism' in itself however does not allow for differentiation of the different hormonal axes. Hence, an additional scoring of the most important pituitary-thalamic hormones (GH, TSH, prolactin, ACTH, gonadotrophins) is needed. For these hormones both the timing and evolution of changes is of the utmost importance for accurate evaluation and interpretation of deficiency. In patients who received a low dose (D_{mean} < 20 Gy EQD2) to the pituitary gland or hypothalamus, these analyses are regarded as optional (level II). All patients who received a significant (D_{mean}≥ 20 Gy EQD2) dose to the pituitary gland or hypothalamus should be screened for endocrinopathies (blood test) (level I). We propose the following basic lab tests: electrolytes, cortisol (before 10 AM), TSH/ free T4, prolactin, FSH/LH, in women oestradiol and in men (at 9 AM) testosterone and sex hormone binding globulin (SHBG). Insulin-like growth factor (IGF)-1 is often decreased, and can be normal in GH deficiency. Other basal tests, as well as specific hormone stimulation tests, need to be performed in well-defined conditions and interpreted under the supervision of an endocrinologist (table A.1)(level II). All evaluations should be carried out at least at

baseline and after 1, 2.5, 5, 10 and 15 years of follow-up; however an annual endocrine follow-up is preferred.

6. Visual pathway

Introduction/OAR: The visual system comprises not only the eye as a sensory organ but the entire visual pathway from the optic nerve to the occipital cortex. Higher-order processing of the visual system, located at the parietal and temporal lobes might also be affected. Critical endpoints regarding visual outcome after RT treatment are visual acuity, colour vision and visual field to evaluate optic nerve function to detect radiation-induced optic neuropathy (RION). The associated OARs are the optic nerve and chiasm.

RION is a rare condition, presenting as a painless, sudden uni- or bilateral loss of vision occurring between three months and eight years after radiotherapy [33,34]. According to the CTCAE v5.0 [14], RION is graded from grade 1 being asymptomatic, to grade 4 legal blindness (best corrected visual acuity 20/200 or worse) in the affected eye.
The optic nerves cross in the optic chiasm. A functional loss at the level of the chiasm presents as bitemporal hemianopsia or even complete blindness. Toxicity of the optic chiasm is graded similarly as in RION. Since RION and optic chiasm toxicity share the same pathophysiology, the same constraints apply, i.e., $D_{0.03\ cc} \leq 55$ Gy EQD2 for the optic pathway (nerve/chiasm), bearing in mind that this dose-constraint can be relaxed at the discretion of the treating physician in order to increase the tumour control probability (i.e. skull base chordoma abutting the optic apparatus) [5].

Recommendation: The EPTN proposes to evaluate the presence of visual problems (yes/no) in level I at all time points (minimally at baseline and after 1, 2.5, 5, 10 and 15 years of follow-up). When symptomatic or when exceeding the threshold dose of the optic pathway: $D_{0.03cc}$ chiasm and/or optic nerve ≥ 40 Gy EQD2, the patient should be referred to an ophthalmologist, who can perform a visual field test, examination of visual acuity (Snellen Chart and CTCAE v5.0 [14] term 'optic nerve disorder') and refraction to examine these deficiencies more precisely. Toxicities should be evaluated at all time points, or even more frequent when clinically relevant (level II).

7. Ocular function (lens, retina, cornea, lacrimal gland) and ocular motility

Introduction/OARs: Normal ocular motility requires intact function of the third, fourth and sixth cranial nerves, their nuclei and interconnections in the brainstem and cerebellum. The relevant OARs concerning the ocular function are the retina (including fovea and macula), cornea, lacrimal glands and the lens. Depending on tumour location, irradiation of orbital structures is often inevitable.

The retina is essential in perception and contains the macula and fovea. The macula lies lateral to the optic disc; at the centre of the macula is the fovea centralis which contains the highest density of cones in the retina. The macula and fovea process sharp, clear vision, while the optic disc is responsible for the blind spot. RT-induced toxicity of the retina is called radiation-induced retinopathy (RIRP). The latency period of RIRP is typically between six months and three years, although longer periods have been described [35-38]. The retinopathic changes following radiation exposure are more severe in the posterior than in the anterior retina, probably due to the increased number of capillaries and higher blood flow of the macular region, leading to a visual loss with a significant impact on QoL [37,39,40].

The lacrimal gland system consists of the main lacrimal gland, accessory lacrimal glands and the lacrimal duct system. Radiation injury to any of these structures might result in xerophthalmia or the so-called dry eye syndrome (DES). Symptoms of the latter are blurry vision, photophobia, foreign body sensation and pain [41,42].

The cornea is the outer layer of the eye, covering the pupil, the iris, and anterior chamber. Damage to the corneal tissue can be due to a dual effect of RT dose (direct effect) and DES [43]. Dose constraints are therefore difficult to establish. Moreover, corneal ulcers are extremely hard to treat due to uncertain results of corneal graft and bad tolerance of bandage lenses in irradiated patients [35].

The lens is very radiosensitive, with toxicity being manifest as post-RT cataract. Symptoms include faded colours, blurry or double vision and halos around light.

Constraints: For these OARs, the EPTN proposed the $D_{0.03cc}$ to the retina to be kept below 45 Gy EQD2, the $D_{0.03cc}$ to the cornea not to exceed 50 Gy EQD2 (if the orbit is not part of the target volume) and the mean dose to the lacrimal gland to be kept below 25 Gy EQD2. The dose to the lens should be kept ALARA and the $D_{0.03\ cc}$ below 10 Gy EQD2 if possible [5]. However, cataract surgery is a minor surgical intervention, so target volume coverage should not be compromised in an attempt to avoid the lenses. Younger patients should be warned that normal accommodation is lost after cataract surgery.

Recommendation: In level I, 'dry eye' and 'eye pain' should be scored according to CTCAE v5.0 [14], distinguishing three grades of xerophthalmia and pain. Moreover, oculomotor function impairment should be assessed (yes/no). When exceeding the abovementioned threshold doses of the retina ($D_{0.03cc} \geq$ 40 Gy EQD2), cornea ($D_{0.03cc} \geq$ 20 Gy EQD2) and/or lacrimal gland ($D_{mean} \geq$ 30 Gy EQD2), follow-up by an ophthalmologist is indicated. However, underlying disease, e.g. diabetic retinopathy might even lower the threshold. We recommend the following ocular tests to be performed by an ophthalmologist (level II): pupil function, slit-lamp, fundoscopy, optical coherence tomography (OCT), Schirmer test and ocular motility tests. To grade these ocular motility dysfunctions (oculomotor/trochlear/abducens) CTCAE v5.0 [14] should be used. Moreover, retinopathy, keratitis, corneal ulcers and cataract can be objectified according to CTCAE v5.0 [14] by the ophthalmologist. Since symptoms may manifest over an extended time frame, ocular function should be evaluated at least at baseline and after 1, 2.5, 5, 10 and 15 years of follow-up.

8. Auditory function

Introduction/OAR: Irradiation of the temporal bone may cause sensorineural hearing loss and vestibular dysfunction. The inner ear contains the cochlea, necessary for hearing, and the vestibular and semi-circular canal (VSCC), important for balance. Other essential structures in hearing and balance are the vestibulocochlear nerve, brain stem and cerebellum.

Constraints: There are two RT-induced complications of the cochlea. The first is sensorineural hearing loss (SNHL) of which the high hearing frequencies are most affected. This effect is dose-dependent, but especially observed with a D_{mean} to the cochlea > 45 Gy [5,44]. Prior or concomitant chemotherapy (such as cisplatin [CDDP]) might lower the threshold [44]. For the prevention of SNHL, the ALARA principle applies. EPTN advises the D_{mean} to the cochlea to be kept at least ≤ 45 Gy in EQD2.
The second potential RT-induced complication is tinnitus, for which the EPTN advises a D_{mean} to the cochlea < 32 Gy EQD2 [5]. There are two kinds of tinnitus. The first is subjective tinnitus caused by damage to the cochlea or brain, causing a perception of sound to compensate for this damage. The second is the objective tinnitus caused by mechanical mechanisms like vascular pulsations. Only subjective tinnitus can originate after RT. The most reliable way of measuring tinnitus is by using a validated questionnaire [45].

Few data exist on the acute side effect of radiation to the VSCC, causing nausea at a D_{mean} > 40 Gy [46]. The long-term effects after RT to the VSCC are vertigo, dizziness and imbalance inducing problems in

daily functioning. No dose-effect data are available yet, underlining the importance of adequate registration of VSCC related side effects.
Vertigo is characterized by a sensation as if the external world revolves around the patient (objective vertigo) or as if he himself revolves in space (subjective vertigo). When vertigo is provoked by movement, the cause is located within the VSCC.
Several tests detect deficiencies to the VSCC, e.g. the manual head impulse test, the dynamic visual acuity test (DVA) or the Romberg on foam [47]. The aforementioned tests register deficits to both VSCCs at the same time and not individually, which would be most relevant to detect RT-induced toxicity. To detect alterations to the left and right VSCC separately the Video head impulse test or the Calorie test are the most suited, the latter being the most accurate but also the most difficult to perform.

Recommendation: The EPTN recommends scoring tinnitus, vertigo and vestibular disorder according to CTCAE v5.0 [14] at baseline and after 1, 2.5, 5, 10 and 15 years of follow-up, minimally (level I). Moreover, CTCAE v5.0 [14] should be used to score impaired hearing (not enrolled in a monitoring program). A validated hearing test (level II), using air- (0.25 to 20 kHz) and bone- (0.5 to 4 kHz) conduction including high frequencies tests (1,2,3,4,6 and 8 kHz), is needed to score impaired hearing for patients enrolled in a monitor program (CTCAE v5.0 [14]). This test can objectively quantify the amount of hearing loss [44]. Nowadays, this can only be performed by the audiometrist, which may cause extra logistic and organizational challenges. Validated web-based solutions are under investigation enabling the patient to perform these tests at home.
Tinnitus is evidenced by the Tinnitus Functional Index (TFI), a validated questionnaire that can be easily implemented in clinical practice but is more time consuming (level II). Other specialized tests, such as the Video Head Impulse test and scoring of middle ear inflammation (CTCAE v5.0 [14]), should be performed by an audiometrist/ENT specialist. We advise to refer patients to these specialists when exceeding the threshold dose, D_{mean} cochlea of 35 Gy EQD2, or even 30 Gy EQD2 when ototoxic medication is given concomitant or prior to RT.

9. Radiological outcome

Introduction: RT induces many anatomical and functional changes, including inflammation, vascular changes, necrosis and impaired neurogenesis [48-53]. On MR imaging, white matter changes have been associated with poorer attention, intellect and working memory in cranially irradiated brain tumour survivors [54-56]. Also, dose-dependent grey matter cortical thinning has been described in the hippocampus and other brain regions, modifying functional connectivity and oxygen supply [57-63].

Anatomical changes can be divided in time. Early-delayed effects can occur in the first 3 months after RT as non-enhancing white matter hyperintensities (T2-signal) on MR imaging. These changes can occur without clinical effect and do not always need intervention. Pseudoprogression appears usually within 6 months after treatment and can be misinterpreted as early tumour progression, since clinical and (conventional) radiological appearance can be quite similar [64-66]. According to the Response Assessment in Neuro-Oncology (RANO) criteria for gliomas, it is defined as a new or enlarging area of contrast enhancement occurring early after the completion of radiotherapy in the absence of true progression [67]. Risk factors are concurrent temozolomide [68]/sequential PCV chemotherapy (procarbazine, lomustine (CCNU) and vincristine) [69] and methylguanine-DNA-methyltransferase (MGMT) promoter hypermethylated tumours [70]. Late-delayed effects may appear with a delay of three months to numerous years after RT and include RN. RN is a result of endothelial apoptosis and neuroinflammation and manifests similarly on conventional neuroimaging with oedema and contrast enhancement. Risk factors for RN include irradiated volume, total RT dose and concurrent use of

chemotherapy [71]. Pseudoprogression, RN and tumour recurrence can have a similar clinical presentation.

Many state of the art MR sequences are used to assess different aspects of neural damage. High-resolution T1-weighted imaging is used to depict white and grey matter neuroanatomical changes; diffusion-weighted imaging (DWI) to investigate white matter microstructural changes; 3D Fluid-Attenuated Inversion Recovery (FLAIR) for the detection of leukoencephalopathy; susceptibility-weighted imaging (SWI) to expose microbleeds and Arterial Spin Labelling (ASL) for cerebral blood flow estimates.

Constraint: To minimize the risk of RN, maximum dose to the brain (D_{max}) should be kept < 60 Gy EQD2 for a risk of RN < 3% [72,73].

Recommendation: EPTN recommends depicting the presence of imaging changes and ischemia/bleeding from the radiology report and to further specify them into new enhancements, RN and white matter hyperintensities (yes/no). RN should be graded according to the CTCAE v5.0 [14]. (level I). In research settings (level III), the latter can be correlated to the radiation fields and dose-volume histograms (DVHs).

More advanced imaging techniques and measurements (level II) include: detection of vasculopathy (SWI images), measurement of brain and hippocampal atrophy (graded according to the Global Cortical Atrophy (GCA) scale and Medial Temporal Atrophy (MTA) scale respectively) and quantifying the T2 hyperintense white matter lesions (using the Fazekas scale). The Fazekas scale uses four grades (0-3) depending on the lesions' sizes and confluence for both periventricular and deep white matter [74]. The GCA scale evaluates atrophy in 13 brain regions in each hemisphere and is best assessed on FLAIR images [75]. The MTA scale is based on a visual rating of the height of the hippocampal formation and the width of the choroid fissure and the temporal horn, resulting in a score between 0 and 4 [76].

Other suggestions for data collection, which can be used in research settings (level III) are specific volumetric measurements of brain structures (e.g. supratentorial brain, hippocampus), diffusion measurements (DWI) and fractional anisotropy (FA) measurements. All level I and II evaluations should be performed minimally at baseline and after 1, 2.5, 5, 10 and 15 years of follow-up.

Discussion

Primary brain and base of skull tumours remain rare entities and accurate RT toxicity data are therefore scarce. Moreover, the currently available toxicity data are often scored at different time points, using various evaluation methods and grading systems. Merging of toxicity outcome data from multiple centres is hampered by the non-uniformity of evaluations. The aim of this consensus guideline is therefore to give clear recommendations for re-structuring the follow-up care of neuro-oncology patients in a uniform way to facilitate future collaborative projects. Hence, we have set up a multinational framework for scoring of different toxicity items. In the future, these data will improve our insights on the prevalence and severity of these toxicities and will help set up prospective trials.

Ahead of their time, QUANTEC aimed to produce practical guidance allowing the clinician to reasonably categorize toxicity risks based on dose-volume parameters or model results. Within the EPTN working group it was established that this 'call' for uniform data collection is still essential. In order to obtain uniformity, standardization of the different aspects of RT is required [77]. We aimed to do this in three consensus papers. In the first consensus paper, relevant OARs in neuro-oncology were selected and delineation guidelines proposed [4], which were recently updated and extended [3]. In a second paper, we reviewed the available evidence on the dose–toxicity relationship for the previously defined OARs

and dose-volume constraints were suggested [5]. This third manuscript provides a consensus among experts on brain tumour patients' follow-up after treatment.

In this consensus, we divided all evaluations into three levels, where level I evaluations are considered to be basic or routine. We strongly encourage that at least all level I evaluations should be implemented in all patients' follow-up. However, this framework is merely an advice, set-up for data collection on long-term toxicities after RT. In clinical practice, some brain tumours patients will need a more frequent follow-up schedule. This is nonetheless beyond the scope of this project, which aims at compiling uniform data at some clinically relevant timepoints and can be used for guidance and illustrating follow-up of toxicity for patients in clinical routine. If level I toxicity scoring can be routinely implemented, we can collect standardised data to (1) develop NTCP models and (2) increase our knowledge of these RT-induced toxicities, paving the path to new insights and changing our clinical practice accordingly. We realise that only a minority of patients will be still in clinical follow-up 5 years after radiotherapy. However, by assembling these rare data over different centres, we aim to collect sufficient toxicity events in order to make predictions on long-term toxicity outcomes (> 5 years after RT).

Collaboration is thus crucial to move forward in understanding the toxicity we observe in our patients. As these toxicities are often complex and multifactorial, the best way to model this is to build NTCP models with classical dose-volume, as well as clinical parameters [78]. The models may be different for photon and proton radiotherapy. Therefore, large quantities of uniform toxicity data are needed. At present, we still lack information about which brain areas are most vulnerable and susceptible to clinically relevant radiation-induced damage. Gaining this knowledge, together with the use of highly conformal RT techniques, will allow us to selectively spare the OARs from excessive dose, and thus decrease RT-related toxicity. These NTCP models will consequently allow for an informed decision on the optimal treatment modality or plan regarding the OARs to spare, including the trade-off for other OARs. By doing so, we could optimize treatment plans in a more patient-tailored approach.

Many knowledge gaps still have to be filled. These toxicity data can be used to increase our knowledge of several of these RT-induced toxicities and their evolution. For example, multiple OARs have been identified to play a role in neurocognitive function, including the supratentorial brain, cerebellum (anterior and posterior), corpus callosum and hippocampus (anterior and posterior). However, the reciprocity of these OARs and the pathophysiology of the underlying mechanisms of RT-induced neural damage are complex and poorly understood. Large quantities of clinical, biological and neuroimaging data can be used to perform in-depth analyses, highlight new insights and guide future prospective trials in which these findings can be validated. This will provide us with methods to detect these toxicities at an earlier timepoint, potentially minimizing the impact on the patients' QoL [79].

The next step will be to pool all these data across the different centres willing to partake in this effort. Several strategies are possible for this collaborative data analysis. Centralised data platforms such as ParticleCare (EORTC 1833-RP) or ProTRAIT project in the Netherlands can serve as examples of how to set up these data collection harvesting environments. Recently, the large-scale Health-RI initiative was granted a 68,5 million euros investment to build a national data-sharing infrastructure based on the FAIR principles (Findable, Accessible, Interoperable and Reusable), decentralised privacy-preserving principles, which allows for distributed learning on high-quality healthcare data [80].

As the aforementioned recommendations are based on the currently available data and knowledge of the effects of radiation keeps on increasing, it is evident that the relevant endpoints will also evolve. Therefore, this guideline is to be considered as dynamic and will be adapted and updated over the coming years, similar to the previous EPTN recommendations [3]. To aid in the implementation of this

guideline, we provide an online instrument for toxicity scoring and follow-up [7]. With successful adoption of this standard, we can consequently develop a central digital platform to store and share these data, which would allow transparency and collaboration between different centres [81].

Conclusion

In adult patients with primary brain tumours, radiation-induced toxicities can result in long-term sequelae with an important impact on QoL. We have developed a consensus recommendation guideline for follow-up after RT. This will enable the community to collectively provide and use large amounts of uniformly defined high-quality toxicity prediction data.

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Disclosure of conflicts of interest

The authors have no conflicts of interest to declare

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.

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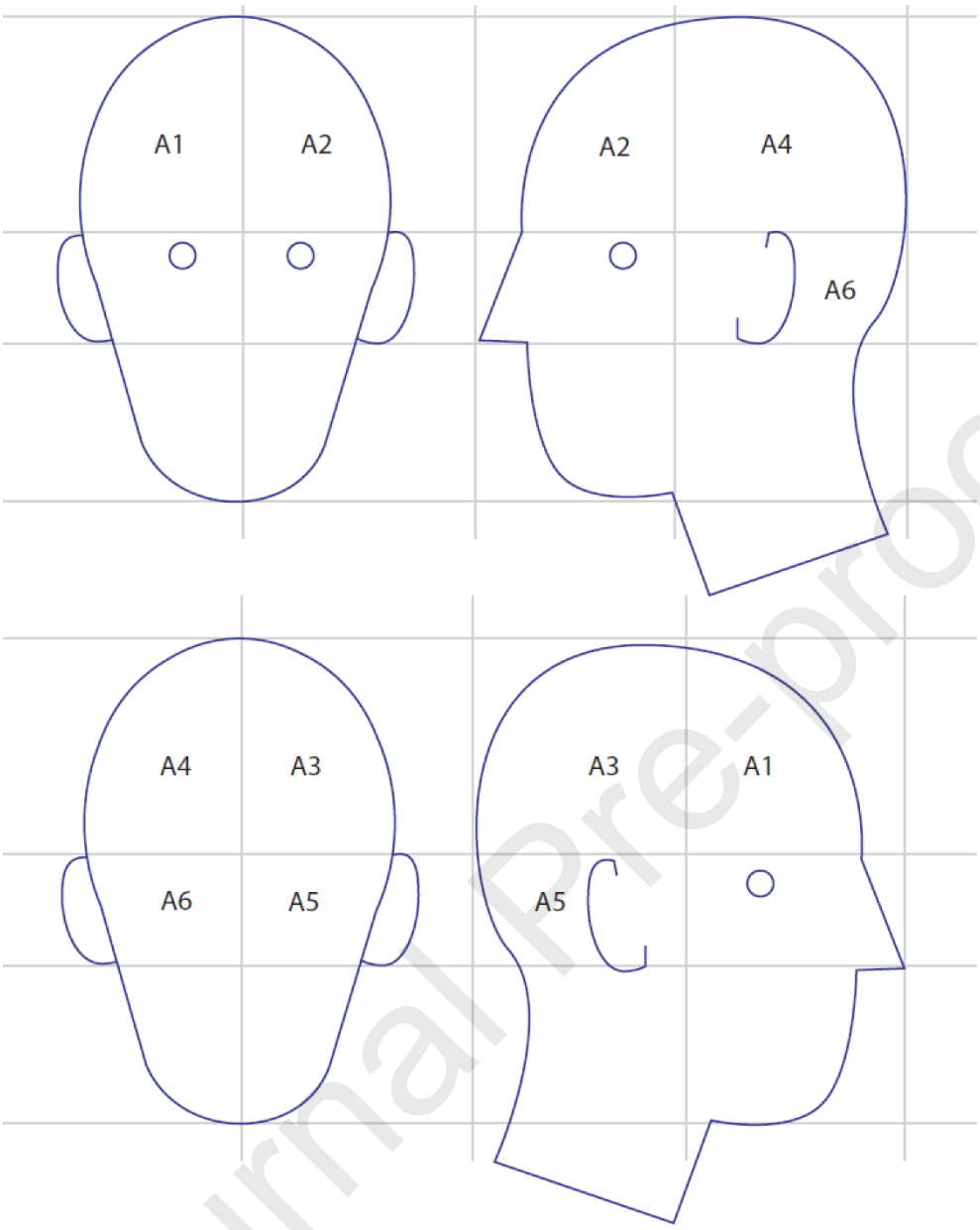

Figure 1: detailed mapping of the six alopecia (A1-A6) regions to the actual skin dose distribution (level II)

Table 1: levels of recommendation

Level I = basic or routine level

All evaluations within this level should be manageable and easily implemented within the current standard practice and can be performed in telehealth consultations (e.g. during the covid-19 pandemic). They are recommended for all patients in all centres.

Level II = advanced level (optional)

These evaluations might require extra time or specialist care, thus are optional per centre.

Level III= research level

Can be done in research settings

Table 2: Threshold dose for referral to organ specialist

Organ specialist	***Dose parameter***	***Threshold dose (EQD2)(Gy)***	***Toxicity***	***α/β (Gy)***
Endocrinologist	D_{mean} Hypothalamus and/or pituitary gland	≥ 20	Endocrine dysfunction	2
Ophthalmologist	$D_{0.03cc}$ Optic nerve and/or chiasm $D_{0.03cc}$ Cornea $D_{0.03cc}$ Retina D_{mean} Lacrimal gland	≥ 40 ≥ 20 ≥ 40 ≥ 30	Optic neuropathy Erosion/ ulceration Loss of vision Keratoconjunctivitis sicca	2 3 3 3
ENT/audiometrist	D_{mean} Cochlea $_{\text{with or prior ototoxic medication}}$ D_{mean} Cochlea $_{\text{without ototoxic medication}}$	≥ 30 ≥ 35	Hearing loss/ tinnitus Hearing loss/ tinnitus	3 3

Table 2: Organ at risk threshold doses for referral to organ specialists (photon and proton therapy). EQD2: Equivalent dose in 2 Gy fractions, Dmean: mean dose, D0,03cc: dose received at 0.3 cc. ENT: ear-nose-throat specialist

Highlights

- Consensus on time- and endpoints to evaluate toxicity on relevant outcome domains
- This framework will facilitate international collaboration and data collection
- Goal: develop individualized risk assessments for brain tumour patients after RT
- An interactive spreadsheet is available at www.cancerdata.org