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Dose constrains in brain

Organs at risk in the brain and their dose-constraints in adults and in children: A radiation oncologist's guide for delineation in everyday practice

Silvia Scoccianti ^{a,*}, Beatrice Detti ^a, Davide Gadda ^b, Daniela Greto ^a, Ilaria Furfaro ^a, Fiammetta Meacci ^a, Gabriele Simontacchi ^a, Lucia Di Brina ^a, Pierluigi Bonomo ^a, Irene Giacomelli ^a, Icro Meattini ^a, Monica Mangoni ^a, Sabrina Cappelli ^a, Sara Cassani ^a, Cinzia Talamonti ^c, Lorenzo Bordi ^d, Lorenzo Livi ^a

^a Radiation Oncology; ^b Neuroradiology Unit; ^c Medical Physics; and ^d Neurosurgery, Azienda Universitaria Ospedaliera Careggi, Florence, Italy

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Keywords: Radiotherapy atlas Organs at risk Brain contouring atlas Normal tissue Dose-constraints Optic chiasm

ABSTRACT

	<i>Purpose:</i> Accurate organs at risk definition is essential for radiation treatment of brain tumors. The aim of this study is to provide a story life of entry life of entry wide to deliver to be 0.0 Pa in the brain entry is a story wide to be					
December 2014	would be done in the everyday practice of planning radiotherapy for brain cancer treatment.					
2015	<i>Methods:</i> Anatomical descriptions and neuroimaging atlases of the brain were studied. The dosimetric constraints used in literature were reviewed.					
	<i>Results</i> : A Computed Tomography and Magnetic Resonance Imaging based detailed atlas was developed jointly by radiation oncologists, a neuroradiologist and a neurosurgeon.					
	For each organ brief anatomical notion, main radiological reference points and useful considerations are provided.					
	Recommended dose-constraints both for adult and pediatric patients were also provided.					
	Conclusions: This report provides guidelines for OARs delineation and their dose-constraints for the treat-					
	ment planning of patients with brain tumors.					
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The delineation of intracranial OARs is one of the most crucial points in the planning of brain tumors because radiotherapy (RT) to the brain can lead to visual and hearing deficits, hormonal impairment and neurological and neurocognitive alterations.

Moreover, accurate delineation of OARs is essential for the inverse-planning process of intensity modulated radiation treatment.

Although cerebral normal structures are not always easily recognizable on the imaging used for RT planning, to date, the anatomic delineation of these structures has not been standardized for planning purposes.

This guide might be a tool for daily practice and for decreasing the discrepancies in intracranial OARs delineation between radiation oncologists.

Methods

Anatomical descriptions and neuroimaging atlases of the brain were studied [1–9].

* Corresponding author. E-mail address: silvia.scoccianti@unifi.it (S. Scoccianti).

http://dx.doi.org/10.1016/j.radonc.2015.01.016 0167-8140/© 2015 Elsevier Ireland Ltd. All rights reserved. A simplified but detailed anatomy atlas on Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) of the brain has been developed in order to significantly improve the contour accuracy and concordance. For each organ at risk we added some main notions of neuroanatomy, we also defined structures that are easy to identify to be used as landmarks; lastly, we stated some useful considerations for helping in contouring. The atlas was then critically reviewed, discussed, and edited by radiation oncologists, a neuroradiologist and a neurosurgeon.

The following regions of interest were defined: optic chiasm, cochlea, hippocampus, brainstem, pituitary gland, circle of Willis, retina, lacrimal gland and lens.

This report also provides for all the above-mentioned OARs a brief review for the recommended dosimetric constraints both for adult and pediatric patients.

Results

Optic chiasm

Anatomical notions

The optic chiasm, probably the most crucial intracranial organ at risk is the convergence of the optic nerves in front and the







divergence of the optic tracts behind. With conventional CT or MRI, the optic tracts are visible for only 1–2 cm posterior to the optic chiasm before the fibers spread and blend into the rest of the brain parenchyma.

The optic chiasm lies below the hypothalamus, the third ventricle and its optic recess. It rests upon the tuberculum sellae, in the so-called chiasmatic groove. The chiasm is surrounded by the cerebrospinal fluid contained in the chiasmatic cistern. The anterior cerebral arteries and the anterior communicating artery are located ventral to the chiasm. Lateral to the optic chiasma are the internal carotid arteries. The crossing of the optic fibers occurs just anterior to the pituitary stalk.

Landmarks

The structures that need to be identified in order to have a correct contouring are the optic canals (Supplementary Fig. sl: sla, slb, sle, slf) from which optic nerves originate (Fig. 1a and b), the anterior clinoid processes of the sphenoid bone (Supplementary Fig. sl: sla, slb, sle, slf) and the internal carotid arteries (Fig. 1a and b) on each side (Fig. 1g), and, posteriorly, the pituitary stalk (Fig. 1a) or the infundibular recess (Fig. 1c and d).

Both CT (Supplementary Fig. sl) and MRI images (Fig. 1) are useful to identify these reference structures.

The pituitary stalk is the most important landmark because it lies just behind the crossing of the fibers. It is not difficult to be found because it is hyperintense in T1-weighted images, but also slightly hyperdense in CT images, even when the contrast is not used.

In the superior slices, behind the chiasma the infundibular recess (Fig. 1c and d) can be found instead of the pituitary stalk (that is caudally placed). This structure is well-recognizable because it lies in the same median position as the pituitary stalk but it is ring-shaped.

Useful considerations

The optic chiasm measures about 14 mm in its transverse width, with an antero-posterior width of about 8 mm and a thickness of only 2–5 mm.



Fig. 1. Region of the optic chiasm as it appears on axial T1-weighted MRI scan with contrast. Optic chiasm is contoured as a dotted line. (g) Anatomy of the optic chiasm and its relationship to the circle of Willis.

The chiasm is usually slightly sloping upward and backward. This is the reason why, depending on the orientation of the scan plane relative to the brain, the optic nerve and chiasm can appear on multiple images.

Moreover, the location of the chiasm and the grade of its sloping vary widely. In almost 80% of cases the chiasm is found superiorly to the posterior 2/3 of the sella but it can also overlay or lie behind the dorsum sellae.

Contouring the optic pathway with continuity is crucial, because gaps in the structures will lead to missing essential volume for the computing of the dose–volume histogram.

Checking the contour on a sagittal (Supplementary Fig. II: slla) and on a coronal view (Supplementary Fig. II: sllb) is strongly recommended because the anatomy will appear clearer and the contours can be confirmed.

Dose recommendations

The constraints for chiasm are the following: maximum dose less than 54 Gy as primary criteria [10-11] (being the optic neuropathy unusual for doses <55 Gy [11,12]), less than 60 Gy as secondary criteria [10] (being the incidence of optic neuropathy less than 7% for doses ≤ 60 Gy [12]) (Table 1).

No differences in constraints between adults and children have been reported.

Cochlea

Anatomical notions

The cochlea is a spiral structure around a central bony structure, the so-called modiolus. Fibers originated from the endolymphatic receptor system of the cochlea, reach the internal acoustic canal. Here, they form the cochlear nerve that joins the superior and inferior vestibular nerves, forming the VIII cranial nerve (Fig. 2c), and traveling together with the facial nerve through the pontocerebellar cistern until they reach the brainstem.

Landmarks

The cochlea is located in a bony cavity in the petrous portion of the temporal bone, anterior to the labyrinth, lateral to the internal auditory canal. Although the cochlea is not directly visible on CT scan due to its small size and its deep location in the temporal bone, its volume can be defined on CT images as the bony cavity where it lies, using an appropriate bone window/level (Supplementary Fig. sIII). The structures of the inner ear are well visible in the MRI images (Fig. 2), especially when high-resolution 3D imaging techniques such as the balanced Steady-State Free Precession (bSSFP) sequences or the sampling perfection with application-optimized contrasts by using different flip angle evolutions (SPACE) sequences are used [13].

Useful considerations

Since the average volume of the cochlea usually does not exceed 0.60 mL image thickness ≤ 1.0 mm is recommended.

Dose recommendations

Because of the small volume of the cochlea a dose–volume analysis is not feasible and only recommendations about the mean dose can be found in literature.

The recommended dose constraints vary a lot between children and adults, being the limits for pediatric patients significantly lower. Several studies in series of adult patients have attempted to relate mean cochlear dose to the development of sensorineural hearing loss and they reported a significant increase in hearing loss when the mean dose received by the cochlea was >45–50 Gy [10,14,15]. In the case of children, hearing loss was rare below 30 Gy and increased at doses of 40 Gy [16,17]. Therefore, in children, the mean dose to the cochlea should be kept below 35 Gy.

The synergistic toxicity of chemotherapy when combined with RT has to be taken into consideration, especially when patients receive cisplatinum-based chemotherapy [18].

Hippocampus (dentate gyrus)

In recent years, based on experimental and clinical evidence, some authors have suggested that irradiation of the hippocampal dentate gyrus can lead to neurocognitive impairment due to the presence of neural stem cells [19].

Because the cognitive dysfunction seems to be proportional to the volume and amount of irradiated tissue in this location, the delineation of this portion of hippocampus has recently become a crucial point during the treatment planning process. Gondi et al. [20] have recently published the contouring guidelines for the hippocampus.

Table 1

Dose constraints and recommendations for intracranial organs at risk when conventional fractionation is used.

OAR	Constraints for adults		Constraints for children (if different from the ones reported for adult patients)		
	Primary criteria	Secondary criteria			
Optic chiasma	D _{max} < 54 [10,11] D _{max} < 55 [12]	D _{max} < 60 [10]			
Cochlea	$D_{\text{mean}} \leqslant 45 \text{ Gy } [13,14]$ $D_{\text{mean}} < 50 \text{ Gy } [10]$		D _{mean} < 35 Gy [16]		
Hippocampus	Hippocampus $D_{max} \leq 6$ Gy and $V_{3 Gy} \leq 20\%$ Hippocampal avoidance volume $D_{max} < 25.2$ Gy and $V_{20 Gy} \leq 20\% [21,22]$ $D_{max} < 12$ Gy [23] $V_{7.2 Gy} < 40\% [25]$ $D_{mean} < 30$ Gy [24]				
Brainstem	D _{max} < 54 Gy [10,29]	D _{max} < 60 Gy [10] D _{59 Gy} < 10 cc [29]			
Pituitary gland	D _{max} < 50 Gy [34] D _{max} < 60 Gy [10]		D _{mean} < 25 or 30 Gy [32] D _{max} < 42 Gy [35]		
Retina	D _{max} < 45 Gy [10, Yamazaki] D _{max} < 50 Gy [Shaffer]				
Lacrimal gland	V _{30 Gy} < 50% [Sreeraman] D _{max} < 40 Gy [Jeganathan]				
Lens	D _{max} < 6 Gy [Piroth] D _{max} < 10 Gy [10, Yamazaki]				



Fig. 2. Region of the cochlea as it appears on axial SPACE (sampling perfection with application-optimized contrasts by using different flip angle evolutions) MRI scan.

Anatomical notions

Since the hippocampus is mainly made of grey matter, focusing on the T1-hypointense signal would be suggested. The grey matter that constitutes the hippocampus is easily distinguishable from the other surrounding structures except for the amygdala that, in the more caudal slices, lies anteriorly to it and that is formed by grey matter as well. The amygdala should be excluded from the contour of the hippocampus [6-8,20] in order to the subgranular zone where the neural stem cells occur [21]. The hippocampus is easily recognizable at the level of the curve of the temporal horn, the socalled uncal recess, because it is the grev matter included in the curve and is bound anteriorly, laterally, and medially by the cerebrospinal fluid in the temporal horn (Fig. 3c and d). At this level the boundary from the amygdala is easy to define because the amygdala is the grey matter located medially to the temporal horn of the lateral ventricle. The boundary between the hippocampus and the amygdala is not evident in the more caudal slices (Fig. 3a and b): thus, it has to be extrapolated from more superior slices where the uncal recess is visible. In its lower portion the hippocampus reaches the caudal extremity of the temporal horn, remaining medial to it.

Coming back to the uncal recess and continuing in an upward direction, the hippocampus is the most medial grey matter strip in the temporal lobe, just lateral to the midbrain and it moves progressively posteriorly (Fig. 3e and f). At this level, the lateral margin of the hippocampus is surrounded by cerebrospinal fluid from the lateral ventricle, while the medial boundary is limited from the CSF-containing space lateral to the brainstem, the so-called ambient cistern (Fig. 3d and e). Cranially, the medial boundary of the hippocampus is defined by the lateral edge of the quadrigeminal cistern (Fig. 3e).

The hippocampal tail curves medially toward the splenium of the corpus callosum, remaining posterior to the thalamus. The cranial extent of the hippocampal tail is located antero-medially to the atrium of the lateral ventricle. Also in its superior extent, the hippocampus remains lateral to the quadrigeminal cistern and medial to the atrium of the lateral ventricle (Fig. 3h). The T1hypointense area of the hippocampus is no further visible when the splenium of the corpus callosum can be visualized posteriorly.

Landmarks

The grey matter of the hippocampus remains medially to the temporal horn of the lateral ventricle throughout its extent, and so, it can be used as a consistent reference. The ambient and the quadrigeminal cisterns serve as medial landmarks.

Useful considerations

The literature describes considerable age and disease specific variability in hippocampal size and location: this limits the applicability of any autocontouring technique for the delineation of the hippocampus using a population-generated atlas [8]. Furthermore, automated atlases do not specifically focus on the dentate gyrus that is the hippocampal portion of concern for memory function.

Only certain MRI sequences such as SPGR (three-dimensional spoiled gradient), MPRAGE (magnetization-prepared rapid gradient echo) or TFE (turbo field echo) sequences permit accurate definition of the dentate gyrus.

Very thin slice-thickness is necessary to visualize the hippocampus: slice-thickness of 1–2 mm has been suggested [20].

Orientation of the MRI slices along the axis of the hippocampus allows a better hippocampal visualization [7].

Identifying the hippocampus is not difficult on sagittal images where its overall "banana" shape, located in the plane of the lateral ventricle, can easily be seen. Thus, the sagittal view can be useful to check the contours drawn on the axial images (Supplementary Fig. IV).

Dose recommendations

The constraints used for the hippocampus vary a lot in the literature [20–26] but they have seldom been associated with clinical outcome (Table 1). At this time there is no evidence to conclusively support a particular recommendation. Recently, Gondi et al. [25] found that doses greater than 7.3 Gy to 40% of the bilateral hippocampus were associated with impaired memory function in a small retrospective series of 18 patients affected by low-grade adult brain tumors. Noteworthy, most authors recommend lowering the doses to the bilateral hippocampal volume, however, if the ipsilateral hippocampus cannot be spared due to its proximity to the PTV, only the contralateral hippocampus can be contoured and spared [26].



Fig. 3. Hippocampus as it appears on axial T1-weighted MRI scan with contrast. Hippocampus is contoured as a dotted line.

Recently, Gondi et al. [27] published the results of the RTOG 0933, a single-arm phase II study that demonstrated that avoidance of the hippocampus during whole brain radiotherapy is associated with preservation of quality of life and memory. In this series, 100% of the hippocampus could not exceed 9 Gy, and maximal hippocampal dose could not exceed 16 Gy in 10 fractions.

Only further prospective trials evaluating neurocognitive function will provide more consistent dose volume constraints associated with lower risk of cognitive impairment.

Brainstem

Anatomical notions

The brainstem comprises the midbrain, pons and medulla oblongata (Fig. 4a–d). It starts from the superior limit of the posterior clinoids to the inferior limit of the foramen magnum. It continues superiorly with the diencephalon and inferiorly with the spinal cord.

Landmarks

The brainstem is surrounded by the cerebrospinal fluid contained in the cisterns: these structures can help to define the borders of the brainstem. Starting from the top, quadrigeminal and ambient cisterns (Fig. 4b) are situated dorsally and laterally to the midbrain. The interpeduncular cistern (Fig. 4a) lies anteriorly to the midbrain, while the prepontine cistern (Fig. 4a and c) surrounds the ventral wall of the pons and it contains the basilar artery that is well-recognizable both in CT and MRI images. Going downward, there is the premedullary cistern (Fig. 4a and d) and, laterally, the pontocerebellar cistern (Fig. 4c) that is located in the angle between the cerebellum and the pons, containing the V, VII and VIII cranial nerves. Inferiorly, the cisterna magna (Fig. 4a and d) lies between the cerebellum and the dorsal wall of the medulla oblongata, containing the IX, X, XI and XII cranial nerves.

Useful considerations

Visualization of sagittal plane may be helpful when defining the brainstem (Fig. 4a).

The midbrain is about 2 cm in length. The midbrain is inferior to the third ventricle. Its posterior part is represented by the quadrigeminal plate. Anteriorly, it is limited by the two mammillary bodies (portion of the hypothalamus) (Fig. 4a and b).

The pons is the thicker portion of the brainstem of about 25– 30 mm in length. It bulges from the midbrain and medulla and is separated from them by the superior and inferior pontine sulci. It is posteriorly covered by the cerebellum, united to it by means of the middle cerebellar peduncles.

The medulla oblongata is the lowest part of the brainstem. It continues caudally with the spinal cord.

Dose recommendations

On the basis of the available data, the entire brainstem may be treated to 54 Gy using conventional fractionation with limited risk of severe or permanent neurological effects [28,29]. Smaller volumes of the brainstem (1–10 mL) may be irradiated to maximum doses of 59 Gy for dose fractions of 2 Gy [10,29].

There is no evidence that the tolerance of the pediatric patient differs from the adult.

Pituitary gland

Anatomical notions

The pituitary gland appears as an oval-shaped structure and lies within a bony cavity of the sphenoid bone in the base of the skull, the so-called sella turcica. It lies immediately below the brain and is connected by the stalk to the hypothalamus (Fig. 5). The gland is divided into two lobes: the neurohypophysis and the adenohypophysis, each with its own embryological derivation and array of secretory hormones.

Landmarks

The pituitary gland lies on the sella turcica that is clearly visible on a CT scan when an appropriate bone window/level is used. Laterally, the pituitary gland is surrounded by the cavernous sinuses: they are well visible structures on images (Fig. 5c) when contrast is used. As mentioned, the pituitary stalk lies behind the crossing of the optic fibers in the chiasma (Fig. 1a, b and g).



Fig. 4. Brainstem on sagittal T1-weighted MRI scan (5a) and on axial T1-weighted MRI scan with contrast (5b: image at level of midbrain; 5c: image at level of pons; 5d: image at level of medulla oblongata). Brainstem is contoured as a dotted line.

Useful considerations

The CT density of the pituitary gland is similar to the brain parenchyma and is readily discernable from the surrounding CSF. When contrast is used, the gland may appear slightly more hyperdense compared to the brain parenchyma due to its more vascular nature. The pituitary gland's anterior and posterior parts are distinguishable on an MRI. The anterior part is isointense on both T1 and T2-weighted images. The posterior pituitary is often a thin layer of tissue that is hyperintense on T1 images and hypointense on T2weighted images.

The craniocaudal dimension of the pituitary gland varies over time and is affected by the hormonal state (ranging from 6 mm for infants to 12 mm for pregnant women).

The pituitary stalk has a normal thickness of 2 mm, and should not exceed a maximum of 4 mm or the width of the basilar artery.

Dose recommendations

Hypothalamic-pituitary axis dysfunction may occur in up to 80% of patients treated with RT. Frequency, time to onset and severity of symptoms are related to the total dose, to the fractional dose, to the age at the time of irradiation and to the length of follow-up.

Selective radiosensitivity of the cell populations accounts for different incidence of the hormonal deficits, with the GH axis the most radiosensitive, followed by gonadotropin, ACTH and TSH axes [30,31].

The impairment of GH production occurs in 30% and in 50% of patients who received 30 Gy and dose ranging between 30 and 50 Gy, respectively [30]. Isolated GH deficiency may be seen also after low-dose cranial RT (18–24 Gy) [32], and even after total-body-irradiation for doses of 10 Gy [33].

Gonadotrophin deficiency is usually a long-term complication following a radiation dose of 30–40 Gy with a cumulative incidence of 20–50% after long-term follow up [30,34]. In contrast, irradiation may cause premature activation of the hypothalamus-pituitary-gonadal axis resulting in precocious puberty after doses of 30 Gy [30] with different timing of onset of puberty: the younger the age at exposure to irradiation, the earlier the onset of puberty [31]. TSH and ACTH deficiency occur after doses >30 Gy with a long term cumulative frequency of 3–9% but the frequency may significantly increase in the longterm follow-up if the doses are higher than 50 Gy [30,31].

Hyperprolactinemia, due to a radiation-induced reduction in the inhibitory neurotransmitter dopamine, has been described in female adults treated with radiation doses >40 Gy [30].

Age at irradiation influences hypothalamic–pituitary axis vulnerability to radiation damage [35]; hormone deficiencies are more frequent in children than adults, and in younger children compared with older ones. This is probably the reason why in literature regarding adult patients, the constraints for the pituitary gland are often higher, ranged between 50 and 60 Gy [10,34]. A longterm follow-up of patients who received significant doses to the pituitary gland is crucial, because early replacement therapy may avoid endocrinological syndromes.

Internal carotid artery and the circle of Willis

Anatomical notions

The internal carotid artery enters the cranium through the carotid canal. The carotid siphon is an S-shaped portion of the internal carotid artery inside the cavernous sinus, lateral to the sella turcica (Fig. 5b–d). The artery arches upward and backward and then, after a horizontal tract, arches again upward and forward. In this stretch the internal carotid artery is separated from the blood contained in the sinus only by the endothelium and it lies medial to the cranial nerves contained therein (III, IV and VI cranial nerves and ophthalmic branch of the trigeminal nerve).

The circle of Willis is a ring-shaped circulatory anastomosis (Fig. 5e–h), that connects the internal carotid and vertebral arteries, ensuring supply of blood to the brain should one of these vessels be occluded. It is located in the interpeduncular cistern, in the cranial base.

The anterior half of the circle of Willis is formed by the internal carotid arteries when they enter the cranial cavity bilaterally and branch into the anterior cerebral artery and middle cerebral artery. The anterior communicating artery joins the anterior cerebral arteries. Posteriorly, the basilar artery, formed by the left and right



Fig. 5. Pituitary gland, carotid siphon and circle of Willis as they appear on axial T1-weighted MRI scan with contrast. Pituitary gland appears as a dotted line.

vertebral arteries, divides at the upper border of the pons into a left and right posterior cerebral artery, forming the posterior portion of the polygon. From each internal carotid artery, a posterior communicating artery arises and runs back to join the ipsilateral posterior cerebral artery, completing the circle of Willis.

Useful considerations

The knowledge of anatomic relationship between the circle of Willis and the optic chiasm may be helpful in the contouring process (Fig. 1g). The chiasm passes through the circle of Willis, being the optic structures subtended anteriorly through the ring of the circle. In other words, the anterior cerebral arteries and the anterior communicating artery lie cranially to the chiasm (Fig. 5g and h), whereas the posterior communicating arteries lie caudally to the optic tracts (Fig. 5e and f).

Dose recommendations

Little is known about the long-term risk of cerebrovascular morbidity associated with radiation therapy to the circle of Willis. Haddy et al. [36] estimated the radiation dose delivered to different anatomical sites of interest in the brain of more than 4000 long-survivors of a childhood cancer. They found that risk of death from cerebrovascular disease is related to the radiation dose to the prepontine cistern: patients who had received >50 Gy to the prepontine cistern had a 17.8-fold higher hazard ratio of death if compared with cases who had not received radiotherapy. The authors suggested that the dose to the prepontine cistern could be an indirect measure of the dose to the circle of Willis. A relationship between higher doses to the circle of Willis (mean dose 61 Gy; range 54–79.5 Gy) and cerebrovascular disease was suggested also by Omura et al. [37].

Previous reports showed that radiation therapy could cause progressive occlusion of major cerebral arteries resulting in chronic cerebral ischemic condition and neovascularization with abnormal network of vessels. This condition, is called "radiation induced moyamoya-like syndrome" for the clinical and radiological similarities with the moyamoya congenital disease and it has been frequently observed among patients treated with radiotherapy at a pediatric age [38], probably because immature nervous system has a greater ability to induce neoangiogenesis in chronic cerebral ischemia [39].

Age ≤ 10 years during radiation treatment [38], radiotherapy volume involving the cranial base [39], time interval after radiotherapy >5 years [39] and neurofibromatosis-1 [40,41] are recognized as risk factors for this syndrome. Total doses >45 Gy [40] or 50 Gy [41] have been related to a greater risk but even doses as low as 12 Gy have been reported in cases that developed this syndrome (12 Gy [42]).

Eye

Useful considerations

A field strength of 3T or higher, a surface coil and ultra-high resolution sequences are required for visualization of the finest structures of the eye. Since the orbital fat may show similar signal intensity as the globe wall and the lacrimal gland on T2- and contrast-enhanced T1W-sequences, sequences with saturation of fat tissue signal (FAT–SAT) should be used [43].

Retina

Anatomical notions

The retina is the innermost of the three layers that form the wall of the eyeball (sclera, uvea/choroid and retina). Its function is to convert light into electrical nerve signals.

It is an approximately 0.25 mm-thick neurosensorial membrane with a rich vascularization and it lines the posterior wall of the eye.

The retina cannot be directly visualized on the standard MRI sequences for the orbit. It can be drawn as a membrane that lays in the posterior 5/6 of the bulb, extending nearly as far as the ciliary body (Supplementary Fig.: V: Va–Vg). On axial images the anterior limit of the retina is between the insertion of the medial rectus muscle and the insertion of the lateral rectus muscle, posteriorly to the ciliary body.

Dose recommendations

Radiation retinopathy is a complication of radiation exposure to the retina. Ionizing radiation induces a slowly progressive occlusive vasculopathy with transudation, edema and neoangiogenesis. The latter can result in glaucoma, exudative retinal detachment, vitreous hemorrhage and, eventually, in blindness [44,45].

The risk of radiation-induced retinopathy is based on total dose, fraction dose, the presence of comorbidities (e.g., diabetes), and exposure to radiation sensitizers such as chemotherapy [44]. Although numerous treatments have been tested (corticosteroids, anticoagulation, laser photocoagulation, hyperbaric oxygen therapy, and bevacizumab), effectiveness for any option still needs to be proven and the therapeutic management remains controversial [46].

Retina maximum dose should be less than 45 [10,47] or 50 Gy [48].

Lacrimal gland

Anatomical notions

The lacrimal gland lies in the supero-lateral extraconal portion of the orbit, medially to the zygomatic process of the frontal bone; it can be easily identified superiorly to the lateral rectus muscle and laterally to the superior rectus muscle (Supplementary Fig.: V: Vd–Vh). Its size varies a lot with maximum diameters reaching 20 mm in the craniocaudal length, 15 mm in the axial length and up to 5 mm in the anteroposterior length [49].

Dose recommendations

Radiation-induced damage can lead to the impairment of tear production with results ranging from a less effective lubrification of the cornea and the conjunctiva to a dry-eye syndrome.

A steeply increasing risk for dry eye syndrome has been reported at doses >40 Gy, whereas irradiation of the lacrimal gland with doses >57 Gy results in a 100% rate of atrophy and fibrosis of the lacrimal gland with permanent loss of tear secretion [50].

Sreeraman et al. [51] found a correlation between dose to the lacrimal gland and its acute dysfunction, suggesting to maintain V30 less than 50%.

Lens

Anatomical notions

The lens of the eye is a biconvex avascular structure, located between the vitreous and the iris (Supplementary Fig.: V: Vc–Ve). Its diameter measures up to 10 mm.

Dose recommendations

Radiotherapy may cause abnormalities of its fibers resulting in a cataract for dose exceeding 2 Gy. For doses less than 6.5 Gy there is a 33% risk that the cataract will be progressive with a latency of 8 years, while for doses between 6.5 and 11.5 Gy there is a 66% risk of cataract progression with a latency of 4 years [50]. Recommended dose constraints for adults range between 5 [52] and 10 Gy [10,47] as maximum dose. Although these constraints are used also in paediatric literature [53], the threshold for cataract formation may be lower in childhood [50].

Conclusions

This report might represent a tool if or radiation oncologists in everyday practice providing the recommendations for contouring the intracranial OARs and listing their dose-constraints for RT planning.

Conflict of interest statement

All the authors declare that actual or potential conflicts of interest do not exist for the following manuscript: "Organs at risk in the brain and their dose-constraints in adults and in children: a radiation oncologist's guide for delineation in everyday practice". All the authors disclose any financial and personal relationship with other people or organisations that could inappropriately influence their work.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.radonc.2015.01. 016.

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