



Original Article

ESTRO ACROP guideline for target volume delineation of skull base tumors



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ARTICLE INFO

Article history:

Received 30 October 2020

Accepted 13 November 2020

Available online 10 December 2020

Keywords:

Skull base tumors

Target volumes

Radiotherapy

Consensus guidelines

ABSTRACT

Background and purpose: For skull base tumors, target definition is the key to safe high-dose treatments because surrounding normal tissues are very sensitive to radiation. In the present work we established a joint ESTRO ACROP guideline for the target volume definition of skull base tumors.

Material and methods: A comprehensive literature search was conducted in PubMed using various combinations of the following medical subjects headings (MeSH) and free-text words: “radiation therapy” or “stereotactic radiosurgery” or “proton therapy” or “particle beam therapy” and “skull base neoplasms” “pituitary neoplasms”, “meningioma”, “craniopharyngioma”, “chordoma”, “chondrosarcoma”, “acoustic neuroma/vestibular schwannoma”, “organs at risk”, “gross tumor volume”, “clinical tumor volume”, “planning tumor volume”, “target volume”, “target delineation”, “dose constraints”. The ACROP committee identified sixteen European experts in close interaction with the ESTRO clinical committee who analyzed and discussed the body of evidence concerning target delineation.

Results: All experts agree that magnetic resonance (MR) images with high three-dimensional spatial accuracy and tissue-contrast definition, both T2-weighted and volumetric T1-weighted sequences, are required to improve target delineation. In detail, several key issues were identified and discussed: i) radiation techniques and immobilization, ii) imaging techniques and target delineation, and iii) technical aspects of radiation treatments including planning techniques and dose-fractionation schedules. Specific target delineation issues with regard to different skull base tumors, including pituitary adenomas, meningiomas, craniopharyngiomas, acoustic neuromas, chordomas and chondrosarcomas are presented.

Conclusions: This ESTRO ACROP guideline achieved detailed recommendations on target volume definition for skull base tumors, as well as comprehensive advice about imaging modalities and radiation techniques.

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The skull base is an anatomically complex area encompassing portions of the anterior cranial fossa, clivus, petrous bone, middle cranial fossa, cavernous sinus and infratemporal fossa that includes critical endocrine, nervous, and vascular structures. Skull base tumors represent a very heterogeneous group of lesions with different degrees of aggressiveness; most common histologic types

include meningioma, pituitary adenoma, acoustic neuroma, cranio-pharyngioma, chordoma and chondrosarcoma.

Due to the intricate anatomy of the skull base, any treatment can potentially be associated with severe side effects; therefore, interdisciplinary decision making is essential. Only recently, several clinical practice guidelines have provided recommendations for the management of skull base tumors [1–6]. In most cases, surgery is the first step in treating skull base tumors and the vast majority of patients can be successfully treated by surgical resection alone, notably those with less aggressive and favorably located tumors. Radiation therapy (RT) is usually recommended to improve local tumor control in patients with incomplete resection of large tumors at higher risk of surgical complications and in those with completely resected tumors that display histological features associated with aggressive behavior [7–13]. In addition, RT has been established as an effective first-line treatment for selected tumors, e.g. vestibular schwannoma or cavernous sinus meningioma [3,6]. Additionally, data available today for RT indications includes large and pooled series from experienced institutions underlining the growing role of RT in the interdisciplinary context [14].

The radiation oncologist is challenged in the skull base region. Over the years, technological advances have led to improvements in every step of the radiation treatment process, including imaging techniques, treatment planning, dose delivery, and accuracy of patient repositioning. Modern stereotactic treatment techniques, either stereotactic radiosurgery (SRS) or stereotactic radiotherapy (SRT), using Gamma Knife (GK), CyberKnife (CK), and dedicated linear accelerator (LINAC)-based technologies, have resulted in further improvement of target dose coverage, conformity and organs at risk (OARs) sparing. In addition, there has been a renewed interest in using particle therapy for such tumors due to technological advances in the delivery of proton and carbon ion RT [15–17]. Along with greater accuracy of dose delivery and patient repositioning, more improvements in imaging techniques such as new sequences in MRI or novel tracers for PET-imaging have enabled tumor spatial accuracy, contributing to reduce inter-observer variability in target delineation [18–20]. As for other steps in the treatment planning process, an accurate delineation of tumor volumes and OARs is mandatory for a precise calculation of the spatial dose distribution, and for choosing the optimal radiation dose and fractionation schedule.

The purpose of the present guideline article is to provide recommendations on target volume delineation for skull base tumors.

Methods and materials

An ESTRO task force of 16 European experts consisting of radiation oncologists (12), neuroradiologists (2) and physicists (2) discussed and analyzed the body of evidence concerning skull base tumors target delineation. The PubMed database was searched using combinations of the following medical subjects headings (MeSH) and free-text words: “radiation therapy” or “stereotactic radiosurgery” or “proton therapy” or “particle beam therapy” and “skull base neoplasms” “pituitary neoplasms”, “meningioma”, “craniopharyngioma”, “chordoma”, “chondrosarcoma”, “acoustic neuroma/vestibular schwannoma”, “organs at risk”, “gross tumor volume”, “clinical tumor volume”, “planning tumor volume”, “target volume”, “target delineation”, “dose constraints”. In parallel, abstracts from ESTRO and ASTRO were analyzed. Searches were completed by May 15, 2020. Based on the initial searches, a total of 8483 articles and abstracts were identified. With the participation of all authors, 171 relevant papers containing data on target delineation of skull base tumors and clinical outcomes following photon or proton RT in adult patients were chosen for the final

guidelines. Open questions were identified and decisions were met according to the majority view.

Results

Preparation

For treatment planning, patients are generally placed in the supine position with the head fixed using an individual mask system, commonly a thermoplastic mask. In general, a neutral position usually ensures a good position reproducibility and high treatment accuracy throughout the course of treatment; however, a flexed head position is performed in some centers since tilting can facilitate a simpler beam arrangement above the eyes.

With SRS, which traditionally refers to the use of frame-based SRS, a stereotactic head frame is typically fixed to the skull under local anesthesia. As onboard imaging has advanced, SRS technology has evolved with the development of frameless SRS, with patients who are usually immobilized in a high precision mask fixation system and the SRS dose is precisely delivered with approximately 1-mm targeting accuracy to intracranial targets in one to five fractions via stereotactic guidance [21]. Currently, there are several terms that have been used interchangeably for fractionated SRS; they include “multi-fraction SRS”, “multi-dose SRS”, “multi-session SRS”, “hypofractionated SRS”, “hypofractionated stereotactic radiotherapy”. With the same fixation systems and level of accuracy, the dose can be delivered in more than five fractions, so-called stereotactic RT (SRT) using either conventionally fractionated (1.8–2.0 Gy per fraction) or hypofractionated (fraction sizes greater than 2 Gy) schedules. Several commercial stereotactic mask fixation systems are currently available with a reported repositioning accuracy of 1–3 mm [22]. A customized mouth-bite attached to a thermoplastic cast that conforms to the teeth and/or maxilla is used in some centers with similar accuracy.

A computed tomography (CT) scan should be performed using thin slice, generally 1–2 mm thickness from the vertex to the bottom of the third cervical vertebra (C3). Intravenous contrast should be considered for all patients with enhancing tumors when MRI fusion is unavailable or if additional information from a contrast-enhanced CT will be used for treatment planning.

Imaging for treatment planning

Magnetic resonance imaging (MRI) using pre- and post-contrast T1-weighted and T2-weighted images is mandatory for precise radiation treatment of skull base tumors. Improvements for treatment planning accuracy include correction of geometric distortion in MR images, minimization of the time interval between MRI and treatment delivery, and the use of specific sequences for target delineation. Several mechanisms may cause significant distortions in MR images and jeopardize precise treatment delivery [23–27]. Image distortions causing significant GTV displacement arise mainly from magnetic field inhomogeneities and gradient field nonlinearities [26,27], and typically increase with distance from the isocenter and at air-bone interfaces, e.g. tumors near the paranasal sinuses and mastoid cells [24,25]. Minimization of image distortion to less than 1 mm can be obtained by using three-dimensional (3D) vendor specific geometric distortion correction algorithms, patient-specific active shimming in the scanner software, higher readout bandwidth, and isotropic 3D sequences [28]. Performing MRI in the treatment position with an immobilization mask could reduce errors due to nonrigid tissue deformation and uncertainties related to image registration; however, similar high registration accuracy can be obtained using planning CT and MR images with a thin (1 mm) slice thickness while maintaining the head and neck in a neutral position. Registration

between MR and CT should be carefully reviewed; in presence of different head extension, registration accuracy can be increased by using the region of interest instead of the whole head.

The time interval between imaging and treatment delivery should be as short as possible; the interval should not exceed one week in patients with aggressive and malignant tumors due to the high risk of tumor increase or resection cavity volume changes, whereas longer time intervals up to three-four weeks can be safely applied in those with benign tumors.

MR images should be discussed with the radiologist, since requirements on MRI for RT may differ from routine diagnostic imaging. Contrast-enhanced 3D fast gradient echo T1-weighted sequences obtained with a voxel size of $1 \times 1 \times 1$ mm, named MPRAGE, 3D FLASH, 3D FGRE, 3D FSPGR, 3D TFE, 3D FFE depending on the manufacturer, should be recommended for their high spatial resolution and accurate characterization of subtle enhancement patterns in the surrounding neurovascular structures, and along the course of the optic nerves [29–31]. In addition, they allow reformatting of 3D data for viewing in all three planes without loss of resolution, and are less susceptible to B0 inhomogeneity-related distortions than 2D-sequences. Contrast-enhanced T1-weighted images with fat suppression are helpful to suppress the bright signal of fat tissue of the skull base that might obscure the accuracy of tumor contouring and to discern postoperative changes. T2-weighted images can be sensitive in identifying brain parenchymal abnormalities, e.g. tumor infiltration and peritumoral edema; a cerebrospinal fluid (CSF) cleft between the lesion and the brain is often seen in benign extra-axial tumors as a T2-weighted crescent, whereas such clefts can be absent when aggressive tumors invade the brain parenchyma. Finally, the use of high-resolution 3D T2-weighted steady-state precession sequences, including three-dimensional Constructive Interference Steady State [3D-CISS] or Fast Imaging Employing Steady-state Acquisition [FIESTA], may be useful for improving the visualization the internal segments of cranial nerves.

For resected tumors, the treatment planning is based on postoperative MRI, although preoperative images may provide useful information regarding either the initial extent of disease or the identification of persistent brain infiltration after resection of aggressive tumors, e.g. chordomas, atypical and malignant meningiomas. In addition, preoperative MRI is helpful to discern postoperative changes from tumor tissue, especially in patients who have undergone several prior surgeries. For planning purposes, MRI scans are subsequently fused with thin-slice non-contrast enhanced CT scans. Of note, CT scans may have a complimentary role in the imaging of skull base, specifically showing the pattern of bone involvement, e.g. hyperostosis and osteolysis, as well identifying intratumoral calcification better than MRI [30]. A contrast-enhanced CT is usually recommended only if MRI cannot be performed. Provided that a robust quality assurance (QA) protocol for registration of CT and MRI data sets for treatment planning is implemented and geometric distortion correction is applied, no additional margins would be required to ensure adequate target coverage to compensate for fusion uncertainties.

General target delineation strategy

The gross tumor volume (GTV) is defined as the visible lesion on MRI; typically, this is the contrast-enhancing lesion. The clinical target volume (CTV) is defined as the volume of tissue that contains the GTV and any microscopic disease and potential paths of microscopic spread. In general, additional margin expansion from GTV to CTV is unnecessary for benign skull base tumors; however, a small margin of 1–3 mm may be added to encompass potential areas of microscopic tumor infiltration, e.g. the intracavernous portion of rapidly growing lesions. For specific histologies, such as

atypical and malignant meningiomas or chordomas, large CTV margins in the range of 10–20 mm are frequently utilized to adequately cover the microscopic extent of disease, that may be reduced around natural barriers to tumor growth such as the skull.

The planning target volume (PTV) is defined as the margin accounting for both the internal and external uncertainties in treatment planning and delivery, including those arising from CT-MRI fusion and patient setup. No GTV-to-PTV margin is usually applied to invasive frame-based SRS. With the use of modern frameless SRS systems, either CyberKnife (CK) or dedicated LINAC technology (Novalis Tx™) [32–38], a sub-millimetric accuracy of target positioning has been reported; in clinical practice, a margin of 1–2 mm is generally used for GTV-to-PTV expansion in patients receiving frameless SRS, while a larger margin up to 3 mm is applied for those undergoing SRT; in this regard, each department should audit their setup results and apply the margins on the basis of their own measurements. When using conventionally fractionated 3D-conformal RT or intensity-modulated radiotherapy (IMRT), larger PTV margins of about 3–5 mm are required, being similar to those used for proton beam therapy. With the aim of decreasing the variability of clinical target volume delineation, it is important to develop a rigorous peer reviewed QA process at the departmental level [39]. All contouring steps should be supervised by an expert radiation oncologist. Before the planning process, an additional review done by other radiation oncologists is recommended to improve target volume delineation and to decrease inter-observer variability.

Organs at risk

The skull base region contains important endocrine, nervous, and vascular structures; then, a careful delineation of all organs at risk (OARs) including brain parenchyma, optic nerves and chiasm, brainstem, pituitary stalk, pituitary gland, cochleae, hippocampi, eyes, and lenses are essential to predict and hopefully prevent normal tissue injury. An example of OARs delineation on MRI in a patient with a skull base tumor is shown in Fig. 1. Definition of OARs delineated in Fig. 1 is summarized in Table 1. An atlas of brain OARs relevant to neuro-oncology has been recently created by the ESTRO taskforce “European Particle Therapy Network (EPTN)” and is available online on www.cancerdata.org [40]. Expansion of OARs to create a planning risk volume (PRV) for each OAR may be applied; the margin, as for the PTV, should reflect the accuracy of daily set-up. Overlaps between PRVs and PTV may occur; however, the delineation of the primary PTV margins should not be compromised and caution should be used when the reduction of the dose to the OARs may result in inadequate dose coverage of the PTV.

Techniques in skull base radiation oncology

Both SRS and SRT are employed for skull base tumors. Brain SRS, delivered in a single-or few (2–5) fractions, is typically performed using GK, CK, and LINAC-based SRS technologies. GK uses 192 radioactive cobalt-60 sources that are hemispherically arranged in a single internal collimation system via collimators to focus their beams to a center point. The tungsten collimators are organized into eight sectors of 24 sources each with three different apertures of 4, 8, and 16 mm, which deliver the radiation dose to the target using one or multiple isocenters depending on the size, shape, and location of lesions. Traditionally, patients who undergo GK are placed in a rigid stereotactic frame with a target accuracy <0.5 mm [32,33], although in its latest version (Icon GK) the dose can also be delivered as mask-based SRS.

The CK combines a compact 6-MV linear accelerator mounted on a robotic arm with 6 degrees of freedom. It uses adjustable

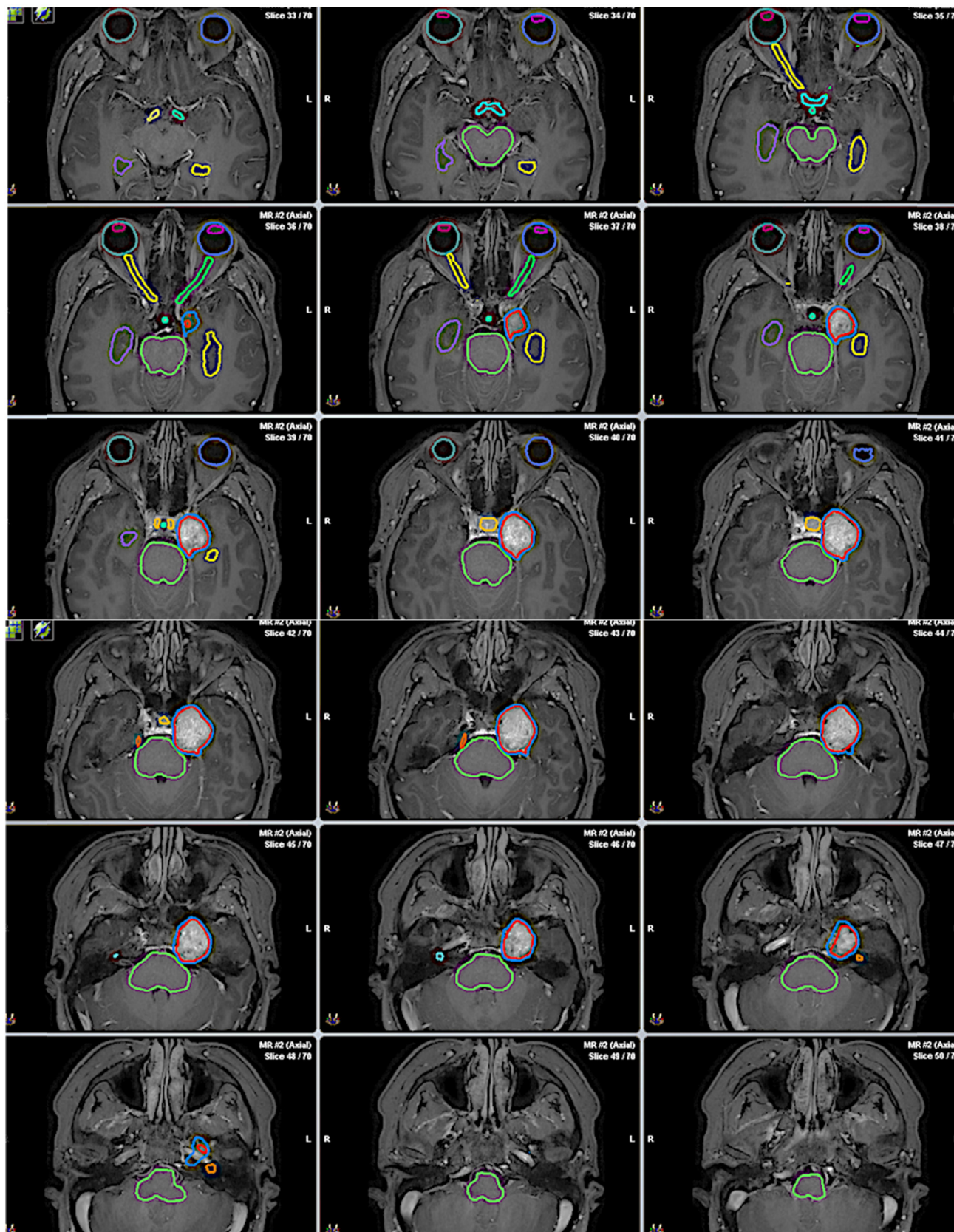


Fig. 1. An overview of target volumes and organs at risk (OARs) delineation of a skull base tumor (cavernous sinus meningioma) slice per slice is presented on post-contrast T1-weighted MRI sequences. The gross tumor volume (GTV) is presented in red and the planning tumor volume (PTV) in blue. The following OARs have been contoured: brainstem (green); optic chiasm (cyan); left optic nerve (lime green); right optic nerve (yellow); left eye (dark blue); right eye (aquamarine); right optic tract (lemon); left optic tract (light green); left lens (pink); right lens (dark red); pituitary gland (cheddar); pituitary stalk (turquoise); right hippocampus (purple); left hippocampus (gold); right fifth nerve (redorange); right cochlea (light blue); left cochlea (orange). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1
Description of main organs at risk (OARs) contoured in the skull base tumor illustrated in Fig. 1.

OAR	Description
Left optic nerve (lime green; panels 3–6) and right optic nerve (yellow; panels 3–5). Thick, 2–5 mm Optic chiasm (cyan; panels 2–3). Thick, 2–5 mm	The optic nerve is delineated from the posterior edge of eyeball to the optic chiasm (panel 2–3). Visible on both MRI and CT, the latest useful for the relationship with bony optic canal The optic chiasm is located in the suprasellar region (about 1 cm from the pituitary gland) anteriorly to the pituitary stalk. It is formed by the convergence of the optic nerves anteriorly (panel 3) and by the divergence of the optic tracts posteriorly (panel 1); laterally it is in contact/close proximity to the Internal carotid artery. For a better delineation, coronal and sagittal images are recommended. The optic chiasm is better delineated on T1-weighted MRI sequences, visible also on CT
Right optic tract (lemon; panel 1) and left optic tract (light green; panel 1). Thick 2–5 mm Right (aquamarine) and left (dark blue) retina (posterior part of eyeball; panel 1–8). Thick, 2–3 mm Pituitary gland (cheddar; panels 7–10). Volume 0.25–0.5 cc	The optic tracts are visible posteriorly to the optic chiasm and anteriorly/laterally to the midbrain for 10–20 mm. Better delineation on T1-weighted MRI sequences, visible also on CT The retina is delineated on MRI and CT as the posterior part of the eyeball The pituitary gland lies on the sella turcica with a cranio-caudal dimension of 10–12 mm and bilaterally is bordered by cavernous sinuses. Visible on axial T1-weighted contrast-enhanced MRI. For a better delineation, coronal and sagittal images are recommended
Pituitary stalk (turquoise; panels 3–7). Thick 1–2 mm	The pituitary stalk has a length of 7–10 mm; it is delineated from hypothalamus (cranial limit) just behind the optic chiasm to the pituitary gland (caudal limit). For a better delineation, coronal and sagittal T1-weighted contrast-enhanced MR images are recommended
Brainstem (green; all panels)	The brainstem is seen on both MRI and CT. In craniocaudal direction, the midbrain, pons and medulla oblongata (up to the tip of C3 dens) are delineated. On panels 10 and 11, the right trigeminal nerve (fifth nerve) is delineated from the pons to the entrance of the nerve into Merckel's cave (redorange)
Right hippocampus (purple; panels 1–7) and left hippocampus (gold; panels 1–7). Volume, 2.5–4.0 cc	The hippocampus is constituted by grey matter and is easily distinguishable on T1-weighted MRI sequences. It is delineated as hypointense area medial to the curve of the temporal horn of the lateral ventricle (from panel 7), then continuing in the upward direction, bordered medially by the lateral edge of the quadrigeminal cistern (panel 1). Sagittal images can help OAR delineation
Right cochlea (light blue; panels 13–14) and left cochlea (orange; panels 15–16). Volume 0.5–0.6 cc	The cochlea is a spiral structure located in a bony cavity in the petrous portion of the temporal bone, anterior to the labyrinth, lateral to the internal auditory canal. It can be delineated on the basis of CT or MRI (better T2-weighted MR images) without inclusion of the semicircular canals (located laterally and cranially of the cochlea)

collimator cones ranging from 5 to 60 mm to generate highly conformal treatments with up to 200 overlapping beams which are delivered non-isocentrically to the target [41–43]. As for other LINAC-based SRS systems, patients are fixed in a thermoplastic mask and submillimeter target positioning accuracy is achieved with the use of regular high-resolution kV imaging acquired throughout the treatment.

With LINAC-based SRS, doses are delivered through multiple fixed beams or dynamic conformal arcs using either circular collimators or micro-multileaf collimators (MLC) with a leaf width of between 2.5 and 5 mm. Dose conformity is improved using IMRT and volumetric-modulated arc therapy (VMAT) techniques [44]. Patients are usually immobilized in a high precision frameless stereotactic mask fixation system and submillimeter accuracy of patient positioning in the treatment room is achieved using modern image guided radiation therapy (IGRT) technologies, such as orthogonal x-rays (ExacTrac®Xray 6D system) or cone beam CT (CBCT) [34–38].

For patients with large complex skull base tumors receiving conventionally fractionated SRT, IMRT and VMAT planning techniques are increasingly being used over 3D conformal RT because of its better target coverage and OARs sparing, although at the cost of larger volumes receiving low dose radiation. Precise immobilization and improved patient positioning can be achieved using sophisticated immobilization and image guidance systems as seen for LINAC-based SRS. Regardless of the used technique, strict protocols for QA must be followed since SRS and SRT require levels of precision and accuracy that surpass the requirements of 3D conformal RT and IMRT techniques.

Particle therapy, including protons and carbon ions, have been employed for skull base tumors using either fractionated RT or SRS [15,45–48]. A physical advantage of protons over photons is that they deposit most of their energy at the end of their range, with very little exit dose beyond the target volume. This narrow region of energy deposition is known as the Bragg peak and it may allow for a reduction in integral dose delivered to the surrounding normal tissues. Currently, there are two types of proton

therapy delivery: passively scattered and pencil beam proton therapy. In passive scattering, a spread-out Bragg peak is generated by modulations of multiple mono-energetic beams to ensure a uniform dose distribution across the target through a single or double scattering, the latter required for larger volumes. Dose conformation is achieved through the use of range shifter wheels and patient-specific apertures and compensators [49,50]. In active scanning (often called pencil beam scanning or spot scanning), proton dose dosimetry optimization can be achieved using narrow pencil proton beams, with a near monoenergetic Bragg peak, superposition of which constitutes the treated volume [51–53]. Intensity modulated proton therapy (IMPT) represents an advanced pencil-beam delivery optimization strategy; using this proton beam technology, both the scanning speed and the intensity of the beam are modulated to improve the PTV dose homogeneity and conformity, thus minimizing the dose delivered to OARs. Although different techniques and dose fractionation schedules can be used for treating skull base tumors, GTV and CTV target delineation strategies remain similar.

Planning details

The overall goal of radiation treatment planning is to ensure the optimal coverage of the target with the prescription dose while respecting all the OARs dose constraints. Depending on the technique, dose is prescribed to the 40–95% isodose surface. For LINAC-based and CK SRS treatments, the dose is typically prescribed to 70–80% isodose [21,54]. This is because the dose gradient falls off most quickly outside the target, between the 80% and 40% isodose surfaces [55]. Therefore, prescribing in this range minimizes the integral dose to all normal tissues, therefore affording the most OAR sparing. For multiple isocenter plans, this optimal surface shifts to the 40–50% isodose surface and can be extended to isodose surfaces as low as the 40% isodose surface, as is often the case in GK plans [56]. Prescription isodoses are typically higher when larger skull base tumors are treated with hypo- or conventional fractionation.

The risk of toxicity following irradiation of skull base tumors is influenced by different factors, including the total dose, dose per fraction, and the volume of normal tissue irradiated at high doses. A summary of dose/volume data and clinical risk estimates for central nervous system (CNS) structures following conventionally fractionated RT and SRS, based on a combination of clinical observations and reviews, is presented in Table 2 [57–73]. A recent consensus report of OAR dose constraints in neuro-oncology has been recently published by the European Particle Therapy Network of ESTRO with the aim to create a model-based approach comparing photon and proton beam irradiation [74].

Target volume definition for specific indications

Pituitary tumor

Transsphenoidal surgery is the first-line treatment for most pituitary tumors, either nonfunctioning or secreting tumors, such as ACTH- and GH-secreting tumors. Radical resection is achieved in a significant proportion of patients with a low incidence of peri- and post-operative complications [2,75–78]. Based on recent guidelines, RT is generally used in patients with large residual or recurrent pituitary tumors [4,5,12]. The reported local control of large retrospective series following either SRS or SRT [79] is in the range of 90–95% at 5–10 years, with normalization of hormone excess observed in about 50–60% of secreting pituitary adenomas; the time in reaching normalisation is related to the initial hormone level. Dose and fractionation are usually chosen on the basis of the type, size and location of the tumor. In current clinical practice, single-fraction SRS at doses of 13–16 Gy and 16–25 Gy is a feasible approach to patients with non-functioning and secreting pituitary adenomas less than 2.0–2.5 cm in size at safe distance from the optic chiasm (maximum point dose less than 8–10 Gy; see Table 2), respectively. Few studies report on fractionated SRS, usually 21 Gy in 3 fractions or 25 Gy in 5 fractions, showing tumor control rates consistent with that observed after single-fraction SRS [79,80]. For larger lesions and/or those involving the anterior optic pathway, fractionated RT, including either SRT or IMRT, is usually recommended. Doses of 45–50.4 Gy are typically delivered in 25–28 fractions of 1.8–2.0 Gy per fraction, with higher doses used when treating secreting pituitary adenomas; doses up to 54 Gy may be used for large aggressive pituitary tumors and carcinomas [5,81].

The GTV is defined as the visible lesion on MRI. Target delineation should be performed using pre- and postcontrast-enhanced isotropic 3D T1-weighted sequences with 1 mm slice thickness. Preoperative and contrast-enhanced T1-weighted images with fat suppression may be helpful to discern postoperative changes from the tumor (including fat or biomaterial apposition), especially in patients who have undergone several surgeries. When MRI is contraindicated, a contrast-enhanced thin-slice CT through the pituitary region should be performed before and after contrast administration. Additional margin expansion from GTV to CTV is unnecessary; however, a margin of 2–3 mm may be added in case of invasive and aggressive pituitary tumors to encompass all potential areas of microscopic tumor infiltration, e.g. fast-growing tumors invading the cavernous sinus. For fixed-frame SRS, no GTV-to-PTV margin is generally necessary, whereas an additional safety margin of around 1–3 mm is usually used for frameless SRS and SRT depending on institutional practice. If advanced image guided techniques are not available, larger margins up to 5 mm should be employed. OARs include optic nerves and chiasm, brainstem, pituitary stalk, pituitary gland, cochleae, hippocampi, normal brain, eye, and lenses.

Meningioma

Intracranial meningiomas represent about one third of all primary brain tumors with an estimated annual incidence of approximately 6 per 100,000 people, generally increasing with age. According to the World Health Organization (WHO) classification scheme [82], meningiomas are histologically characterized as benign (grade I), atypical (grade II), or malignant (grade III). Typical characteristics of grade II meningiomas are a mitotic count of 4–19 per HPF and/or brain invasion. Grade III meningiomas are characterized by elevated mitotic activity (20 or more per HPF) or frank anaplasia. Surgery is the treatment of choice for the majority of symptomatic and enlarging meningiomas, with the aim of alleviating symptoms, relieving mass effect, and providing histology. Complete resection of the tumor and any involved dura or bone is the gold standard for meningioma and is associated with long term local control in more than 80% of patients at 5–10 years [3,83].

RT is usually employed in patients with residual or recurrent benign meningiomas following surgical resection, for those with unresectable tumors or not amenable to surgery, and with atypical

Table 2
Summary of normal tissue constraints using standard fractionated RT (2 Gy per fraction) and SRS (1–5 fractions).

Organ	Type of radiation	Dose constraint (toxicity rate)	Type of toxicity	References
Brain	Standard fractionation	Dmax <60 Gy to whole organ (<3%)	Symptomatic necrosis	[57,60,63,72,73]
	Single-fraction SRS	12 Gy to <5–10 ml (<10–20%)		
	3-fraction SRS	18 Gy (6 Gy/fx) to <26 ml (3%)		
Brainstem	Standard fractionation	Dmax <54 Gy to whole structure (<5%)	Permanent cranial deficit or necrosis	[57,60,63,65]
	Single-fraction SRS	Dmax <12.5 Gy (<5%; 1% if to 1/3 of brainstem)		
	3-fraction SRS	Dmax 18 Gy (6 Gy/fx) to <1 ml (<3%)		
Optic nerve/chiasm	5-fraction SRS	Dmax 26 Gy (5.2 Gy/fx) to <1 ml (<3%)	Optic neuropathy	[57,58,66,69]
	Standard fractionation	Dmax <55 Gy to whole structure (<3%)		
	Single-fraction SRS	Dmax <8 Gy (<3%), Dmax 8–12 Gy (<10%)		
Cochlea	3-fraction SRS	19.5 Gy (6.5 Gy/fx) (<3%)	Hearing loss	[57,60,61]
	5-fraction SRS	Dmax 25 Gy (5 Gy/fx) (<3%)		
	Standard fractionation	Mean dose ≤45 Gy to whole structure (<15%)		
Pituitary gland	Single-fraction SRS	Dmax ≤14 Gy (<25%)	Hypopituitarism	[59,64,67,68,70]
	3-fraction SRS	Dmax 20 (6.67 Gy/fx) (<3%)		
	5-fraction SRS	Dmax 27.5 (5.5 Gy/fx) (3%)		
Hippocampus	Standard fractionation	Dmax ≤45 Gy to whole gland (20–40% at 5 years)	Memory impairment	[71]
	Single-fraction SRS	Dmax <15 Gy (2–30% at 5 years)		
Medulla Oblongata	Standard fractionation	Dmax ≤7.3 Gy to 40% of structure (impairment in Wechsler Memory Scale-III Word List delayed recall)	Myelopathy	[57,60,62]
	Single-fraction SRS	Dmax 54 Gy (1%) and 61 Gy (10%)		
	3-fraction SRS	Dmax 13 Gy (1%)		
	5-fraction SRS	Dmax 22.5 Gy (6.67 Gy/fx) (1%)		
		Dmax 30 Gy (6 Gy/fx) (1%)		

RT, Radiation Therapy; SRS, Stereotactic radiosurgery; Dmax, maximum dose.

or malignant tumors [3,11,13]. For benign meningiomas, local control rates after fractionated RT and SRS ranges from 85% to 95% at 5–10 years, with a reported low neurological and endocrinological toxicity [11,13,84–86]. Similar results have been shown after proton beam RT [17,87,88]. Typical doses used for SRS are 13 to 15 Gy given in a single fraction and 21–25 Gy given in three to five fractions. As for other skull base tumors, fractionated schedules with doses of 50–55 Gy in 25–33 daily fractions of 1.67–2.0 Gy, commonly 54 Gy at 1.8 Gy per fraction, are employed in the treatment of tumors larger than 3 cm in size or involving sensitive brain regions, i.e. brainstem or optic apparatus, while single-fraction SRS has been widely used to treat smaller lesions away from the optic chiasm.

Using doses of 54–60 Gy in 30–33 daily fractions of 1.8–2.0 Gy, two prospective phase II trials published by the Radiation Therapy Oncology Group (RTOG 0539) and the European Organisation for Research and Treatment of Cancer (EORTC) have shown progression-free survival rates of about 94% and 89%, respectively, at 3 years [89–91]. Although these trials suggest progression-free survival benefits of fractionated RT in patients with atypical meningiomas at three years with acceptable toxicity, the question if early adjuvant RT may reduce the risk of tumor recurrence after gross total surgical resection of a WHO grade II meningioma remains unanswered. A phase III intergroup trial is currently recruiting patients with atypical meningiomas who are randomized between observation and adjuvant treatment following surgery [92]. RT remains the treatment of choice in all malignant meningiomas, regardless of the type and extent of surgery although evidence of benefit is not clear.

For benign meningiomas, the GTV is generally defined as the visible lesion on contrast-enhanced T1-weighted MR images with 1–2 mm slice thickness. An example of target delineation for a cavernous sinus meningioma is given in Fig. 1. For atypical (Grade II) and malignant (Grade III) meningiomas, the GTV delineation should be based on the resection cavity (if available) plus any residual tumor without inclusion of the perilesional edema. Additional images that can help to improve target delineation include T2-weighted high-resolution gradient and fast spin echo sequences with and without fat suppression, and fluid attenuated inversion recovery (FLAIR) sequences. Specifically, T2-weighted sequences can also be useful to assess the extent of peritumoral edema and dural tail abnormalities [93,94]. In addition, extra-axial growth can be verified on T2-weighted images by cerebrospinal fluid (CSF) cleft interposed between the tumor and the parenchyma. CT is valuable for the detection of calcification of varying degrees within the tumor and hyperostosis of adjacent bone. In selected cases, PET imaging mainly with DOTATOC- or DOTANOC-tracers has shown to improve target volume definition, e.g. patients with large tumors infiltrating the parapharyngeal soft tissues or for those located in the bony structures which are difficult to be distinguished on MRI and CT [95–102].

The majority of meningiomas are durally based, and the question is whether the dural tail, which is the linearly enhanced dura trailing off from the meningioma for several millimeters, should be included or not in the GTV. Dural tail, that can be accurately identified in post-gadolinium T1-weighted images [93,94], is typically composed entirely or almost entirely of hypervascular dura [83,103–105] with microscopic clusters of meningioma that have been only occasionally observed in the dura adjacent to the tumor [106]. Although the issue remains matter of debate, there is no clear evidence that recurrences are more likely to occur within the dural tail than any other portion of dura next to the main tumor mass [107–109]. According to RTOG 0539 and EORTC 1308 trials, only clearly thickened dural tail should be considered as target and included in the GTV (Fig. 2); in contrast, linearly enhanced dura and non-enhancing but thickened dura trailing off

the tumor would not be included in the GTV. The same goes for the hyperostotic bone; only directly invaded bone and clearly hyperostotic bone should be included in the GTV using a CT bone window setting to improve target delineation (Fig. 3), as applied for EORTC 1308 and RTOG 0539 trials. For meningiomas characterized by diffuse and extensive dural involvement (so called “en plaque meningiomas), usually with extracranial extension into calvarium, orbit, and soft tissues, all dural thickening and enhancement should be included in the GTV.

In general, additional margin expansion from GTV to CTV is unnecessary for benign meningiomas; however, a small margin of few millimeters may be added to encompass potential areas of microscopic tumor infiltration in case of rapidly growing tumors, e.g. the intracavernous portion or the proximal region of the dural tail (avoiding extensive coverage of the distal portion). For Grade II and III meningiomas, the CTV is defined as the GTV plus a 1–2 cm margin and might include the pre-operative tumour bed, the peritumoral edema, hyperostotic bone changes, and the dural enhancement or thickening as seen at diagnosis; margins may be smaller (3–5 mm) around natural barriers to tumor growth such as the skull, and into surrounding brain parenchyma unless there is evidence of invasion.

Depending upon localization method and reproducibility, an institution-specific margin up to 5.0 mm is usually added to the CTV to generate the PTV. As for other skull base tumors, OARs have to be defined through MR (e.g., optic chiasm and nerves, pituitary gland and stalk, brainstem, carotid artery, hippocampi, lacrimal gland) and CT scan (lens, cochlea) in all plans.

Craniopharyngioma

Surgery is the initial treatment modality for most patients with a craniopharyngioma; complete resection is associated with a 5-year tumor growth control of 70–90% in adult and pediatric series, although aggressive surgical management is associated with a high risk of complications [110–114], particularly relating to hypothalamic damage. Limited surgery followed by radiation is an alternative to aggressive surgical treatments associated with comparable outcome and lower risk of long term sequelae [112,115–119].

For incompletely resected and recurrent tumors, conventionally fractionated postoperative RT is the recommended treatment. Using doses of 50–55 Gy in 25–33 daily of 1.67–2.0 Gy with either photons or protons, several large retrospective series report tumor control rates of 85–95% and survival rates of 90–100% at five years [15,17,120–123]. Compared with 3D conformal RT, IMRT-based stereotactic techniques and IMPT can offer improved dose conformity and reduced dose to adjacent normal structures [15,17]. SRS may represent an alternative treatment option in selected patients with small residual or recurrent craniopharyngiomas. Both single-fraction SRS up to 18 Gy and fractionated SRS (20–25 Gy in 3/5 fractions) have been employed in selected patients with a small tumor away from the optic chiasm; few retrospective series with limited number of patients report tumor control rates of 60 to 80% at five years, with long-term toxicity occurring in 3–7% of patients, mainly visual deterioration [124–129].

The GTV is defined as the visible lesion on post-contrast T1-weighted and T2-weighted MRI sequences with a 1–2 mm slice thickness to ensure the accuracy of target delineation. The solid portion of craniopharyngiomas is more precisely contoured using the contrast-enhanced 3D T1-weighted images, whereas fast spin-echo T2-weighted images with and without fat suppression allow for better visualization of cystic components of the tumor. The GTV has historically been expanded by a margin of 10–20 mm to generate the CTV and the PTV, given less reliable immobilization and image guidance; however, margins have progressively reduced. Currently, some institutions include a 3–5 mm

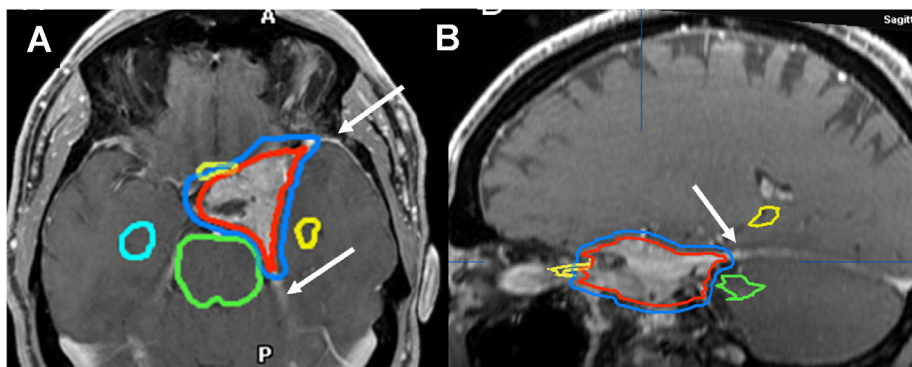


Fig. 2. Example of delineation of the dural tail for a skull base meningioma on axial (A) and sagittal (B) post-contrast T1-weighted MRI. Only thickened dural tail was included in the GTV (blue contour); in contrast, linearly enhanced dura (white arrows) was not included in the GTV. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

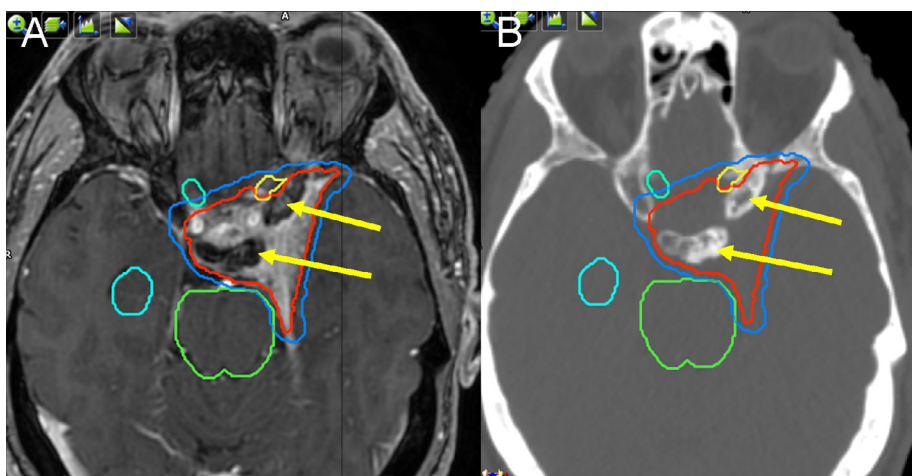


Fig. 3. Example of bony hyperostosis associated with a skull base meningioma on MRI (A) and CT (B) images. All areas of hyperostotic bone (yellow arrows) and potential bony tumor invasion were included in the gross tumor volume (GTV, red contour) using a CT bone window setting to improve target delineation. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

GTV-to-CTV margin to take into account potential microscopic areas of tumor infiltration and changes of cystic components of the tumor during the treatment that may occur in up to 40% of patients [130]; as for other skull base tumors, margins can be reduced at sites where tumor invasion is unlikely, e.g. skull base bones. The surgical report provides additional information that may help to identify all areas of adhesion noted intraoperatively into the CTV. Of note, few series have shown an excellent long-term control after fractionated SRT using smaller or no GTV-to-CTV expansion, then supporting the noninfiltrative nature of this tumor and the use of a reduced GTV-to-CTV margin [120,122]. Because a challenging component of craniopharyngioma management is the potential for cystic growth, a close surveillance imaging during the treatment is mandatory when reduced margins are used. For OARs delineation and dose constraints see above (Fig. 1). As for other tumors, PTV margins depends on institutional practice and used radiation technique.

Vestibular schwannoma

Vestibular schwannomas originate from the Schwann cells surrounding the eighth cranial nerve. Generally, they are benign, slow growing lesions and are associated with 1–3 mm growth per year [131–133]. Unilateral vestibular schwannoma is the most common

form (95%); neurofibromatosis-2 (NF2) accounts for 5% of all vestibular schwannomas and typically affects the VIII nerve bilaterally and young people [134,135]. Common symptoms include hearing loss or impairment, dizziness, tinnitus, and gait uncertainties.

Current treatment options for vestibular schwannoma include observation, surgical resection, SRS, and SRT. The choice of treatment depends on clinical presentation, tumor size, and expertise of the treating center. Small lesions which are asymptomatic can be observed with serial MRI scanning and audiological monitoring without any tumor-directed treatment [6,136]. Surgery is considered as the primary treatment to remove a symptomatic lesion or potentially life-threatening mass effect, although the treatment may also be considered for smaller tumors [6,137,138]. Gross total resection or near total resection is associated with local control rates of 80–90% [137–142]; in experienced surgical centers, the probability of hearing preservation in patients with small lesions and normal hearing is about 50–75% and 25–50% after 5 and 10 years [139,140], respectively, and the risk of persisting facial palsy is between 3% and 15%. [141].

RT is a safe and effective treatment for vestibular schwannomas; depending on the size of the lesion, it can be applied as SRS or fractionated SRT with comparable local control of 90–99% at

5 years, hearing preservation rates of 50–79%, facial nerve preservation rates of 95–100%, and trigeminal preservation rates of 80–99% [135,143–155]. Dose of single-fraction SRS should be in the range of 12–13 Gy. For patients receiving conventional fractionation, total doses ranging from 45 to 54 Gy given in 25–30 daily fractions of 1.8–2.0 Gy are currently recommended [6]. Hearing preservation rates are in the range of 60–90%, with patients with useful hearing prior to RT having the highest chance to fully preserve their hearing function [152–155]. Few retrospective series indicate that hypofractionated schedules may represent an effective treatment option for large vestibular schwannomas, typically 18 Gy in 3 fractions or 25 Gy in 5 fractions [156,157].

For GTV delineation, thin slice CT and MRI with and without contrast enhancement are recommended. The GTV is represented by the lesion visible on isotropic contrast-enhanced 3D T1-weighted sequences with 1 mm slice thickness. Additional sequences are represented by high resolution 3D T2-weighted sequences (e.g. CISS/FIESTA) may improve the visualization of cisternal segments of the lower cranial nerves and their relationship with the tumor. For contouring, bony CT windows are helpful since the enlargement of the vestibular canal can be visible representing the tumor volume. For frame-based SRS, no additional safety margin is necessary as precise positioning is established. With frameless SRS and SRT, a GTV-to-PTV safety margin of around 1–3 mm can be necessary depending on immobilization and IGRT techniques used at different institutions.

Chordoma/Chondrosarcoma

Chordomas and chondrosarcomas are rare, locally aggressive tumors occurring in one third of cases in the base of the skull. The mainstay of treatment is maximal tumor debulking. En bloc resection is the recommended treatment with 5-year local recurrence free-survival rates of more than 50% [1,158–160]; however, en bloc resection with R0 margins for skull base chordomas and chondrosarcomas (negative microscopic margin of 1 mm or greater of normal tissue around the tumor) is very rarely achievable, despite major advances in cytoreductive surgical interventions. Surgery should be practiced in referral centers, since the quality and extent of surgery are the principal determinants of outcome, together with tumor size, quality of RT, and patient age [161,162].

Proton beam therapy has been traditionally used for the radiation treatment of chordomas with doses of 72–76 Gy achieving a local tumor control between 60% and 81% at 5 years [7,162–164]. Moderate hypofractionation with 16–22 fractions of 3–4.2 GyE per fraction is feasible using carbon ions [1]. Using photon radiation, a few studies have reported 5-year local control rates of 50–76% after conventionally fractionated SRT using doses up to 70 Gy at 1.8–2.0 Gy per fractions and GK SRS using marginal doses of 13–20 Gy [15,165–170]. Using similar doses, retrospective series have reported better local control rates in the range of 94–100% at 10 years for chondrosarcomas [8,171], although it is questionable if these patients need high-dose radiation, as tumors with good prognostic factors (i.e. small residual tumors, young age, no brainstem/optic apparatus abutment) rarely recur and treatments can carry significant risk of radiation-induced toxicity, including but not limited to temporal lobe necrosis and optic neuropathy.

For the target delineation of these challenging tumors, the GTV is usually delineated as the tumor remnant observed on MRI sequences with 1–2 mm slice thickness, including T1-weighted, T2-weighted, and contrast-enhanced T1-weighted imaging fused to the planning CT. Even though there is no unanimous consensus on optimal target delineation of these tumors, it is key to include comprehensive margins in the delineation process, as inadequate ‘radiosurgical’ margin reduction can be associated with a higher rate of treatment failure. The CTV should encompass all potential areas at risk of microscopic spread of disease and is typically based

on preoperative tumor volume and postoperative residual tumors and resection margins.

In many proton centers, two distinct CTV volumes receiving different doses are applied: the primary CTV (CTV1, 54 GyRBE) is usually defined by preoperative tumor volume with an anisotropic margin of 10–20 mm plus the residual tumor and surgical resection margins. Normal structures previously compressed by the tumor that re-expand after surgery are not included in the CTV1, e.g. brainstem, chiasm, temporal lobe parenchyma, or pharynx (in case of tumor extension to the cervical spine). Similarly, peritumoral edema, as seen in cases of initial compression of the temporal lobe, does not require inclusion in the CTV. The surgical tract is not comprehensively treated in skull base chordomas since this delineation strategy would result in a substantial increase of normal tissue irradiation, and bearing in mind that surgical pathway failure after surgical seeding is rare (i.e. 1–2%) [34,172]. For patients receiving a transsphenoidal approach, the posterior part of residual sphenoid sinus is routinely included in the CTV1. A second CTV (CTV2) receiving a higher boost-dose of radiation (74–76 GyRBE for chordoma, 70–72 GyRBE for chondrosarcoma) should comprise the residual tumor with a geometrical expansion of 5–10 mm (reduced around natural barriers to tumor growth) plus the resection margins at higher risk of residual disease. In case of macroscopically radical resection, CTV2 is limited to the resection margins. Depending on radiation techniques and available technology, a variable CTV-to-PTV margin up to 5 mm is applied, with protons usually requiring larger margins than photon stereotactic techniques.

Conclusions

More accurate and uniform target delineation guidelines for skull base tumors should help to promote equality and improvement of outcomes. A summary of recommended imaging modalities for target volumes delineation and dose fractionation using either fractionated RT or SRS for different skull base tumors is reported in table 3. While recognising that there is a range of approaches to defining the target volume of the different tumor entities, the ESTRO ACROP guideline committee proposes the following pragmatic algorithm:

- Immobilization with a fixed or relocatable frame or a closely fitting thermoplastic mask system, planning CT with 1–2 mm slice thickness.
- Fusion with MRI obtained at the time of radiation treatment, usually isotropic contrast-enhanced 3D T1-weighted sequences with 1 mm slice thickness. Other examinations, including preoperative MRI, unenhanced T1-weighted MRI, and high-resolution 3D T2-weighted MRI sequences may allow more precise target delineation.
- GTV defined as the T1-weighted contrast-enhancing lesion. For atypical and malignant skull base tumors, e.g. chordomas and atypical and malignant meningiomas, GTV includes the resection cavity (if available) plus any enhancing residual tumor.
- No margin around the GTV should be applied to generate the CTV in benign tumors, but this can be edited to take into account possible microscopic disease, e.g. cavernous sinus or brain parenchyma in rapidly growing, invasive tumors. A variable GTV-to-CTV margin of 1–2 cm is applied in aggressive and malignant tumors.
- No CTV-to-PTV margin is usually necessary for invasive frame-based SRS; 1–2 mm margin expansion is generally used in patients receiving frameless SRS and up to 3 mm for those undergoing SRT depending on accuracy of patient immobilization, positioning and monitoring systems. If IGRT techniques

Table 3
Summary of imaging modalities for target volumes delineation and dose/fractionations for skull base tumors.

Tumor type	WHO grading	Imaging for target delineation	Gross Tumor Volume (GTV)	Clinical Tumor Volume (CTV)	Planning Target Volume (PTV)	Dose and fractionation
Pituitary tumor	Typical adenoma or high-risk adenoma (rapid growth, radiological invasion, high Ki-67 proliferation index)	Isotropic pre- and post-contrast-enhanced 3D T1-weighted MRI sequences with 1 mm thick slices	Visible lesion on MR images	Margin expansion from GTV-to-CTV is unnecessary for typical adenoma; a GTV-to-CTV margin of 2–3 mm may be added in aggressive pituitary tumors and carcinomas	For fixed-frame SRS, no additional safety margin is necessary; for frameless SRS and SRT, a GTV-to-PTV margin of 1–3 mm is usually used	16–25 Gy using single-fraction SRS; 21–25 Gy in 3–5 fractions using fractionated SRS; 45–50.4 Gy at 1.8–2.0 Gy per fraction using fractionated RT (large tumors involving the optic apparatus). Higher doses up to 54 Gy for high-risk tumors)
Meningioma	WHO grade I	Isotropic post-contrast-enhanced 3D T1-weighted MRI sequences with 1 mm thick slices and T2-weighted images. PET-Imaging with DOTATOC- or DOTANOC-tracers may improve GTV delineation in selected cases	Visible lesion on MR images; only thickened dural tail should be included in the GTV (not linearly enhanced dura and non-enhancing tickened dura)	Margin expansion from GTV-to-CTV is usually unnecessary	For fixed-frame SRS, no additional safety margin is necessary; for frameless SRS and SRT, a GTV-to-PTV margin of 1–3 mm is usually used	13–15 Gy using single-fraction SRS; 21–25 Gy in 3–5 fractions using fractionated SRS; 50–55 Gy at 1.67–2.0 Gy per fraction using fractionated RT (usually large tumors involving the optic apparatus)
	WHO grade II WHO grade III	Isotropic pre- and post-contrast-enhanced 3D T1-weighted sequences with 1 mm thick slices and T2-weighted images. PET-Imaging may improve GTV delineation in selected cases. CT can be useful for the detection of calcification within the tumor and hyperostosis of adjacent bone	Tumor bed on postoperative contrast-enhanced T1-weighted MR images with inclusion of any residual nodular enhancement. Clearly hyperostotic bone should be included in the GTV	The CTV is defined as the GTV plus 1–2 cm margins and should include the pre-operative tumor bed, peritumoral edema, hyperostotic bone changes, and dural enhancement or thickening. Smaller margins (5–10 mm) around natural barriers to tumor growth, such as the skull, and into surrounding brain parenchyma unless there is evidence of invasion	A CTV-to-PTV margin up to 5.0 mm are usually added (institution specific)	54–60 Gy in 30 daily fractions of 1.8.2.0 Gy is recommended; SRS 14–16 Gy may be an option for small recurrent tumors
Craniopharyngioma	WHO grade I	Isotropic pre- and post-contrast T1-weighted and T2-weighted MRI sequences with 1 mm thick slices.	Visible lesion on contrast-enhanced T1-weighted MR images. T2-weighted fast spin-echo technique may allow for better visualization of cystic components of the tumor.	GTV-to-CTV expansion is unnecessary as for other non-infiltrative tumors.; however, some institutions use 3–5 mm GTV-to-CTV margin with fractionated RT.	For fixed-frame SRS, no additional safety margin; for frameless SRS and SRT, a GTV-to-PTV margin of 1–3 mm is usually used according to Institutional practice.	50–55 Gy at 1.67–1.8 Gy per fraction; single-fraction SRS (12–18 Gy) or fractionated SRS (21–25 Gy in 3/5 fractions for selected patients with small tumors away from optic chiasm.
Vestibular Schwannoma	WHO grade I	Isotropic pre- and post-contrast T1-weighted and T2-weighted MRI sequences with 1 mm thick slices. Additional images include high resolution 3D T2-weighted sequences (e.g. CISS/FIESTA)	Visible lesion on contrast-enhanced T1-weighted MR images. High resolution 3D T2-weighted sequences may improve visualization of the target and cranial nerves	Margin expansion from GTV to CTV is usually unnecessary	For SRS, no additional safety margin is necessary; with frameless SRS and SRT, a GTV-to-PTV safety margin of 1–3 mm is usually used	12–13 Gy using single-fraction SRS; 18–25 Gy in 3–5 fractions using fractionated SRS; 45–54 Gy at 1.8–2.0 Gy per fraction using fractionated RT (large tumors, e.g. >3 cm in size)
Chordoma	Well-	Isotropic pre- and	Visible lesion on MR	The CTV is typically	A CTV-to-PTV margin	With proton

(continued on next page)

Table 3 (continued)

Tumor type	WHO grading	Imaging for target delineation	Gross Tumor Volume (GTV)	Clinical Tumor Volume (CTV)	Planning Target Volume (PTV)	Dose and fractionation
Chondrosarcoma	differentiated or dedifferentiated (chordomas) WHO grade I–III (chondrosarcoma)	post-contrast-enhanced 3D T1-weighted sequences with 1 mm thick slices and T2-weighted images	images	based on preoperative tumor volume and postoperative residual tumors/resection margins. Two different CTVs generally employed: – CTV1, preoperative tumor volume with anisotropic margins of 1–2 cm plus the residual tumor and surgical resection margins (54 Gy); – CTV2 encompassing the residual tumor with an expansion of 5–10 mm plus resection margins (74–76 Gy)	up to 5 mm is applied, with protons usually requiring larger margins than photon stereotactic techniques	irradiation, 72–76 GyRBE at 1.8–2.0 Gy per fraction (use 70–72 GyRBE for chondrosarcoma); with photon irradiation, fractionated RT at doses of 66–70 Gy at 1.8–2.0 Gy per fraction; SRS at doses of 13–20 Gy

are not available, larger margins up to 5 mm should be employed.

- Single-fraction SRS, fractionated SRS (2–5 fractions) or conventionally fractionated SRT are commonly used, depending on tumor types, target volumes and involvement of critical OARs.
- Conventionally fractionated RT using IMRT and VMAT technology for improving dose conformity is usually delivered at doses of 45–60 Gy in 25–33 daily fractions of 1.67–2.0 Gy according to different tumor types and grade (higher doses reserved for aggressive tumors, e.g. atypical and malignant meningiomas); SRS doses of about 13–22 Gy in single fraction and 21–25 Gy in 3–5 fractions are typically utilized according to the different histologies.
- Doses up to 74–76 Gy in 1.8–2.0 Gy fractions for chordomas; lower doses for chondrosarcomas.

Abbreviations

- ACROP, Advisory Committee on Radiation Oncology Practice
- ASTRO, American Society for Radiation Oncology
- CBCT, Cone-beam computed tomography
- CISS, Constructive Interference Steady State
- CK, CyberKnife
- CNS, Central nervous system
- CT, Computed tomography
- CTV, Clinical target volume
- EORTC, European Organisation for Research and Treatment of Cancer
- ESTRO, European Society for Radiotherapy & Oncology
- FIESTA, Fast Imaging Employing Steady-state Acquisition
- FLAIR, Fluid-attenuated inversion recovery
- GK, Gamma Knife
- GTV, Gross tumor volume
- LINAC, Linear Accelerator
- IGRT, Image-guided radiotherapy
- IMPT, Intensity-modulated proton beam therapy
- IMRT, Intensity-modulated radiotherapy
- MRI, Magnetic resonance imaging
- OARs, Organs at risk
- PET, Positron-emission tomography
- PTV, Planning tumor volume
- PRV, Planning organ at risk volume

- RT, Radiation therapy
- RTOG, Radiation Therapy Oncology Group
- SRS, Stereotactic Radiosurgery
- SRT, Stereotactic Radiotherapy
- VMAT, Volume Modulated Arc Therapy
- MPRAGE, Magnetization prepared rapid acquired echoes
- 3D FLASH, Three-dimensional fast low angle shot
- 3D FGRE, Three-dimensional fat-suppressed 3D fast gradient echo
- 3D FSPGR, Three-dimensional fat-suppressed spoiled gradient echo
- 3D TFE, Three-dimensional turbo field echo

Preparation of the guideline

The guideline was prepared following the ESTRO procedure policy for guidelines. GM and SC coordinated the guideline panel and drafted the manuscript. BB, MB, AB, MB, LF, AF, UG, ALG, FLL, MN, TN, IP, DCW, and CB were part of the expert panel and contributed to the development, preparation and shaping of the manuscript. All authors read and approved the final manuscript.

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Conflicts of interest:

Ian Paddick works as an ad-hoc consultant for Elekta. All other authors declare no conflicts of interest.

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