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SIOPE Guideline

SIOPE – Brain tumor group consensus guideline on craniospinal target volume delineation for high-precision radiotherapy

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ABSTRACT

Objective: To develop a consensus guideline for craniospinal target volume (TV) delineation in children and young adults participating in SIOPE studies in the era of high-precision radiotherapy.

Methods and materials: During four consensus meetings (Cambridge, Essen, Liverpool, and Marseille), conventional field-based TV has been translated into image-guided high-precision craniospinal TV by a group of expert paediatric radiation oncologists and enhanced by MRI images of liquor distribution.

Results: The $CTV_{cranial}$ should include the whole brain, cribriform plate, most inferior part of the temporal lobes, and the pituitary fossa. If the full length of both optic nerves is not included, the dose received by different volumes of optic nerve should be recorded to correlate with future patterns of relapse (no consensus). The $CTV_{cranial}$ should be modified to include the dural cuffs of cranial nerves as they pass through the skull base foramina. Attempts to spare the cochlea by excluding CSF within the internal auditory canal should be avoided. The CTV_{spinal} should include the entire subarachnoid space, including nerve roots laterally. The lower limit of the spinal CTV is at the lower limit of the thecal sac, best visible on MRI scan. There is no need to include sacral root canals in the spinal CTV.

Conclusion: This consensus guideline has the potential to improve consistency of craniospinal TV delineation in an era of high-precision radiotherapy. This proposal will be incorporated in the RTQA guidelines of future SIOPE-BTG trials using CSI.

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Craniospinal spinal irradiation (CSI) continues to play a significant role in the multidisciplinary management of brain tumours in children and adults [1–3]. Postoperative CSI with chemotherapy is the current standard of care of medulloblastoma [1,2,4]. CSI is also used for brain tumours with proven spread in the cerebrospinal fluids [5–8].

Paediatric radiotherapy techniques have evolved rapidly in recent years and high-precision conformal radiotherapy techniques are now being used in most tumour sites [9–11]. Intensity-modulated radiotherapy (IMRT) aims to deliver a homogeneous radiation dose to the clinical target volume (CTV) with the lowest possible dose to neighbouring structures [12]. Image-guided adaptive radiotherapy (IGART) may further reduce the planning target volume (PTV) while maintaining a homogeneous dose delivery to the CTV [9,13,14]. The potential clinical advantages of proton beam therapy (PBT) in terms of reduction in long-term toxicities including the risk of second cancer are particularly appealing for paediatric oncology practice [10,11,15].

In high-precision RT, the accuracy of CTV delineation is of utmost importance to ensure optimal clinical outcome. There is overwhelming evidence that inadequate coverage of the cribriform

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plate, the temporal lobes, and the inferior aspect of the thecal sac can lead to an increased risk of recurrence after craniospinal irradiation (CSI) for medulloblastoma [16–19]. A recent planning study also highlighted that high-precision radiotherapy may inadvertently miss parts of the CTV if these structures were not clearly delineated [20]. Conventional field-based craniospinal radiotherapy (CSI) techniques adequately encompass the whole of the subarachnoid space, including the cranial nerve roots with their individual 'dural sheaths' and spinal nerve roots as they emerge from neural foramen within the high-dose radiotherapy region (Table 1). The observation on MRI of CSF flow beyond the inner table of the skull into cranial nerve foramina and canals raises the issue of accurate delineation of all CSF spaces as CTV for CSI [21]. Existing guidelines dating back from the 2D- (and 3D) era vary at least subtly (Table 1). For example, the SIOPE approach recommends a 5-mm margin inferior to the cribriform plate and 10-mm below the rest of the skull base whereas Children's Oncology Group (COG) advises a uniform margin of 5 mm below the skull base.

The purpose of this study is to develop a consensus guideline on target volume delineation for CSI in children and young adults, applicable for highly-conformal radiotherapy, including particle beam therapy.

Methods and materials

In order to translate conventional field-based techniques into a high-precision guideline for CSI, four meetings were organised: Cambridge (October 2015), Essen (March 2016), Liverpool (June 2016) and Marseille (November 2016). These meetings were attended by expert paediatric radiation oncologists from different European institutions active in the SIOPE-BTG. A subsequent online survey was conducted (September 2017) to capture technical details used in different institutions.

Cranial and spinal nerves have 'dural cuffs' containing CSF as they exit through their respective skull base and intervertebral foramina. The extent of the flow of CSF beyond the inner table of skull base along the cranial nerve dural reflections is not quantified. The findings of two independent studies [21] Janssens et al, *personal communication*) conducted during the development of this guideline were discussed in the consensus meetings.

Results

Preparation & immobilization

Patients may be treated either supine or prone with the neck in a neutral to hyperextended position. Although a supine position is more comfortable and stable, the prone position has the advantage of making it possible to visualise and monitor skin gaps for junctional matching and shifts. When using image-guided therapy, daily portal imaging or cone beam CT verifications, visualisation of skin gaps is no longer an issue.

Immobilisation techniques vary among institutions. In the supine position, patients are immobilised using 3- or 5-point thermoplastic cranial masks with individualised body vacuum mattresses with knee support. Optimal sparing of the larynx and proximal oesophagus can be obtained, using a 5-point mask, hyperextension of the head, and the shoulders depressed.

Imaging techniques

A planning CT scan is obtained using 1–2.5 mm slice thickness from the vertex to the lower border of C3 vertebrae and 2–5 mm slice thickness from the lower border of C3 vertebrae to the upper part of the femur (2–2.5 mm for younger children). One mm slice thickness at the base of skull is preferred for identifying skull base foramina. A planning CT scan co-registered to the latest diagnostic or planning MRI whenever possible, may improve accuracy of identifying cranial nerve dural sheaths. A Fast Imaging Employing Steady-State Acquisition (FIESTA) MRI sequence, which clearly demonstrates CSF extensions within the dural reflections is ideally recommended [21].

Target delineation

Since the entire CSF space is at risk of disease dissemination, the entire arachnoid space is defined as the CTV.

$CTV_{cranial}$

An accurate delineation of $CTV_{cranial}$ is established through the following three steps:

Firstly, the inner table of the skull is outlined using bony window settings (suggested CT Window/level: 1500–2000/300–350,).

Secondly, ensure that the cribriform plate (suggested CT window/level: 3000/400), the most inferior parts of the temporal lobes, and the whole pituitary fossa, which contains CSF are included in the $CTV_{cranial}$.

Thirdly, the $CTV_{cranial}$ is modified to include the extension of CSF within the dural sheath of cranial nerves as defined (Table 2) below:

Olfactory nerve fibres are encompassed in the CTV while covering the cribriform plate. While the majority of institutions include the whole length of the *optic nerves* in the CTV, a few institutions that routinely use PBT include only the posterior part of the optic nerves to avoid any potential risk of optic retinopathy and to spare the lens [22,23]. An MRI study (in 10 healthy volunteers) by Janssens et al. (*personal communication*) showed that CSF extends up to

Table 1
Guidelines for target delineation for CSI according to SIOPE and COG trials.

SIOPE (PNET4/5, SIOP CNS GCT II)	COG (ACNS0332, ACNS 0331, ACNS 0122)
Cranial CTV: 'includes brain with entire frontal lobe and cribriform plate. The geometric edge of the shielding should extend **at least 0.5 cm inferiorly below the cribriform plate and at least 1 cm elsewhere below the base of the skull**' *Spinal CTV*: 'extend laterally to cover the intervertebral formina. Inferior border of Spinal CTV must be determined by imaging the lower limit of the thecal sac on a spinal MRI; **inferior treatment field border should be set 1 cm below this**'	*Cranial CTV*: 'whole-brain field shall extend anteriorly to include the entire frontal lobe and cribriform plate region. Inferiorly, the CTV shall be at **least 0.5 cm below the base of the skull at the foramen magnum**' *Spinal CTV*: 'The spinal target volume will be the entire thecal sac. The field to cover this volume should extend laterally on both sides to cover the recesses of the entire vertebral bodies, with at least a 1 cm margin on either side. The inferior border of the treatment volume will be placed after review of the spinal MRI. **The border will be 2 cm below the termination of the subdural space**' *Proton therapy* 'For proton therapy, the spinal target volume will include the vertebral bodies for skeletally immature patients to minimise the risk of unequal vertebral growth. The spinal target volume in skeletally mature patients will include the spinal subarachnoid space with a margin of 3–5 mm into the vertebral body to allow for interfraction set up variation'

Table 2
Description of the areas of interests that need to be include in the $CTV_{cranial}$ for CSI.*

Skull base foramen/Canal	Cranial nerve(s)	Anatomical description
Cribriform plate	Olfactory nerve	Cribriform plate is a thin horizontal plate of ethmoid bone which is bounded laterally by vertical lateral lamella
Optical canal of sphenoid	Optic nerve**	Optic canal is situated in the lesser wing of sphenoid, supero-medial to the superior orbital foramen
Superior orbital fissure	Oculomotor, trochlear, and first branch of trigeminal, and abducens nerves	Superior orbital fissure is located between the greater and lesser wings of sphenoid
Foramen rotundum	Second branch of trigeminal nerve	Foramen rotundum is located in the greater wing of sphenoid. It is supero-lateral to the vidian (pterygoid) canal and postero-infero-medial to the superior orbital fissure
Foramen Ovale	Third branch of trigeminal nerve	Foramen ovale is located in the greater wing of sphenoid and is postero-lateral to the foramen rotundum
Internal auditory meatus	Facial and vestibulo-cochlear nerves	Internal auditory meatus is located in the petrous temporal bone and is antero-superior to the jugular foramen
Jugular foramen	Glossopharyngeal, vagus, and accessory nerves	Jugular foramen is located supero-lateral to the foramen magnum and inferior to the carotid canal
Hypoglossal canal	Hypoglossal nerve	Hypoglossal canal is located in the occipital condyle and infero-medial to the jugular foramen

* Foramina are outlined on bone window settings (see Appendix A).
** Optic nerve using window width 350 and level 40.

the posterior aspect of the eyeball in all scans (Fig. 1A). For this reason, the majority of expert paediatric radiation oncologists are in favour of including the whole optic nerves in the CTV. However, the consensus group acknowledges that the exact risk of isolated recurrence after partial irradiation of optic nerve is not known and would be difficult to study.

The *oculomotor, abducens* and *trochlear* nerves are thin nerves without a dural cuff. The *trigeminal nerve* consists of sensory and motor roots and exits from the ventral aspect of the pons. In the middle cranial fossa, the sensory root expands to form the trigeminal ganglion which is located in the trigeminal cave lateral to the cavernous sinus (Fig. 1B). The ophthalmic and maxillary divisions of the trigeminal nerve arise from the periphery of the trigeminal ganglion and exit through the superior orbital fissure and foramen rotundum. The motor root of trigeminal nerve runs along the floor of the trigeminal nerve and forms the mandibular division which exit via the foramen ovale. The CSF within Meckel's cave along the trigeminal nerve is enclosed by the medial part of the middle cranial fossa CTV.

Two studies looking at the flow of CSF within the cranial nerve 'dural sheaths' in the posterior cranial fossa were presented at the consensus meetings. Noble et al. evaluated the CSF flow beyond the inner table of skull into the internal auditory meatus (IAM, with the *facial* and *vestibulocochlear nerves*), jugular foramen (the *glossopharyngeal, vagal and accessory nerves*), and hypoglossal canal (*the hypoglossal nerve*) using FIESTA) MRI [21]. This study based on 96 FIESTA sequences showed that the CSF extends beyond the inner table of skull up to 16 mm in the IAM and up to 11 mm in the JF (Fig. 1C-D). The second study by Janssens et al. in 10 healthy volunteers showed that CSF within the dural sheaths of the facial and auditory nerves (IAM) extends up to 12 mm beyond the inner cranial table and the extension is in close proximity to the cochlea (*personal communication*) CSF within the jugular foramen flows up to 12 mm beyond the inner table of the skull while liquor flow up to 10 mm has been observed in the hypoglossal canal (Fig. 1E). CT scan correlation suggests that CSF within these dural sheaths does not extend beyond the outer table of the skull.

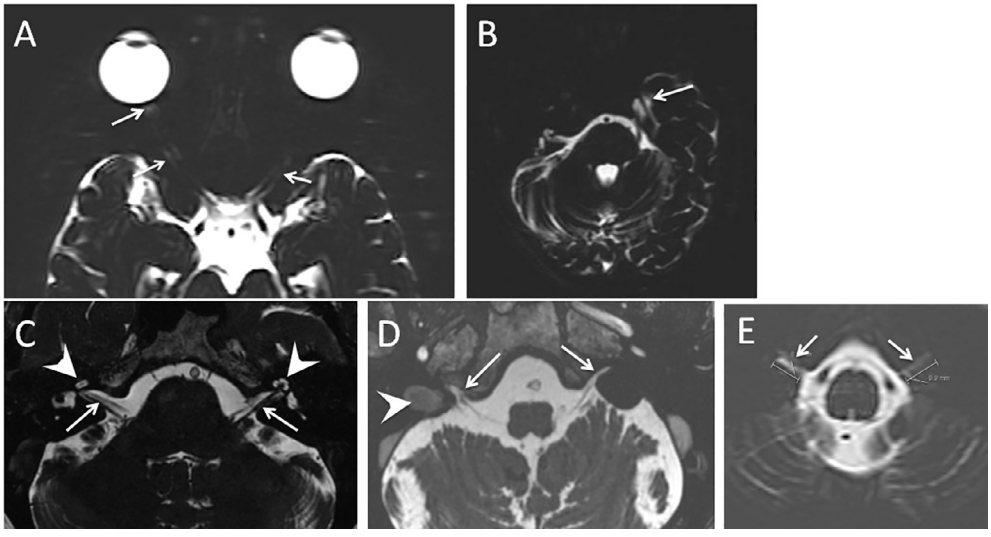

Fig. 1. (A) CSF tracks around the optic nerve and reaching up to the back of the globe (white arrows). (B) CSF in Meckel's cave (white arrow), adjacent to the medial site of the temporal lobe. (C) CSF in the IAM (white arrows) lies in close contact with the cochlea (white arrow head). (D) CSF flow in the jugular foramen JF (white arrows). Note carotid lies in the pars vascularis of jugular foramen (arrow head) (E) CSF in the hypoglossal canal (white arrows) (courtesy of Janssens and Noble et al.).

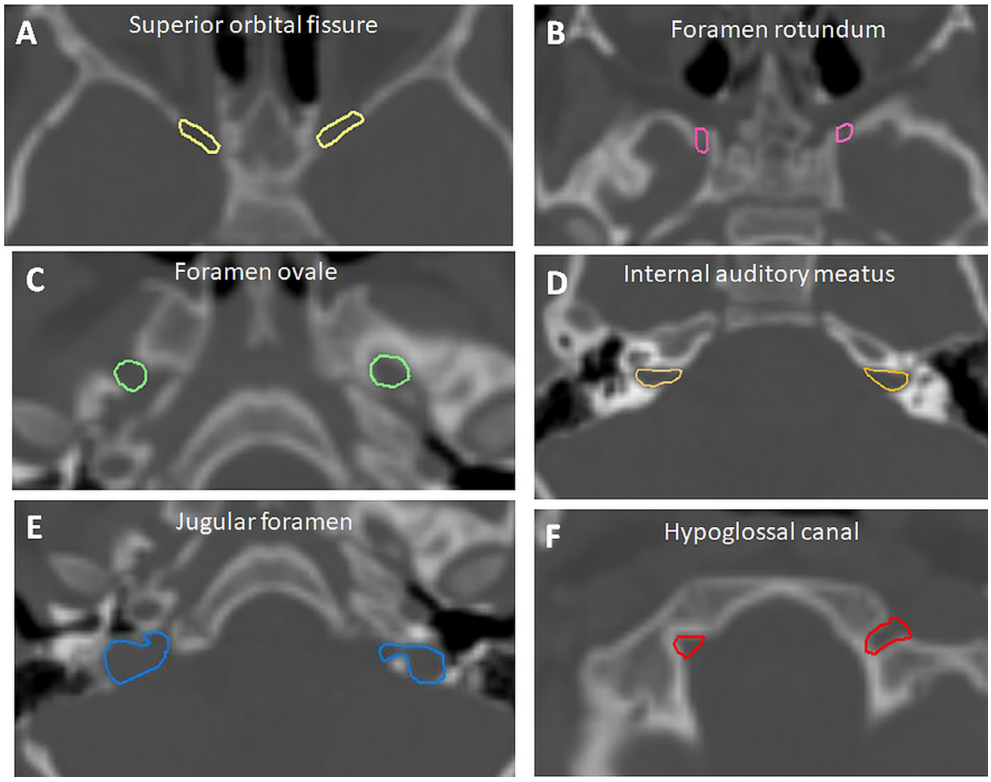

Fig. 2. Illustrations of the skull base foramina relevant for CSA delineation.

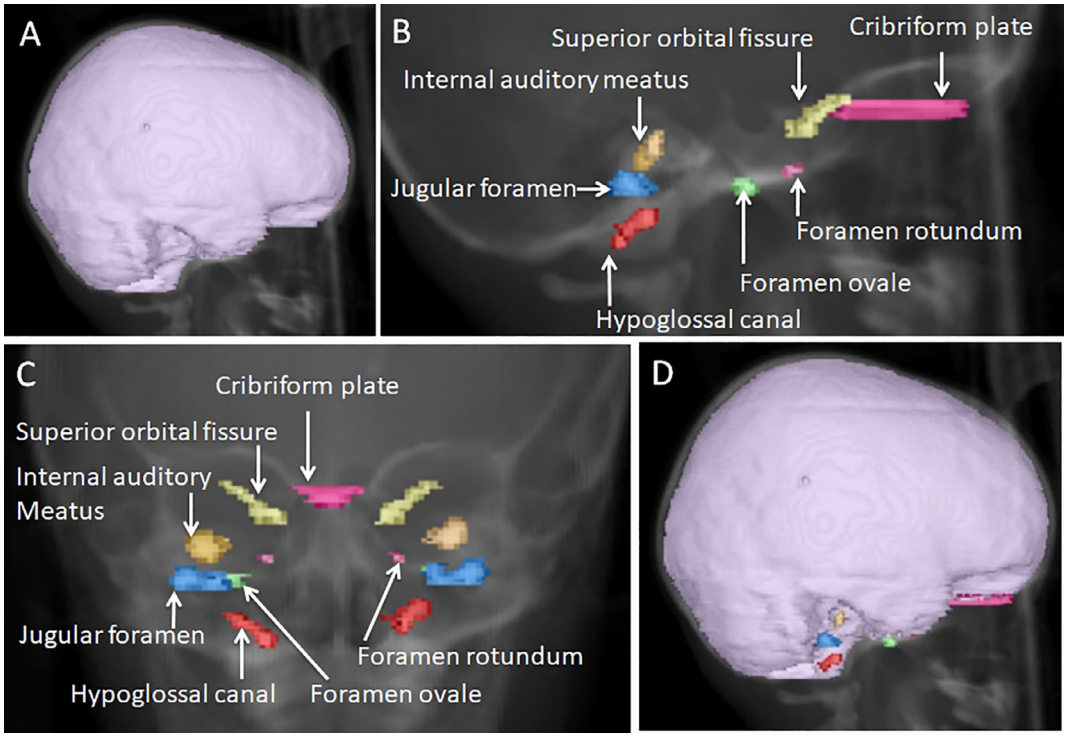

Fig. 3. (A) The brain CTV (purple) without the skull base foramina. B and C: Sagittal (B) and coronal (C) projection of various skull base foramina. (D) Recommended $CTV_{cranial}$ including CSF in 'dural sheaths'.

In routine clinical practice, it may be difficult to obtain an appropriate MRI to delineate CSF within the dural sheaths of cranial nerves. However, a planning CT scan taken at a slice thickness of 1 mm along the skull base may clearly show the bony anatomy of skull base foramina and canals which can be outlined using bony windows on the planning CT scan (Figs. 2 and 3) [21]. Appendix A illustrates delineation of CTV for CSI.

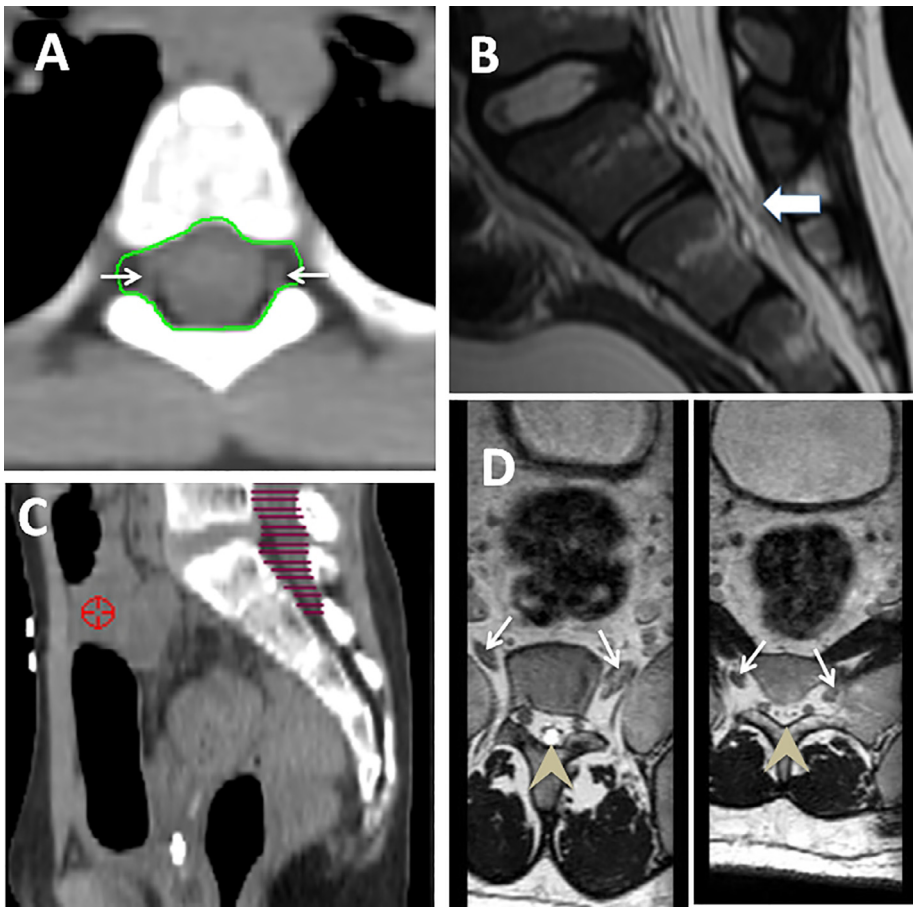

Fig. 4. (A) CTV_{spinal} including the entire arachnoid space with nerve roots (white arrows). (B) Lower level of CSF (white arrow) on sagittal T2W MRI, (C) Lower limit of CTV_{spinal} on planning CT scan, (D) Absence of CSF around sacral nerve roots (white arrows). Note CSF within spinal canal (arrow heads).

CTV_{spinal}

The CTV_{spinal} should include the entire subarachnoid space to encompass the extensions along the nerve roots laterally (Fig. 4A). The inferior limit of the CTVspinal is best determined by imaging the lower limit of the thecal sac on the latest spinal MRI. This usually comes down to the bottom of S1 vertebra as an obvious CSF space but there is often elongation which is less obvious extending down to the bottom of S2 or even further inferiorly (Fig. 4B-C). In case of doubt, it is best to seek expert neuroradiological advice about this landmark. In a study of 10 healthy volunteers, MRI did not show any CSF around the sacral nerve roots or in the sacral nerve root canals (Fig. 4D) (Janssens et al., *personal communication*) and these areas are therefore not included in the CTV_{spinal}.

Organs-at-risk (OAR)

The OARs to be delineated for the $CTV_{cranial}$ include the eye balls, lens, cochlea and the parotid and submandibular salivary glands. Adjacent to the CTV_{spinal}, the OARs to delineate include the larynx, oesophagus, thyroid gland, breasts in females, lungs, heart, liver, stomach, intestine, pancreas, kidneys and the gonads. In growing children, partial vertebral irradiation leads to spinal deformities [24–26]. Therefore, it is important to ensure uniform radiotherapy dose to the vertebrae in the region of the CTV_{spinal} in growing children to avoid non-uniform growth cessation. The parts of the vertebrae bearing growing plates (the body of the vertebra, the posterior element and facet joints; but not the lateral elements and transverse processes) should be enclosed to a uniform minimum dose (18–20 Gy) [25,27]. The methods for irradiating the growing vertebrae to the lowest uniform growth-restraining dose vary between institutions (e.g. PTV covering uniform dose of 20 Gy, vertebra covering a fixed-isodose level etc.) and the SIOPE is currently developing a consensus guideline for optimal delineation and dose prescription for growing vertebrae.

Planning target volume (PTV) and techniques

The PTV margin should be based on departmental data. Most institutions add a 3–5 mm margin to $CTV_{cranial}$ and a 5–8 mm margin to CTV_{spinal}. A number of treatment techniques such as 3-D conformal, IMRT, VMAT, Tomotherapy and proton therapy are used for CSI. A recent comparison of different techniques of craniospinal radiotherapy across 15 European centres showed that highly conformal radiotherapy techniques have dosimetric advantages compared with 3D-conformal radiotherapy and proton therapy often leads to the lowest mean dose to OARs (Seravalli et al., Acta Oncology *in press* 2018). However, for most organs, ranges in mean doses were wide and overlapping between techniques making it difficult to recommend one radiotherapy technique over another.

Discussion

An accurate description of delineation of CTV for CSI using high-precision photon and proton therapies in children should help to promote standardisation and uniformity of practice. While the potential risk of marginal recurrence, when all the areas of

arachnoid space are not covered, is not known, a uniform approach to delineation of CTV would ensure consistency and quality of radiotherapy delivery. A recent report provided guideline for delineation of OAR in the brain [28]. A summary of recommendations of this European consensus is as below:

- Patients may be treated either supine or prone with the neck in a neutral to hyper-extended position.
- In the supine position, patients are immobilised using a 3- or 5-point thermoplastic cranial mask along with an individualised body vacuum mattress with knee support.
- A planning CT-scan is done with 1–3 mm slice thickness, and ideally with a 1-mm slice thickness over the skull base.
- Co-registration of the latest diagnostic or planning MRI scan, (FIESTA sequence recommended) is useful for identification of CSF spaces.
- The $CTV_{cranial}$ includes the whole brain within the inner table of the skull. The $CTV_{cranial}$ should enclose the cribriform plates, most inferior part of the temporal lobes, and the pituitary fossa.
- The $CTV_{cranial}$ should encompass the dural cuffs of cranial nerves as they pass through skull base foramina. (see Appendix A).
- Ideally, the full lengths of optic nerves should be included in the $CTV_{cranial}$.
- Any attempt to spare the cochlea by excluding CSF within the internal auditory canal should be avoided.
- The CTV_{spinal} should include the entire subarachnoid space, including nerve roots laterally.
- The lower limit of the CTVspinal is at the lower limit of the thecal sac, visible on the latest MRI-scan. There is no need to include the sacral root canals in the CTVspinal.
- The outlining of OARs, including the growing parts of vertebrae, is important in minimising long-term side effects and comparing the efficacy of different techniques of CSI.
- OARs related to the CSI include the eye balls, lens, cochlea, the parotid and submandibular glands for the $CTV_{cranial}$ and the larynx, oesophagus, thyroid, breast in females, lungs, heart, liver, stomach, intestine, pancreas, kidneys and the gonads for the CTV_{spinal}.

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Conflict of interest

Authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.radonc.2018.04.016.

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