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Review Article

Tomotherapy for cranio-spinal irradiation

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A B S T R A C T

Tomotherapy is a method of delivering rotational IMRT offering various advantages, notably for complex and large targets such as the cranio-spinal axis. This systematic literature review reports on main clinical outcomes and toxicities in patients with various cancer types that received whole craniospinal axis irradiation (CSI) using Tomotherapy and offers a comprehensive comparison between Tomotherapy and other radiotherapy delivery techniques. Databases including PubMed, PubMed Central, Embase, and Cochrane were searched using the keywords "tomotherapy" AND "craniospinal". Fifty-six papers were included in the review. Patient population was adult in 9 papers, paediatric in 26 papers and mixed in 14 papers. Patients treated with helical Tomotherapy had similar disease-specific clinical outcomes and toxicities as patients treated using other techniques. Compared to any other technique, Tomotherapy provides better target coverage, homogeneity, and conformity in 23, 34 and 22 reports. Tomotherapy showed better organ-at-risk sparing for the thyroid, parotids, cochlea, eyes, heart and esophagus. Beam-On-Time (BOT) was reported to be longer for Tomotherapy in most studies (Median BOT: HT = 11 min, VMAT = 5.49 min, 3DCRT = 1.46 min). In conclusion, Tomotherapy offers good cranio-spinal axis coverage with improved homogeneity and conformity compared to other techniques, but with a considerably longer treatment time. Clinical outcome and toxicities suggest using Tomotherapy for CSI is efficient and safe.

Introduction

Tomotherapy is one potential modality used to deliver highly conformal, image-guided, rotational intensity-modulated radiotherapy (RT), using an integrated unit composed of a LINAC mounted on a circular CT gantry. The technique uses a fan-shaped 6MV beam that delivers radiation in a helical pattern using a binary multi-leaf collimator while the couch is advanced through the circular gantry[1–3]. This technique offers several advantages for treating complex targets with high conformity and homogeneity, supplemented by the ability to treat large volumes without requiring multiple isocenters or multiple abutting fields.

One of the most challenging techniques that involves large, complex targets is whole cranio-spinal axis irradiation (CSI). CSI is mainly indicated for patients diagnosed with CNS tumors, such as Medulloblastoma, Ependymoma, ATRTs (Atypical Teratoid Rhabdoid Tumor), and Germinoma, which mostly occur in the paediatric population, underlining the importance of a highly conformal, efficient, and comfortable treatment.

Conventional techniques[4–7] and the more modern 3DCRT, IMRT and VMAT use multiple abutting fields or arcs with multiple isocentres. The most used approach is having one cranial and one or two spinal isocentres with 2 lateral opposed fields for whole brain irradiation and 1 or 2 posterior spinal fields for spinal irradiation [7,8,17–24,9–16] or combining 2–3 full and/or partial arcs if using VMAT [8,14,21,23,25–27]. These lead to field junctions in which gap and overlaps may create areas of dose inhomogeneity including underdosage or hotspots. Underdosing the target volume may compromise outcome and having significantly higher dose in some regions might lead to severe toxicities, especially with the spine being a serial organ-at-risk. Therefore, dose homogeneity is essential in having the intended outcome. Using helical Tomotherapy (HT) is much simpler in terms of planning, solving the issue of multiple field combinations, collimation, extending skin-surface distance (SSD) [17] or using Electrons for certain spinal segments [13,28]. The Tomotherapy unit delivers a continuous, helical-shaped beam, using a single isocentre, no field junctions and no gaps or overlaps within the entire irradiated volume. This translates to a highly homogenous dose distribution, thus increasing the chances of disease control and lowering the toxicity risk. Moreover, Tomotherapy offers the possibility to perform cranio-spinal irradiation with the patient laying supine, thus facilitating anesthesia when necessary. However, the long treatment time and the relatively large volumes that receive a low dose raise some concerns about its safety and feasibility in clinical practice.

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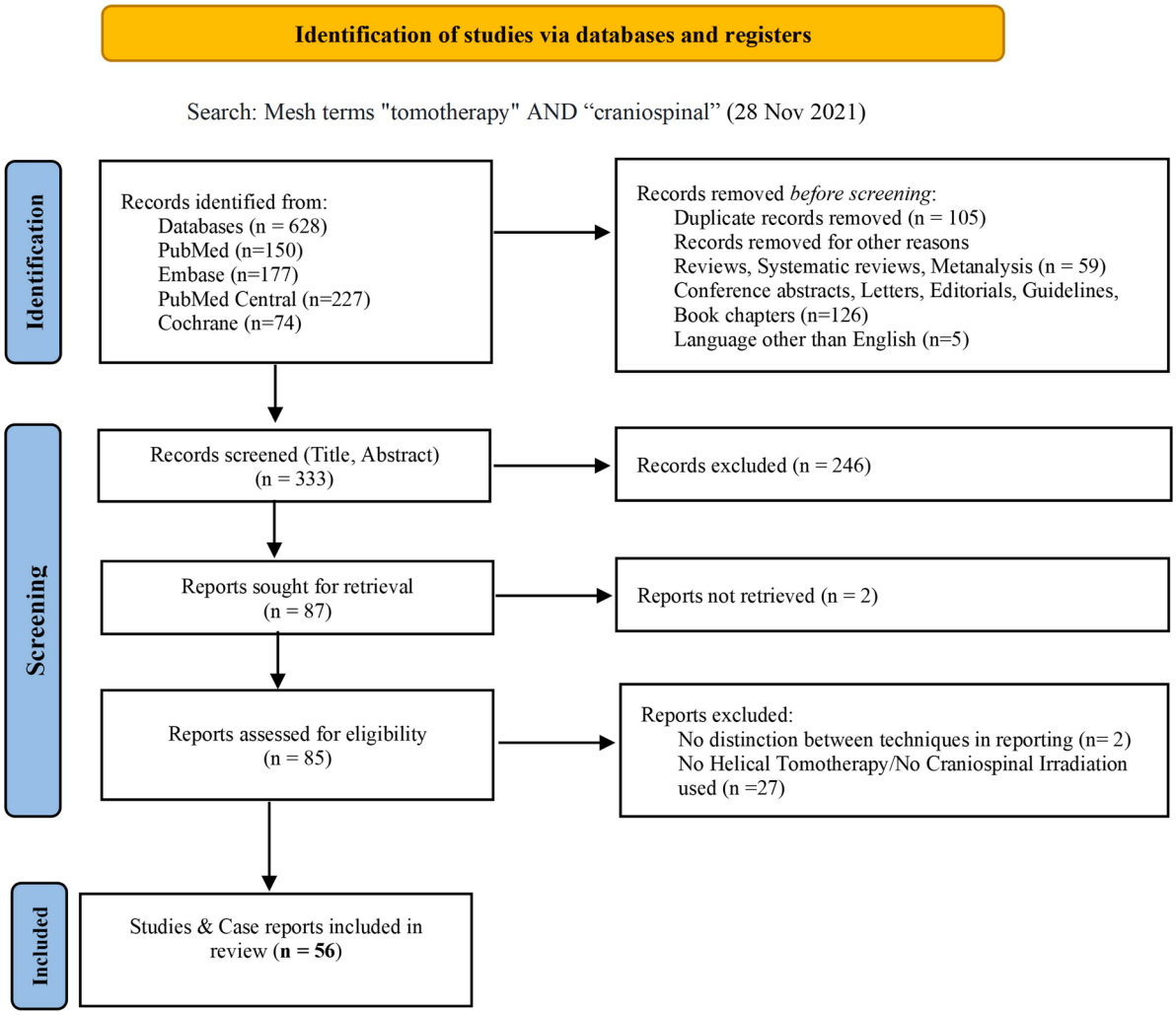

Fig. 1. PRISMA Flow Diagram [29].

This systematic literature review reports on several aspects of craniospinal irradiation performed with helical Tomotherapy, including clinical outcome, toxicities, and technical issues. We assessed the advantages and disadvantages of this technique and compared it to others such as 3DCRT, IMRT/VMAT and PBT. The aim of this paper is to offer a comprehensive overview and facilitate clinical decision making in practice, especially when a radiotherapy department has several techniques available.

Methods

Search strategy and inclusion criteria

We carried out a search in several databases including PubMed, PubMed Central, Embase, and Cochrane (last search date- 27th of November 2021). The terms used were "tomotherapy" AND "craniospinal". No automatic tools or filters were used. The papers were screened and selected as shown in Fig. 1 [29].

Inclusion criteria: All papers that reported on craniospinal irradiation planned or/and delivered using Tomotherapy, including case reports, series of clinical cases/patient cohorts, in-silico (dosimetric) studies, and reports on technique feasibility were included in the review. In total, 56 papers met the inclusion criteria.

Exclusion criteria: We excluded other reviews and *meta*-analysis, conference abstracts, letters and editorials, book chapters, guidelines, and papers in languages other than English. Also, we excluded papers that only reported on either just Tomotherapy or just CSI and the ones that reported on multiple techniques, without distinguishing between Tomotherapy and others.

Data extraction and analysis

We extracted data using predefined tables in Microsoft Excel. The following data were extracted: patient number and characteristic, diagnosis, treatment (including RT dose prescription), outcome (OS = Overall Survival, PFS = Progression Free Survival, DFS = Disease Free Survival, Relapse Rate), toxicities, homogeneity and conformity indices (HI, CI), beam-on- time (BOT), planning parameters (Pitch, Modulation Factor = MF, Beam width), and dosimetric data for structures reported in each study.

Units were standardized as follows: when more than one dose prescription was used, we mentioned the dose range (minimum–maximum); temporal data (follow-up period, survival parameters) was converted into months and beam-on-time into minutes; if individual results were reported for each patient, a mean/average or median value (depending on the distribution of the data) was calculated and included in the analysis.

For the dosimetric comparison studies, to determine if helical Tomotherapy offered any advantage, we used the following rules:

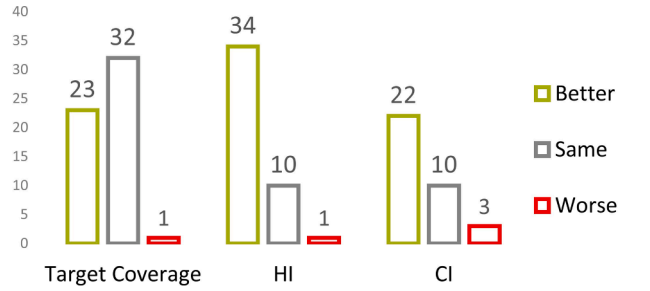

Fig. 2. Target coverage, HI = homogeneity index and CI = conformity index for Helical Tomotherapy compared to other techniques.

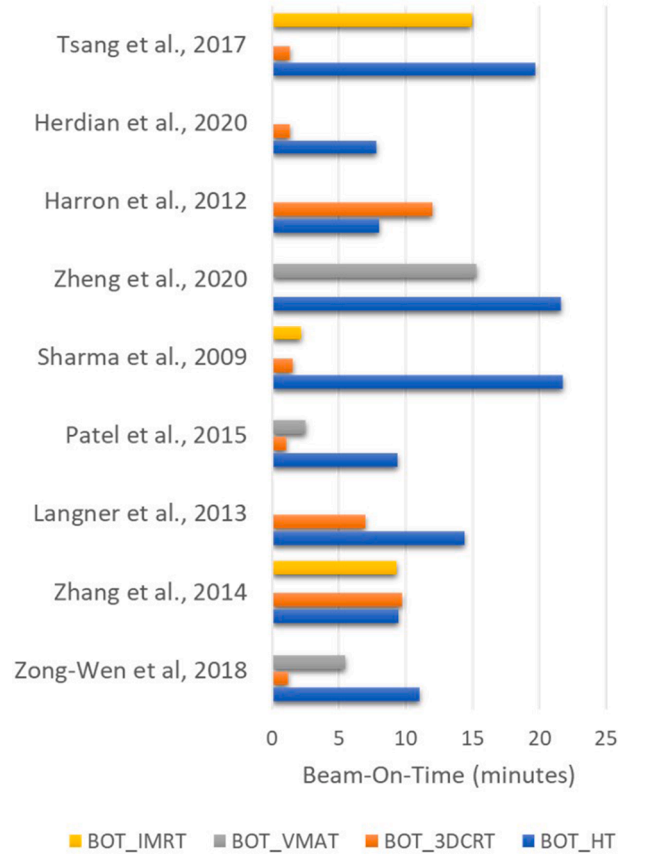

Fig. 3. Comparison of the Beam-On-Time (BOT) in minutes for cranio-spinal irradiation using different techniques; IMRT = Intensity-Modulated Radiotherapy, VMAT = Volumetric Modulated Arc Therapy, 3DCRT- Three-Dimensional Conformal Radiotherapy.

- When the study mentioned a threshold, we used the study's criteria to adjudicate ($p < 0.05$ with statistical difference, 1 or 5 Gy difference, etc.)
- When no rule was mentioned by the authors, we considered that HT was better than other techniques if the HT/Other techniques ratio is < 0.9, same if the ratio is 0.9–1.1 and worse if HT/Other technique $>$ 1.1. The ratio was calculated by dividing the reported doses –Dmean for parallel-like organs-at-risk (OARs) and Dmax for serial-like OARs.

Results

Fifty-six papers were included in the review (Fig. 1). Eleven [6,30,39,31–38] reported on the outcome of patients receiving HT-CSI and 15 on toxicities [5,6,38–47,25,48,30–35,37]. Thirty-eight studies performed a dosimetric comparison between Helical Tomotherapy and other techniques (conventional RT [4–7], 3DCRT [5,7,18–21,23–26,28,34,8,42–47,49,50,9,10,12–15,17], IMRT [7,15,52,53,17,20,22–24,26,50,51], VMAT [8,14,17,21,25–27,53], Proton RT [12,17,26,51]). Six papers[7,36,48,54–56] reported data regarding the setup accuracy while using Tomotherapy for CSI. A total number of 675 patients were included in the 56 studies. Twenty-seven papers [4,7,17–24,26,27,8,28,49–53,57,9–12,14–16] represent retrospective replanning using CT scans from patients that underwent irradiation using helical Tomotherapy or another technique. Nine studies included only adults (>18 years) [25,37,38,40,42,45,55,56,58], 26 studies only paediatric patients [5,6,15–19,21,22,26–28,7,32,41,47,57,59,8–14], 14 both adult and paediatric population[4,20,48,51,53,54,24,31,33,34,36,39,40,44], and 7 papers did not report on patient age [19,23,35,43,50,52,60].

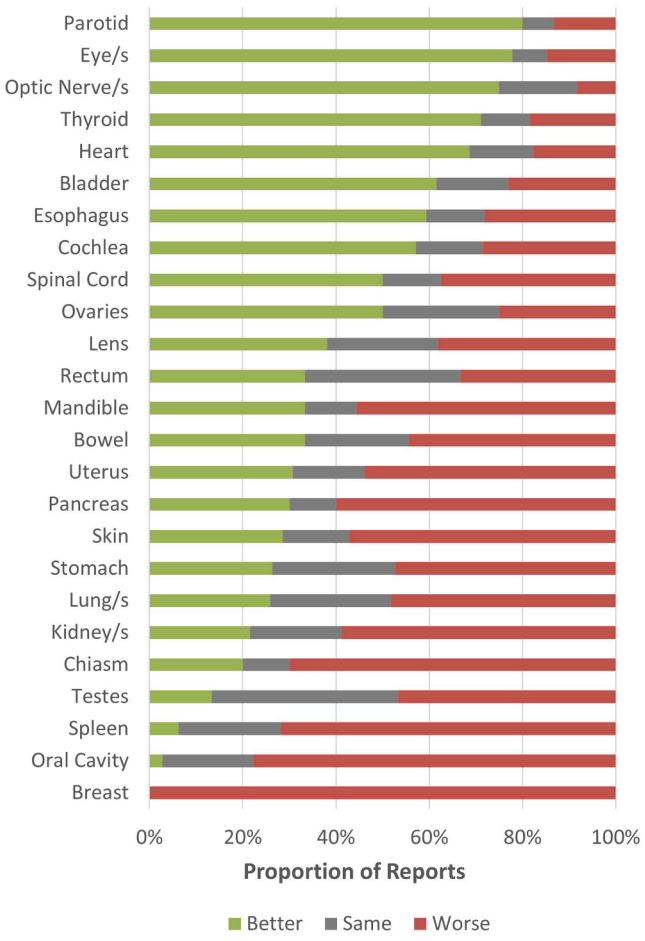

Fig. 4. Proportion of the total number of papers reporting a better, worse, or equivalent sparing capacity of helical Tomotherapy for each OAR, when compared to other techniques (3DCRT, IMRT, VMAT, PBT).

Technical aspects

Simulation and planning

Most papers reported on using both a head or head-and-neck thermoplastic masks and body vacuum cradles, cushions, or body thermoplastic masks for patient immobilization. The simulation CT was mostly performed with 3 mm or 5 mm thick slices (12 and 18 papers respectively). Out of the 56 papers, only 9 reported on using sedation, anaesthesia, or both. Eighteen authors mentioned using co-registered CT and MRI for treatment planning. Intra-venous contrast use during the planning CT was reported in 4 publications.

Table 1
Reported toxicities.

Publication	Total no. of patients	HT-CSI (n)	Paediatric/ Adult	Disease	Dose/CSI (Gy)	D/fr (Gy)	ChT	Top 3 Acute Toxicities	Top 3 Late Toxicities	Greatest toxicity level	SMN/ HT (n)	Comments
Guerra et al., 2014	19	19	Paediatric	MBL	23.4–39	1.3–1.8	Yes	Cytopenia Nausea/Vomiting Skin toxicity	No ≥ G2 toxicities	G3	–	–
Mesbah et al., 2011	66	23	Paediatric	MBL Other	23.4–36	1.8	Yes	Cytopenia Skin GI	–	G4	–	–
Kunos et al., 2008	4	4	Paediatric	MBL	23.4	1.8	Yes	Cytopenia	–	–	–	–
Gupta et al., 2012	1	1	Paediatric	MBL	30–36	1–1.2	Yes	Hematologic	–	G2	0	No treatment interruption
Schiopu et al., 2017	45	45	Paediatric + Adult	LMM MBL ICG EPD PNET Other	16.2–40	1–1.6	Yes	Cytopenia Nausea/Vomiting Alopecia	Learning&memory deficits Headaches/ Dizziness Fatigue	G4	1	1 patient died during RT 1 patient interrupted the treatment
Peñagarícano et al., 2009	18	18	Paediatric + Adult	MBL PBL ICG Other	15–40	1.5–2	Yes	Weight loss Nausea/Vomiting Esophagitis	–	G3	–	No symptomatic Acute Radiation Pneumonitis
Qu et al., 2014	23	23	Paediatric + Adult	ICG	27–36	1.5–2	Yes	Alopecia Cytopenia Nausea/Vomiting	Growth retardation Hormonal inbalance	G4	–	1 patient abandoned treatment - G3 Low GI toxicities
Öztunali et al., 2021	46	19	Paediatric + Adult	MBL	23.4–40	1–2	Yes	Fatigue Skin reactions Nausea/Vomiting	Skin reactions Upper GI Hearing loss	G4	1	5 SMN (1 in HT group,4 in 3DCRT group) No treatment related death/no interruptions
Lee et al., 2021	83	83	Paediatric + Adult	ICG GBM	1.2–3	1.2–3	Yes	Weight loss Nausea Hematologic	–	–	–	Treatment interrupted due to thrombocytopenia in 28 patients (33.7 %)
Gupta et al., 2015	20	20	Paediatric + Adult	MBL ICG	25–40	1.67	Yes	Hematologic Nausea/Vomiting Skin toxicity	Hormonal imbalance Growth impairment Hearing loss	G4	0	No symptomatic Pneumonitis
Sugie et al., 2011	12	12	Paediatric + Adult	ICG MBL ATRT PNET	23.4–40	1.6–1.8	Yes	Hematologic Anorexia Alopecia	–	G4	–	All patients completed without interruptions No > G2 Pneumonitis
Schiopu et al., 2019	15	15	Adult	LMM	18–39.6	1.6–1.8	Yes	Cytopenia Taste disorder/ Xerostomia Alopecia	–	G5	–	1/3 of the patients didn't complete treatment
Petersson et al., 2014*	20	8	Adult	–	–	–	Yes	Hematologic	–	G3	–	Only hematologic toxicities assessed
	3	3	Adult		25.5–35.3	1.6–1.6	Yes		–	G3	–	No treatment interruption

(*continued on next page*)

Table 1 (*continued*)

Publication	Total no. of patients	HT-CSI (n)	Paediatric/ Adult	Disease	Dose/CSI (Gy)	D/fr (Gy)	ChT	Top 3 Acute Toxicities	Top 3 Late Toxicities	Greatest toxicity level	SMN/ HT (n)	Comments
Bandurska-Luque et al.,2015				PNET				Nausea				
				MBL				Skin Hematologic				
Zong-Wen et al, 2018	5	5	Adult	MBL	30.6–37	1.8	Yes	Headache/ dizziness	Menstrual disorders	G3	–	1 patient didn't complete the treatment
								Nausea/Vomiting Hematologic				
Gaito et al., 2019	1	1	Adult	PBL	36	2	Yes	Nausea	Tinnitus	G2	0	–
								Fatigue Hematologic				
El Shafie et al., 2019	25	20	Not reported	LMM	14.4–36	1.6–3	Yes	Fatigue	–	G3	–	5 patients discontinued treatment due to tumour-associated clinical deterioration
								Nausea/Vomiting Cytopenia				

Reported acute and late toxicities, including second malignancies. **HT-CSI** = Helical Tomotherapy Cranio-Spinal Irradiation, **D/fr** = Dose per fraction, Gy = Gray, ChT = Chemotherapy, SMN = Second Malignancy, GBM = Glioblastoma, **ATRT** = Atypical Teratoid Rhabdoid Tumor, PNET = Primitive Neuroectodermal Tumor, MBL = Medulloblastoma, LMM = Leptomeningeal Metastasis, ICG = Intracranial Germ Cell Tumor, PBL = Pineoblastoma, EPD = Ependimoma, N/A = Not Applicable.

* The "Supplementary Appendix" that reportedly contains more data regarding the included patients could not be retrieved.

Treatment planning system and contouring

The most used planning system was TomoTherapy®, followed by the newer Radixact™ system which was reported by 3 authors[602348]. 12 authors reported on using the same system for contouring as for planning (i.e., Tomotherapy station), 20 reported using other contouring software (9 Pinnacle/Philips, 6 Eclipse/Varian) and 24 authors did not mention this aspect.

Pitch, modulation factor, beam width

The most used pitches were 0.287 (16 reports), 0.43 (10 reports) and 0.3 (8 reports). A beam width of 5 cm was most frequently chosen (25 reports), followed by 2.5 cm (17 reports). The majority of the plans were developed using a low modulation factor (1.5–2 reported 17 times). The lowest modulation factor (MF) used was 1.5, the highest was 3, with a median of 2.3. The most used fan beam width was 5 cm (29 reports). Using a higher modulation factor and a narrower beam increases beam-on time. Average BOT when using a 2.5 cm beam was 21.2 min, 12.11 min with a 5 cm beam, 11.84 min with a MF of 2 and 15.13 with a MF > 2. [505958].

Setup accuracy

Six papers looked at setup accuracy when using Tomotherapy for CSI. Inter-fractional or intra-fractional motion were recorded for 169 patients, encompassing>2722 fractions. The maximum setup error was 15 mm in the antero-posterior direction. [5456] Four authors [48543656] reported that the PTV margin used contains the setup error recorded and only one[55] reported the opposite. (Supplementary material- Table 3).

Tomotherapy compared to other techniques

Target coverage, Homogeneity, Conformity, Beam-on-time

Median Homogeneity Index (HI) for HT was 0.07, ranging from 0.04 to 0.17. The median Conformity Index (CI) was 0.92, ranging 0.59 to 1.34. Compared to other techniques (Photon 3DCRT, IMRT, VMAT and PBT), HT showed better coverage, homogeneity, and conformity in 41 %, 75 %, and 63 % of the reports (Fig. 2). The average beam-on time for HT was 13.54 min and the median 12.02 min, with a minimum of 6 min and a maximum of 30 min. Fig. 3 shows the BOT reported for different techniques.

Organs-at-risk dosimetry

The integral dose delivered to the total body, the so-called "dose bath" was reported to be higher with Tomotherapy in 18 papers, the same as with other techniques in 12 papers and lower in only 3 reports. Papers (n = 4) reporting on the vertebrae showed better sparing [5] and homogeneity [18,44,47] with Tomotherapy compared to other techniques. The heart, optic nerves, eyes, cochlea, parotid, and thyroid gland were better spared using Helical Tomotherapy. All reports showed Tomotherapy to be the least effective in breast sparing. When compared to PBT, HT offered similar target coverage (3/4) and conformity (3/3), but worse OAR sparing, except for 1 report in which the parotid was better spared with HT. Similar results were reported when the Integral Dose to OARs was compared between techniques [7,9,13,15,19,23,24,52]. Fig. 4 illustrates the dosimetric performance comparison of Tomotherapy against other techniques.

Five studies [8,12,18,26,57] focused on SMN risk estimation following CSI in paediatric patients. PBT had the lowest estimated risk when compared to any other photon technique. HT and IMRT/VMAT showed similar SMN risk but when compared with 3DCRT, results were inconsistent, with the same papers reporting both higher and lower risk

Table 2
Reported clinical outcomes.

Report	Total no. of patients	HT-CSI (n)	Patient category	Diagnosis	Reported Outcome	Value	Relapse
Gupta et al., 2012	1	1	Paediatric	MBL	PFS	18mo	–
				LMM			
Guerra et al., 2014	19	19	Paediatric	MBL	2y DFS	70 %	–
					3y OS	68 %	
Qu et al., 2014	23	23	Paediatric + Adult	ICG	3y RFS	95.2 %	–
					DFS	100 %	
					3y OS	91.3 %	
Öztunali et al., 2021	46	19	Paediatric + Adult	MBL	5y OS	88 %	16 % HT (n = 3)
					Median TTP	16 mo	11 % 3DCRT (n = 3)
Peñagarícano et al., 2009	18	18	Paediatric + Adult	MBL	OS	89 %	None- cribriform plate
				PBL	DFS	78 %	
				ICG	Cause-specific survival	89 %	
Gupta et al., 2016	20	20	Paediatric + Adult	MBL	Median time to progression	20mo	–
				ICG	5y PFS		
					5y OS	50 %	
						55 %	
Schiopu et al., 2017	45	45	Paediatric + Adult	MBL	3y OS	80 %	24.40 %
				ICG	5y OS	70 %	
				EPD	Median OS	23.5 mo	
Gaito et al., 2019	1	1	Adult	PBL	DSF	36mo	None
Ruppert et al., 2011	1	1	Adult	Glioneuronal tu.	PFS	6mo	
				LMM			
Schiopu et al., 2019	15	15	Adult	LMM	6mo OS	30 %	–
					1y OS	20 %	
					RFS	1mo	
					Median OS	3mo	
El Shafie et al., 2019	25	20	Not reported	LMM	Median OS	19.3 weeks	–

Total no. of patients = total number of patients in the report; Patients receiving HT-CSI = total number of patients that were treated using helical tomotherapy, excluding those receiving CSI with other techniques; HT-CSI = Helical Tomotherapy, CSI = Cranio-spinal Irradiation, MBL = Medulloblastoma, ICG = Intracranial Germinoma, EPD = Ependymoma, PBL = Pineoblasotma, LMM = Leptomeningeal Metastasis, Tu = Tumor, OS = Overall Survival, DFS = Disease-Free Survival, PFS = Progression-free survival, mo = months, 3DCRT = 3D conformal radiotherapy.

for HT depending on the calculation algorithm used.

Toxicities

Several authors reported less, or similar acute toxicities compared to existing data from the literature. The most frequent acute adverse effects reported were cytopenia, nausea/vomiting, fatigue, and alopecia. Tomotherapy was considered to be well tolerated with low and acceptable rates of severe toxicity by most of the authors, with 6 reporting a total number of 41 patients who interrupted treatment, mainly due to haematological toxicity. Reported late effects were neurocognitive impairment, chronic fatigue, hormonal imbalance, and hearing disorders. There were two cases of second malignancies reported in the HT groups. [4034] Table 1 **o**ffers more details on the toxicities reported in the selected papers.

Clinical outcome

Clinical outcome for patients that underwent cranio-spinal irradiation with Tomotherapy aligns with the literature data of patients treated for the same disease using other radiotherapy techniques. The most frequent cancer types that required CSI were medulloblastoma, ependymoma, intracranial germ cell tumours in children and medulloblastoma and leptomeningeal metastasis in adults. Table 2 summarizes all the information on survival and relapses reported in the selected papers.

Discussions

Craniospinal irradiation is a complex treatment that is associated with several technical challenges. The target volume is large (long) and has a complex, irregular shape with almost all Normal tissues at risk of incidental irradiation, as the volume extends from the vertex all the way to the cauda equina. It is mostly used in paediatric patients, a population highly susceptible to toxicities, both acute and late, including second malignancies. Having a conformal dose distribution is necessary in order to spare healthy tissue and organs-at-risk. CSI is also an option for adults diagnosed with leptomeningeal metastasis and other cancers that disseminate via the CSF (Cranio-spinal fluid) and could metastasise anywhere in the cranio-spinal axis.

Using helical Tomotherapy for cranio-spinal irradiation in a variety of cancers (both primary tumours and metastases) was similarly efficient in terms of local control, survival, symptom relief, and relapse as other radiotherapy techniques. It proved to ensure good target coverage with great conformity and showed superiority to other techniques in sparing several OARs, such as the eyes, thyroid, bladder, cochlea, and ovaries. On the other hand, it seemed less performant than other techniques in terms of breast, spleen, optic chiasm, lung, skin, and uterus dosimetry. Vertebral irradiation in pre-pubertal patients, especially when inhomogeneous, could lead to spinal growth defects and deformities such as scoliosis. Thus, if sparing them is not feasible, the vertebrae should be homogenously covered, as recommended by Hoeben et. al, 2019[61]. The included reports indicate a more homogenous irradiation of the

vertebrae using HT. However, despite proving better HI and CI in most reports, the clinical outcomes and toxicity rates were similar to literature reports on other techniques and mostly relate to hematologic toxicities due to irradiation of large volumes of the hematogenous bone marrow. One concern, especially in children, is the large volume of healthy tissue irradiated with low doses, the so-called "dose bath", which may cause second malignancies and was reported to be higher when using Tomotherapy. Two cases of second malignancies were reported in the HT cohort (vs 4 in the 3DCRT cohort), the number being too low to draw any conclusions on whether the incidence is higher in this group. SMN risk estimation studies suggest that HT has similar risk as IMRT/VMAT, but when compared to 3DCRT results are inconclusive, emphasising the need for further investigation in this area.

Regarding simulation and treatment delivery, one advantage of using HT for CSI is having the patient lay in a comfortable supine position without the need of moving them during the treatment (single isocentre) and facilitating a smoother process for anaesthesia and/or sedation when needed, as opposed to standard techniques which require prone positioning and several field junctions. Patient positioning is simple and reproducible, further supported by daily IGRT using the built-in MVCT increases treatment precision.

However, despite the convenient treatment planning and dosimetric benefits, Tomotherapy comes with a significantly longer beam-on-time, and this might be limiting for patients with poor compliance, low performance status or experiencing pain, or those who need anaesthesia or sedation during radiotherapy. However, this could be mitigated by employing several strategies such as projecting movies on the tube ceiling, thus increasing compliance, especially in children. Most authors reported on using a low modulation factor and a large beam width in order to keep the beam-on-time to a reasonable value while keeping a good target conformity, as BOT increases with higher MF and narrower beams.

Limitations

While offering a comprehensive overview of craniospinal irradiation using Helical Tomotherapy, this study also has several limitations. Due to the large heterogeneity in data reporting *(dose prescriptions vary between 18 and 40 Gy, both median and mean values were reported for Dmax, Dmean, and various other Dose-Volume parameters*), only a descriptive analysis was possible, without applying any statistical tests.

Some long-term toxicities such as cognitive impairment and endocrine disfunction are reported, but dosimetric data regarding the hippocampus, cerebellum, hypothalamic-pituitary axis and other brain structures involved in these functions are scarce. In terms of clinical outcomes, a direct comparison between age groups or techniques could not be performed due to data heterogeneity and lack of discrimination between such groups when reporting. Some of the issues could be overcome by a more standardized and harmonized reporting in future radiotherapy publications.

Conclusions

In conclusion, Tomotherapy is a convenient and efficient method for cranio-spinal irradiation both in adults and in paediatric patient, for several disease types. It offers clear dosimetric advantages, good target coverage with high homogeneity and conformity and OAR sparing. However, the long treatment times and potential risk of second malignancies are aspects that might be less appealing, especially for the paediatric population. The choice to use this technique over another should be made on a case-by-case basis, taking into consideration both technical and clinical feasibility and relevance.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2022.11.003.

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