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Craniospinal irradiation using helical tomotherapy for central nervous system tumors

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ABSTRACT

The aim of this study was to describe early and late toxicity, survival and local control in 45 patients with primary brain tumors treated with helical tomotherapy craniospinal irradiation (HT-CSI). From 2006 to 2014, 45 patients with central nervous system malignancies were treated with HT-CSI. The most common tumors were medulloblastoma in 20 patients, ependymoma in 10 patients, intracranial germinoma (ICG) in 7 patients, and primitive neuroectodermal tumor in 4 patients. Hematological toxicity during treatment included leukopenia Grades 1–4 (6.7%, 33.3%, 37.8% and 17.8%, respectively), anemia Grades 1–4 (44.4%, 22.2%, 22.2% and 0%, respectively) and thrombocytopenia Grades 1–4 (51.1%, 15.6%, 15.6% and 6.7%, respectively). The most common acute toxicities were nausea, vomiting, fatigue, loss of appetite, alopecia and neurotoxicity. No Grade 3 or higher late toxicity occurred. The overall 3- and 5-year survival rates were 80% and 70%, respectively. Survival for the main tumor entities included 3- and 5-year survival rates of 80% and 70%, respectively, for patients with medulloblastoma, 70% for both in patients with ependymoma, and 100% for both in patients with ICG. Relapse occurred in 11 patients (24.4%): 10 with local and 1 with multifocal relapse. One patient experienced a secondary cancer. M-status and the results of the re-evaluation at the end of treatment were significantly related to survival. Survival after HT-CSI was in line with the existing literature, and acute treatment-induced toxicity resolved quickly. Compared with conventional radiotherapy, HT offers benefits such as avoiding gaps and junctions, sparing organs, and better and more homogeneous dose distribution and coverage of the target volume.

KEYWORDS: craniospinal irradiation, ependymoma, helical tomotherapy, intracranial germinoma, medulloblastoma, radiation therapy

INTRODUCTION

Standard management for central nervous system (CNS) neoplasms that are prone to cerebrospinal fluid dissemination, such as medulloblastoma, ependymoma, intracranial germinoma (ICG) and primitive neuroectodermal tumor (PNET), includes surgery, chemotherapy and radiotherapy (RT).

Helical tomotherapy (HT) has been available in our department since 2006. In contrast to conventional craniospinal irradiation (CSI), HT offers the possibility of irradiating large target volumes continuously and homogeneously, without gaps and junctions. It ensures irradiation of the entire neuroaxis in one session, short treatment times, and full 360-degree treatment. In addition, elective dose reduction to organs at risk (OARs) and direct image verification of patient position via computed tomography (CT) are available [1–3]. However, due to the rotational beam delivery, a low-dose bath is created.

This work analyzes the dosimetric and clinical results of CSI using HT in a single institution over a single decade.

METHODS

From 2006 to 2014, 45 patients between 4 and 70 years of age at diagnosis (median age, 27 years) required CSI and were treated with HT. The patient, tumor and treatment characteristics are listed in Table 1. Histologic subtypes included classic ($n = 11$), desmoplastic ($n = 4$)

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and anaplastic ($n = 4$) medulloblastoma, and Grade 1 myxopapillary ($n = 4$), Grade 2 ($n = 4$), and Grade 3 anaplastic ($n = 2$) ependymoma. Other neoplasms were acute lymphoblastic leukemia, neuroblastoma, and choroid plexus papilloma. During radiotherapy, routine blood tests were reviewed weekly, and acute side effects were investigated and recorded according to the Common Terminology Criteria for Adverse Events guidelines version 4.0. Regular follow-up appointments took place every 4–6 weeks during the first 6 months, every 3 months for ~2 years and then annually. They included clinical examination, blood chemistry and routine tests, and enhanced cerebrospinal magnetic resonance imaging. The present analysis was approved by the ethics committee of our university on 19 August 2013.

Chemotherapy regimens were administered according to tumor-specific protocols. Nineteen patients with medulloblastoma received concurrent vincristine weekly, whereas 14 received adjuvant chemotherapy (Cis/carboplatin, CCNU, vincristine) and 3 received neoadjuvant chemotherapy (vincristine, carboplatin, VePesid). Two patients with ependymoma received concurrent chemotherapy (vincristine weekly), temozolomide was given in 3 due to tumor progression (adjuvant in 2 and neoadjuvant in 1), and 5 received no chemotherapy. None of the patients with ICG received chemotherapy. Among the patients with PNET, 1 received concurrent chemotherapy (vincristine weekly), 1 received adjuvant chemotherapy (carboplatin, CCNU, vincristine), and 2 received no chemotherapy. In total, 16 patients (5 with ependymoma, 7 with ICG, 2 with plexus papilloma and 2 with PNET) received no chemotherapy at all. Details of prescribed doses and fractionation for HT and information on chemotherapy and treatment completion are listed in Table 2. Doses for targets and OARs are provided in Table 3. All patients were immobilized in a head-first supine position using customized thermoplastic masks with shoulder fixation. Sedation was used in 7 patients (15.6%) to relieve anxiety. Plain and enhanced CT images of 5-mm slice thickness were taken from above the head to the entire pelvis for treatment planning using a Siemens Sensation Open CT system. Planning was performed on a tomotherapy planning work station. The clinical target volume (CTV) included the whole brain, cerebrospinal fluid, spinal canal down to S3, and the neural roots. The CTV to planning target volume (PTV) margin was 5 mm, 10 mm and 20 mm for head and neck, thorax and lumbosacral region, respectively. HT plans were generated with a fan beam thickness of 25 mm in 5 patients and 50 mm in 40, a constant pitch of 0.43, a modulation factor of 1.8–3.0 (median 2.2) and an actual modulation factor of 1.3–2.4 (median 1.8). The total session time including CT image guidance,

Table 1. Patient and tumor characteristics

Patient characteristics	Value (n, %)
Male	27 (60%)
Female	18 (40%)
Age	
≤18 years	15 (33.3%)
>18 years	30 (66.7%)
Median age (years)	27 (range 4–70)
Tumor entities	
Medulloblastoma	20 (44.4%)
≤18 years	9 (45%)
>18 years	11 (55%)
M0	15 (75%)
M1	5 (25%)
Ependymoma	10 (22.2%)
>18 years	10 (100%)
M0	5 (50%)
M1	5 (50%)
Intracranial germinoma	7 (15.6%)
≤18 years	4 (57.1%)
>18 years	3 (42.9%)
M0	4 (57.1%)
M1	3 (42.9%)
PNET	4 (8.9%)
Other	4 (8.9%)
Cohort general information	
M stage, overall	
M0	28 (62.2%)
M1	17 (37.8%)
Extent of surgical resection	
Gross total resection	21 (46.7%)
Subtotal resection/biopsy alone	16 (35.6%)
Karnofsky performance status	
>70%	33 (73.3%)
≤70%	9 (20%)
Not assessed	3 (6.7%)
Median follow-up (months)	52 (range 2–98)

The values listed in the table represent the number (n) and percentage (%) of patients, unless otherwise specified.

Table 2. Treatment characteristics

Helical tomotherapy			
Tumor entity (*n*)	Prescription dose (Gy)	Weekly fractionation (*n* of sessions per week times single dose)	*n* (%)
PNET (1)	16.2	5 × 1.8 Gy	1 (2.2%)
Acute lymphocytic leukamia (1)	18	5 × 1.8 Gy	1 (2.2%)
Medulloblastoma (1)	22.4	5 × 1.6 Gy	1 (2.2%)
Medulloblastoma (4)	23.4	5 × 1.8 Gy	4 (8.9%)
Intracranial germinoma (7)	24	5 × 1.6 Gy	7 (15.6%)
PNET (1)	32	5 × 1.6 Gy	1 (2.2%)
Ependymoma (1)	33.6	5 × 1.6 Gy	1 (2.2%)
Medulloblastoma (12), ependymoma (7), PNET (2), plexus papilloma (1)	35.2	5 × 1.6 Gy	22 (48.9%)
Medulloblastoma (2), ependymoma (2), plexus papilloma (1), neuroblastoma of the suprarenal glands (1)	36	5 × 1.8 Gy	6 (13.3%)
Medulloblastoma	40	5 × 1 Gy[a]	1 (2.2%)
Chemotherapy			
Concurrent			24 (53.3%)
Adjuvant			17 (37.8%)
Neoadjuvant			7 (15.6%)
Concurrent and adjuvant			3 (6.7%)
None			5 (11.1%)
Completion of treatment			
Yes			43 (95.5%)
No			2[b] (4.5%)

The values listed in the table represent the number (*n*) and percentage (%) of patients, unless otherwise specified.
[a]1 Gy twice a day.
[b]One patient died during RT and one interrupted the treatment.

position correction and treatment application was 20–30 min. Survival analysis was performed by the Kaplan–Meier method using the STATA software package (version 12.1). COX regression models were used to examine the effect of age, sex, tumor histology, histological subtype, extent of surgical resection, Karnofsky performance status, M status, concurrent chemotherapy and re-evaluation results for overall survival (OS) and recurrence-free survival (RFS). A significance threshold alpha level of $P = 0.05$ was used.

RESULTS

The average and median beam-on time was 12 min (range, 3–30 min). Thirty-eight patients (84.4%) required a sequential boost to the posterior fossa ($n = 20$; median dose, 19.8 Gy; range, 7.2–30.6 Gy), spinal cord ($n = 9$; median dose, 10 Gy; range, 4.8–14.4 Gy) and to various regions of the brain ($n = 9$; median dose, 16 Gy; range, 16–18 Gy). Moreover, two integrated boosts were applied to the posterior fossa and lumbar spinal cord (8.8 Gy) and to Th4–Th8 segments (9 Gy), respectively, in the patients with ependymoma.

Acute Grade 1 and 2 toxicity

Alopecia, partial ($n = 4$) and complete ($n = 13$), was reported in 37.8% of patients, followed by skin hyperpigmentation ($n = 4$, 8.9%), dry and itchy skin ($n = 5$, 11.1%) and erythema or desquamation ($n = 9$, 20%). Dysphagia occurred in 26.7% of patients ($n = 12$), pain in 13.3% ($n = 6$), and dizziness in 17.8% ($n = 8$). Less frequent toxicities included generalized muscle weakness

Table 3. Dose distribution to the target volume and organs at risk

	Median value	Range		
PTV (Gy)	35.2 Gy	16.2–40 Gy		
V90% (%)	98.0%	97–99.9%		
V110% (%)	0.0%	0.0–5.0%		
OAR	Median absorbed dose as % of PTV	Range (%)	Mean absorbed dose as % of PTV	Mean absorbed dose (Gy)
Right lens	13.7	0.5–35.9	15	4.5
Left lens	12.9	0.5–36.6	15	4.4
Right eye	30.1	0.5–62.3	31.9	9.6
Left eye	32.3	0.5–59.5	32.1	9.6
Thyroid	32.3	11.6–67.7	33.8	10.4
Right lung	20.1	7.4–44.9	20.7	6.3
Left lung	18.8	8.0–42.5	19	5.6
Heart	28.2	13.3–99.9	29.6	9.2
Right breast	11.3	7.8–15.8	11.3	3.5
Left breast	12.2	7.0–16.0	11.3	3.5
Right kidney	17.4	9.1–52.8	18.8	5.6
Left kidney	17.2	10.1–42.8	18.4	5.5
Esophagus	54.8	23.1–116.2	55.3	17
Bowel	36.9	19.4–71.0	36.4	11.2
Right parotid	29.3	1.5–75	32.4	9.7
Left parotid	29.1	2.3–79.6	32.5	9.8

PTV = planning target volume, V90% = volume covered by 90% of prescription dose, V110% = volume covered by 110% of prescription dose, OAR = organ at risk.

(n = 4, 8.9%), mucositis (n = 3, 6.7%), xerostomia (n = 4, 8.9%), other disorders of the digestive system (n = 7, 15.6%), impairment of concentration (n = 2, 4.4%), muscle twitching (n = 1, 2.2%), singultus (n = 1, 2.2%). Low blood pressure, tachycardia and loss of consciousness occurred seldom (n = 3, 6.7%). One urinary tract infection and one fungal infection were treated without complications with antibiotics and antifungal medication, respectively.

Acute toxicity at various levels

Among the patients, 62.2% (n = 28) experienced nausea (Grade 1 in 4, Grade 2 in 21 and Grade 3 in 2 patients), and 31.1% (n = 14) experienced vomiting (Grade 1 in 1, Grade 2 in 10 and Grade 3 in 2 patients).

Acute Grade 3 toxicity

Stomatitis was reported in 4.4% of patients (n = 2). Nutritional support (intravenous, nasogastric tube or hypercaloric drinks) was necessary in 11.1% (n = 5) for this reason, but also when loss of appetite occurred. Treatment-induced aplasia led to infections in six patients (13.3%), atypical pneumonia in two (4.4%), catheter infection in one (2.2%) and fever (Grade 1) in three (6.7%).

Late Grade 1 and 2 toxicity

Of the pediatric patients, 26.7% (three with medulloblastoma and one with ICG) showed learning and memory deficits. Headaches (n = 5, 11.1%), dizziness (n = 2, 4.4%), memory impairment (n = 4, 8.9%), concentration impairment (n = 3, 6.7%), bladder incontinence (n = 2, 4.4%), complete alopecia (n = 3, 6.7%), skin hyperpigmentation (n = 2, 4.4%), somnolence (n = 2, 4.4%) and blurred vision (n = 2, 4.4%) were reported to a lesser extent. Four patients (8.9%) did not recover from fatigue, and three (6.7%) continued to experience nausea. No Grade 3 or higher late toxicity was reported.

Table 4. Overall survival for all patients treated with HT-CSI

	3-year OS (CI)	4-year OS (CI)	5-year OS (CI)	Min. OS (months)
All patients ($n = 43$)	80% (65.0%–89.9%)	80% (65.0%–89.9%)	70% (53.3%–84.5%)	1
By tumor entity				
Medulloblastoma ($n = 19$)	80% (57.9%–94.5%)	80% (57.9%–94.5%)	70% (37.2%–89.6%)	12
≤18 years ($n = 9$)	70% (25.3%–87.2%)	70% (25.3%–87.2%)	70% (25.3%–87.2%)	12
>18 years ($n = 11$)	100%	100%	80% (20.4%–96.9%)	58
M0 ($n = 15$)	90% (59.1%–98.9%)	90% (59.1%–98.9%)	80% (37.1%–94.9%)	23
M+ ($n = 5$)	60% (12.6%–88.2%)	–	–	12
Ependymoma ($n = 10$)	70% (32.8%–89.2%)	70% (32.8%–89.2%)	70% (32.8%–89.2%)	3
M0 ($n = 5$)	100%	100%	100%	63
M+ ($n = 5$)	Median OS calculated between 9 and 32 months			3
ICG ($n = 7$)	100%	100%	100%	–
PNET ($n = 4$)	Median OS calculated between 9 and 10 months			1
Other ($n = 3$)	100%	100%	–	–
By M-stage, overall				
M0 ($n = 27$)	90% (73.0%–98.1%)	90% (73.0%–98.1%)	80% (57.3%–92.8%)	1
M+ ($n = 16$)	60% (32.7–80.5%)	60% (32.7–80.5%)	60% (32.7–80.5%)	3
By re-evaluation Results, overall				
Tumor progress ($n = 6$)	Median OS calculated between 23 and 24 months			3
CR ($n = 25$)	90% (67.3%–95.9%)	90% (67.3%–95.9%)	70% (42.6%–88.1%)	8
PR ($n = 3$)	100%	100%	100%	
Stable disease ($n = 7$)	100%	100%	100%	

OS = overall survival, ICG = intracranial germinoma, PNET = primitive neuroectodermal tumour, M0 = no distant dissemination, M+ = distant dissemination, CR = complete remission, PR = partial remission, CI = confidence interval.

Hematological toxicity

Grade 1–4 leukopenia was observed in 95.6% of patients (6.7%, 33.3%, 37.8% and 17.8%, respectively), anemia in 88.9% (44.4%, 22.2%, 22.2% and 0%, respectively) and thrombocytopenia in 88.9% (51.1%, 15.6%, 15.6% and 6.7%, respectively). Only six patients (13.3%) required transfusion of blood products: three required red blood cells only, one required granulocyte-colony stimulating factor only, and two required red blood cells and platelets.

Leucocytes dropped to a minimum by Week 4 (median range, 3–7 weeks) from the start of HT, recovered to normal levels by Week 10 (median range, 8–11 weeks) and reached the level before HT 23.5–43.5 months after treatment completion. In the absence of concurrent chemotherapy, leucocytes reached the initial level faster, 3.5–4.5 months after radiotherapy. Hemoglobin steadily decreased to a minimum by Week 8 (median range, 6–8 weeks) from the start of HT and reached normal values in 2.5 months (median range, 1.5–3 months) after HT completion. It took between 1.5 and 22.5 months after completing HT for hemoglobin to reach the pretherapy level, but in pediatric patients and those who did not receive concurrent chemotherapy it reached normal levels during Week 10 of treatment. Finally, platelets decreased to a minimum 4 weeks after HT began, rose to normal levels roughly by Week 8 (median range, 5–8 weeks) and reached the level before HT during Weeks 9–11.

OS

At the end of our observation period (December 2014), 32 patients (71.1%) were alive, 11 (24.4%) had died and 2 (4.4%) were lost to follow-up. Table 4 displays the results of OS. The re-evaluation results at the first follow-up appointment showed 26 (57.8%) complete responses, 3 (6.7%) partial responses, 7 (15.6%) patients with

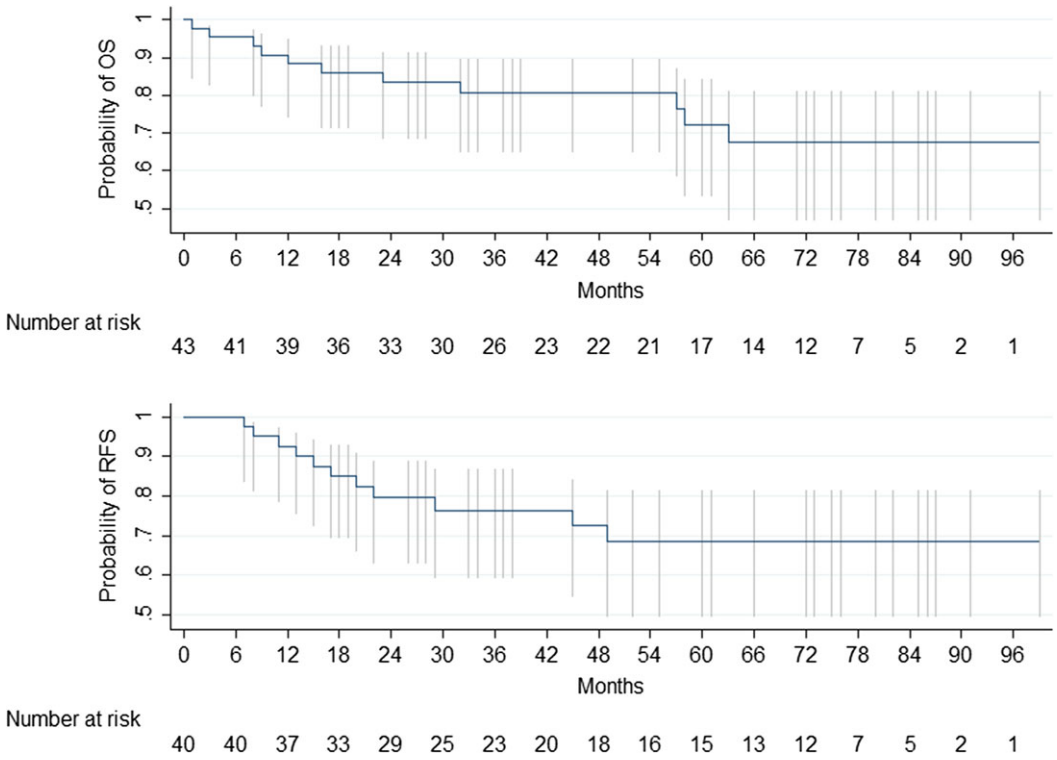

Fig. 1. Kaplan-Meier overall survival and recurrence-free survival estimates: an overview for all patients with primary brain tumors treated with helical tomotherapy craniospinal irradiation. OS, overall survival; RFS, relapse free survival.

stable disease, and 6 (13.3%) with tumor progression. Before HT, 19 patients (42.2%) were neurologically impaired, due to the tumor itself or previous surgery, but symptoms improved in 7 of them.

RFS

Of the 45 patients, 28 (62.2%) were reported to be free of recurrence, whereas 24.4% of patients (5 with medulloblastoma, 3 with ependymoma, 1 with PNET and 2 with choroid plexus papilloma) had a relapse (10 locoregional and 1 multifocal). Furthermore, one patient with medulloblastoma had a secondary tumor (WHO Grade IV glioblastoma). Five patients (12.5%) either showed progression of their condition despite therapy or were lost to follow-up. Rates of 3-, 4- and 5-year RFS were 80% (59.4–87.0%), 70% (54.4–84.4%) and 70% (49.6–81.5%), respectively. The minimum RFS was 7 months. Figure 1 depicts the rates of OS and RFS for all patients who underwent HT.

DISCUSSION

To our knowledge, this is the first study of such a large cohort that comprehensively reports clinical outcomes and dose distributions of HT-CSI and compares the results with the existing literature.

Toxicity and outcome by tumor entity

ICG

The patients with ICG were all alive and disease-free at the time of this analysis, thus confirming the results in the existing literature [4–8]. Only one of our patients displayed deficits in memory and fine motor skills after HT-CSI. However, 71.4% of patients had tumor- or operation-induced endocrine disturbances and were on medication before irradiation. There were no HT-CSI–induced endocrine disturbances, although it has been suggested that hormone replacement is more common after CSI than after chemoradiotherapy (CRT) [9]. Furthermore, the SIOP CNS GCT 96 trial showed a similar frequency of acute Grade 3 and 4 toxicities for both approaches [4].

Medulloblastoma

The results are in agreement with Lee *et al.* [10], who observed a 5-year OS rate of 73% for patients treated in the 2000s with 3DCRT. However, Kumar *et al.* [11] reported a median OS duration of 50 months for medulloblastoma patients treated with CSI; however, more than half of their patients were younger than 14 years. In our analysis, with more than half of our patients being adults, the median OS and RFS durations have not been reached, although failure occurred in 30% of the patients (4 pediatric patients and 2 adults) who had 1 multifocal and 4 local relapses and 1 secondary tumor.

The 3-year rates of OS and RFS of 100% and 80%, respectively, were observed in the adult medulloblastoma patients (vs 50% and 45%, respectively, at 3 years when conventional radiotherapy was used [12]). In our analysis, the OS and RFS rates also remained constant at 4 years, whereas for conventional radiotherapy they were reported to be 89% and 68%, respectively [13]. Although the acute toxicities were similar, none of our patients experienced Grade 3 or higher late toxicity.

Christopherson *et al.* reported a 49% rate of cognitive impairment when they followed up patients for 15 years. Moreover, 41% of the survivors had Grade 3 or higher late toxicity; there were 4 cases of secondary malignancies and 3 treatment-associated deaths [14]. Our analysis allows for speculation that adverse effects could depend on the radiotherapy technique. Intellectual decline was reported by 33% of our patients, and there was only 1 secondary cancer and no long-term Grade 3 or 4 toxicity; however, the trials of Christopherson *et al.* spanned the 1960s to 2008, when HT was not used. Decline in cognitive activity can be attributed to the radiation dose, but also to factors such as young age at diagnosis (<7 years), hearing loss, or posterior fossa syndrome [15, 16]. No hearing loss was reported after HT in our analysis, but the patients with intellectual deficits were 4, 5 and 11 years old, and two showed symptoms of posterior fossa syndrome before HT. However, the follow-up period of this study was not long enough to properly assess cognitive impairment and secondary malignancies.

Ependymoma

Analyses of this tumor entity vary considerably. Spanning decades, they incorporate different techniques of diagnosis and treatment. Patients with recurrent ependymomas, spinal seeding, or re-irradiation have often been excluded, or selection based on certain tumor grades or location. For example, Swanson *et al.* reported less favorable outcomes (5-year OS and RFS rates of 57% and 60%, respectively), possibly because their patients had been treated over a too long a period of time (1964–2006) and because HT was not yet in use [17].

We are in agreement with Mettelus *et al.* [18] in terms of 5-year survival, bearing in mind that these French researchers calculated survival from the time of surgery and not from the starting point of HT-CSI, as we did. Other authors have shown that the extent of resection correlates with better survival rates, but the small size of our cohort did not allow us to confirm this finding [17].

Dosimetric comparison of HT and conventional radiotherapy

Conventional radiotherapy such as 3DCRT or intensity-modulated radiotherapy, in contrast to HT, cannot irradiate the entire neuroaxis at once; thus, junctions and field matching are necessary [19, 20]. Some authors try to establish ways of making junctions more homogeneous to avoid over- or underdosing [20–22]. HT-CSI is superior from this perspective because it allows planning of the entire neuroaxis as one field. Moreover, conformity of dose distribution to the target volume has been shown to be higher for HT than for 3DCRT [8, 20, 23–25]. This can be confirmed by our HT plans.

To compare 3DCRT- and HT-CSI, plans were generated both for immediate treatment and for retrospective planning studies [2, 20, 26, 27]. But irrespective of whether CSI plans were used for treatment, there is a fear that the beam-on time may be too long in the case of HT, which could prove challenging if sedation is necessary during CSI. We report an average beam-on time of 12 min for HT-CSI, which is comparable with that in conventional radiotherapy and other HT planning studies [19, 23, 24].

The possibility of sparing organs is an advantage of HT of which we made full use in planning our patients' dose distribution. When we reviewed the literature, dosimetric comparisons were not always straightforward. Authors often used different parameters in characterizing their HT plans (e.g. certain V*n* values [volume covered by *n* % of the prescribed dose] or maximum/mean dose or homogeneity and conformity indices) [8, 26]. Sugie *et al.* designed HT-CSI treatment plans for 12 patients with various CNS malignancies. The percentage of prescribed dose received by the lenses, lungs, and thyroid and parotid glands was similar to ours. However, our plans showed lower doses for the kidneys and higher doses for the esophagus [23]. Qu *et al.* designed HT-CSI treatment plans for 23 patients with ICG and reported maximum doses to the lenses similar to ours [8]. A retrospective dosimetric study conducted by Sharma *et al.* for four patients with medulloblastoma showed that our plans displayed higher doses to the eyes, thyroid gland, and esophagus as a percentage of the PTV, but were similar for the lungs and kidneys [20]. Penagaricano *et al.*, in a single-patient dosimetric comparison of conventional radiotherapy and HT, reported higher doses to the eyes, lungs, thyroid gland, and kidneys [2]. These differences may result from different fan beam thicknesses and pitch and modulation factors used in optimizing the plans or from the cohort size and the retrospective nature of the studies [20, 28].

In contrast to 3DCRT, larger volumes of normal tissues are irradiated at relatively lower doses in HT, which is thought to increase the risk of secondary cancers [20, 29]. In this context, proton beam treatment (PBT) appears very attractive. First, proton CSI can improve normal tissue sparing while also providing more homogeneous target coverage than photon CSI [30, 31]. Second, PBT was shown to have a lower risk of secondary cancer and non-cancer adverse effects when compared with photon therapy [31].

Yoon *et al.* showed that with the exception of the esophagus, PBT insures a lower dose by far to OARs than does HT-CSI. Differences in dose distribution between photons and protons fade, however, in the head and neck region. According to our calculations, the doses to the lenses, and thyroid and parotid glands expressed as a percentage of the PTV were lower with HT than with PBT [32]. Similarly, in Giebeler *et al.*, the dose distribution to OARs was lower than that achievable by HT, but the mean dose to the eyes and lenses was 1.5–2 times higher than that of HT [33].

Toxicity comparison between different tomotherapy treatments for CNS tumors

It is comforting to report a lesser extent of acute treatment-induced toxicity than that reported by Sugie *et al.*, who observed more severe and frequent hematological toxicity and transfusion of blood products. With the exception of fatigue, which was more frequent in our cohort, other acute Grade 2 or higher toxicities such as alopecia, esophagitis and the need for nutritional support were less frequent [23]. Moreover, in contrast to Qu *et al.*, we did not report any Grade 4 anemia or thrombocytopenia. Also, there were no HT-induced hormone dysfunctions, and nausea and vomiting were less frequent in our patients. However, 6.7% of our patients had complete alopecia over the long term [8].

Some authors, however, reported less acute toxicity. Penagaricano *et al.* evaluated HT-CSI toxicity in 18 pediatric patients with various CNS malignancies; although back pain and esophagitis were comparable, adverse skin effects and nausea and vomiting were less frequent and severe than in our cohort [1]. Even though our patients were followed up thoroughly and adverse effects were recorded in detail, a categorical statement as to HT-induced neurotoxicity cannot be made. However, this may be possible in a prospective trial, which allows a before-and-after assessment of neurologic impairment.

Limitations to our analysis include its small and heterogeneous cohort, the short follow-up period, and the retrospective nature of the analysis. Nevertheless, we believe that our findings are pertinent. HT-CSI ensured survival in line with rates in the existing literature. Compared with conventional radiotherapy, HT-CSI offered benefits with respect to dose distribution, conformity, coverage of PTV and sparing of OARs. Furthermore, gaps and junctions were avoided. Long-term toxicity will require further investigation. The superiority of proton CSI with respect to adverse effects is still under investigation.

CONFLICT OF INTEREST

The authors declare they have no conflicts of interest.

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