Early Outcome after Craniospinal Irradiation with Pencil Beam Scanning Proton Therapy for Children, Adolescents and Young Adults with brain tumors

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Abstract: Central nervous system (CNS) tumors are the most common solid malignancies in children and adolescents/young adults (C-AYAs). Craniospinal irradiation (CSI) is an essential treatment component for some malignancies but it can also lead to important toxicity. Pencil beam scanning proton therapy (PBSPT) allows for a minimization of dose delivered to organs at risk and, thus, potentially reduced acute and late toxicity. This study aims to report the clinical outcomes and toxicity rates after CSI for C-AYAs treated with PBSPT. Seventy-one C-AYAs (median age, 7.4 years) with CNS tumors were treated with CSI between 2004 and 2021. Medulloblastoma (n=42: 59%) and ependymoma (n=8; 11%) were the most common histologies. Median prescribed total PBSPT dose was 54 Gy_{RBE} (range, 18 – 60.4) and median prescribed craniospinal dose was 24 Gy_{RBE} (range, 18 – 36.8). Acute and late toxicities were coded according to Common Terminology Criteria for Adverse Events. After a median follow-up of 24.5 month the estimated 2-year local control, distant control and overall survival was 86.3%, 80.5% and 84.7%, respectively. Late grade ≥3 toxicity free rate was 92.6% at 2 years. Recurrent and metastatic tumors were associated with worse outcome. In conclusion, excellent tumor control with low toxicity rates was observed in C-AYAs with brain tumors treated with CSI using PBSPT.

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Abbreviations

CSI	Craniospinal irradiation
C-AYA	Children, adolescents/young adults
CNS	Central nervous system
PBSPT	Pencil beam scanning proton therapy
PT	Proton therapy
AYA	Adolescent and young adults
RBE	Relative biological effectiveness
CT	Computed tomography
MRI	Magnetic resonance image
CTV	Clinical target voume
PTV	Planning target volume
WHO	World Health Organisation
GTV	Gross tumor volume
LF	Local failure
DF	Distant failure
LC	Local control
DC	Distant control
OS	Overall survival
G	Grade

INTRODUCTION

Craniospinal irradiation (CSI) is an essential treatment component along with surgery and chemotherapy for many children, adolescents/young adults (C-AYAs) with central nervous system (CNS) malignancies that have a tendency to spread throughout the neuroaxis. However, CSI along with multimodal therapy in such young patients often leads to important late toxicities, which may have substantial morbidity and impact the quality of life [1]. Pencil beam scanning proton therapy (PBSPT) is a highly conformal technique that can achieve sharper dose gradients in comparison to conventional photon radiation techniques. The lack of exit dose beyond the Bragg peak, allows for a reduction in radiation doses to organs at risk. Therefore, using proton therapy (PT) for CSI may potentially reduce long-term toxicities and the risk of developing a secondary cancer [2].

Clinical outcomes among patients with medulloblastoma receiving CSI with protons have shown similar progression-free survival rates to conventional photon radiotherapy while presenting acceptable toxicity [3 - 6]. Likewise, retrospective studies of adolescents and young adults (AYAs) treated with proton CSI have also reported promising results in terms of toxicity and tumor control rates [7, 8]. The role of PBSPT for other histologies that may require CSI has been less investigated [9]. The aim of our study was to report clinical outcomes, toxicity and potential prognostic factors of a cohort of C-AYAs referred to our institution to receive CSI delivered with protons.

MATERIAL AND METHODS

Patients

We retrospectively reviewed medical records of C-AYAs who received CSI in a curative or palliative attempt using PBSPT, with (n=5; 7%) or without (n=66; 93%) combined photon irradiation, between January 2004 and January 2021 at our institution (Fig. S1). Patients with any age, with any tumor histology, any tumor stage, any Lansky score (for pediatric patients) or Karnofsky performance status score (for AYAs) were included. Out of 75 patients screened in our institutional database, 4 were excluded due to the following reasons: 2 received a local irradiation only after being initially planned for CSI, 1 died before the start of CSI and in another one CSI was discontinued due to substantial tumor progression. In total, 71 (94.7%) patients were included in the final analysis. All patients were discussed in a multidisciplinary tumorboard during which the therapeutic strategy was defined. Demographic, clinical and treatment data were collected from our electronic medical record. Table 1 summarizes the characteristics of the patients. The vast majority of patients (n=63, 88.7%) was treated according to a protocol (Table 1). Seven (9.9%) were included in the SIOP PNET 5 trial [NCT02066220]. Approval from the competent ethics committee was obtained for this study (Ethikkommission Nordwest- und Zentralschweiz; EKNZ 2021-02013).

Craniospinal irradiation

PBSPT was delivered with an energy-degraded beam from a 250 MeV cyclotron using two clinical gantries. CSI was applied as adjuvant or definitive treatment for primary or recurrent tumors. Combined treatments with protons and photons were allowed (Table 1). Induction, concomitant and maintenance chemotherapy was administered in

49.3%, 8.5% and 53.5% of patients, respectively. PBSPT treatment planning was conducted on the in-house planning system *PSIplan* or *FIonA*. Multi-field optimization and single-field optimization techniques were both used. For PBSPT planning a relative biological effectiveness (RBE) value of 1.1 was used [10].

Children which were assessed to be unable to remain still for the time of treatment delivery (typically children under the age of 7 years) were sedated and monitored by experienced anesthesiologists during irradiation [11]. Planning computed tomography (CT) and planning magnetic resonance images (MRI) were fused. The craniospinal clinical target volume (CTV) comprises a cranial part (CTV_{brain}) and a spinal part (CTV_{spine}). The CTV_{brain} consisted of the whole brain including but not limited to the cribiform plate, superior orbital fissures, optic nerve canals, foramen rotundum, foramen ovale, internal auditory meatus, jugular foramen and hypoglossal canal. For the CTV_{spine} the whole spinal canal including the intervertebral neuroforamina from the first vertrebra until the end of the thecal sac were contoured [12]. A 5 and 7 mm safety margin was added respectively to the CTV_{brain} and CTV_{spine} to create the planning target volumes (PTV) PTV_{brain} and PTV_{spine}. These two volumes were unified to form the whole craniospinal PTV (PTV_{CSI}). For spinal treatment doses up to 24 Gy_{RBE} the vertebral bodies were included in the PTV_{CSI} to minimize the risk of asymmetrical bone growth. Spinal treatment doses above 24 Gy_{RBE} were delivered to the PTV_{spine} in a second series. In 6 (8.5%) patients in whom bone growth was deemed to be complete, vertebral body sparing irradiation was carried out consisting of non-inclusion of the vertebral body in the PTV_{CSI}.

A boost dose to macroscopic tumor lesions and/or the tumor bed followed typically subsequently to CSI. For patients who underwent macroscopic complete resection, the initial gross tumor was delineated in pre-surgery images. The tumor bed was then

delineated in the planning CT and MRI with respect to the initial tumor extension. In case of residual tumor after surgery and for the non-operated patients, a primary gross tumor volume (GTV_p) visualized on the planning CT and MRI was delineated. The CTV_p was defined as the GTV_p or the tumor bed with an additional margin (median, 10 mm). Brain and spinal metastases were contoured to create the GTV_m. To generate the CTV_m an aditional margin (median, 5 mm) was used for intracranial metastasis. For spinal metastasis a larger margin (median, 10mm) was given in the longitudinal axis and adapted axially to be limited by the bone and spinal canal. A safety margin of 5 mm for brain lesion or 7 mm for spine lesions was added to the CTV_p and CTV_m to create the PTV_p and PTV_m.

In 19 (26.8%) patients the radiotherapy treatment plans were sent to the reference center for central review before the treatment [13, 14]. Five (7%) cases received a photon-proton combination treatment. Three (4%) were intended to receive CSI with protons but ultimately received CSI with photons due to technical limitations related to the length of the target volumes. Until 2017, all CSI were delivered with our in-house gantry 1. Dimensions of the PTV should not exceed 68 cm, which corresponded to the maximum possible overlap between imaging scan range at the CT and gantry treatment range. In the last 2 (3%) cases, CSI was performed with protons but they received a boost with photons. One first received the photon boost to the primary tumor in his home country to avoid treatment delay. In the other case, a radiosurgery boost was performed using Cyberknife.

Follow-up and toxicity assesment

All observed adverse events were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events [15]. Acute toxicity was recorded

weekly during PBSPT and assessed within the first 3 months after PBSPT. Subsequent institutional and external clinical notes were collected by our study and research office and reviewed during follow-up meetings to determine disease status and late toxicity. Follow-up images were analyzed in detail and discussed with an experienced neuro-radiologist. Local failure (LF) was either proven histologically after surgery/biopsy or defined radiologically as residual tumor progression (increase of ≥25% in size visible in MRI or CT) or as the development of new nodular contrast enhancement in the surgical bed compared to the baseline images. LFs arising within the 95%, 50-95%, and <50% isodose of the total dose deliered to the primary tumorwere classified as “in-field”, “marginal” or “out-of-field”, respectively. Distant failure (DF) was defined as the development of new distant lesions in MRI or CT follow-up, newly detected vital malignant cells in cerebrospinal fluid or proven histologically by biopsy or resection.

Statistical analysis

Time to event data was calculated from the first day of PT to the date of event or censored at last follow-up using the Kaplan-Meier method. The events for the calculation of local control (LC), distant brain/spinal control (DC), overall survival (OS) and late grade (G) ≥ 3 toxicity were LF, DF, death from any cause and reported G≥ 3 toxicity, respectively. Actuarial 2-year LC, DC, OS and freedom from G≥ 3 toxicity were analyzed using the Kaplan-Meier method and log-rank test. A univariate log-rank analysis was used to investigate potential prognostic factors for LF, DF, and OS. Assessed covariates for univariate analysis were sex, age (<15 years vs. ≥15 years), Lansky or Karnofsky performance status score (<70 vs. ≥70), initial tumor size (<40 vs. ≥40 mm), tumor status before treatment (primary vs. recurrent), presence of metastases (yes vs. no) and surgical resection (yes vs. no). A p-value <0.05 was

considered statistically significant. Statistical analysis was performed using SPSS version 26 (IBM, Armonk, NY, USA).

RESULTS

Patients

Seventy-one patients received CSI irradiation during the study period. Median age at start of PT was 7.4 years (range, 1.7 -21.3). Medulloblastoma (59.2%) was the most frequent diagnosis, followed by ependymoma (11.3%) and germ cell turmors (8.5%) (Table 1). Primary tumors were infratentorial in most of the patients (60.6%). A large number of patients (71.8%) had a WHO grade 4 tumor (Table 1). Sixteen (22.5%) received PT for a recurrent tumor. Thirty-four (47.9%) patients were metastatic, of which 13 (38.2%) had spinal metastases (Table 1). Among the 42 patients with medulloblastoma, 54.8% corresponded to a group 3 or 4, 14.3% to WNT-activated group and 7.1% to the SHH-activated group. Molecular analysis was not available for the remaining 10 patients (23.8%).

Treatment

Treatment characteristics are summarized in Table 1. Overall, surgery was performed in 60 (84.5%) patients, of which 38 (53.5%) had a gross total resection, 18 (25.3%) a subtotal resection and 4 (5.6%) a biopsy. Induction, concomitant and maintenance chemotherapy was administered to 49.3%, 8.5% and 53.5% of patients, respectively (Table 1). Among the 48 patients with an infratentorial tumor, 37 (77%) had a surgical intervention of the primary tumor. Of them, 6 (16.2%) developed a posterior fossa syndrome. Median total radiation dose was 54 Gy_{RBE} in 1.8 Gy_{RBE} per fraction. CSI and boost median doses were 24 Gy_{RBE} and 30.6 Gy_{RBE}, respectively (Table 1).

Tumor control and survival

With a median follow-up of 24.5 months (range, 2-195), 2-year LC , DC and OS were 86.3% (95%CI, 72% - 93.1%), 80.5% (95%CI, 67.6 – 88.4%) and 84.7% (95%CI, 72.5% - 91.7%), respectively. Of note, no AYAs developped any local or distant failure. Kaplan-Meier curves for these outcomes are illustrated in Fig. 1. Four patients (5.6%) had LF only, 11 had DF only (15.5%) and 4 (5.6%) had both. Median time to LF and DF was 24.2 and 10.7 months, respectively. Of the 8 patients with LF (including patients with both DF and LF), 7 were in-field and one was marginal. Twelve (16.9%) patients died, all of them due to progressive disease.

On univariate analysis (Table 2), patients with a recurrent tumor had worse 2-year LC (95% vs. 44%, p <0.0001), DC (88% vs. 54%, p= 0.004) and OS (89% vs. 70%, p= 0.003) than those treated with upfront PBSPT at diagnosis. Inferior outcomes were also observed for metastatic patients in terms of DC (66% vs. 92%, p= 0.009) and of 2-year OS (74% vs. 94%, p= 0.012) and, but not for LC (75% vs. 93%, p=0.187) when compared to non-metastatic patients.

Patterns of failure

Sites of failure are summarized in Table 3. All (87.5%) but one LFs (including LF only and patients that had both LF and DF) were in-field. Counting all DF (DF only= 11 and n=4 LF and DF), site of distant failure were mostly diffuse leptomeningeal disease (n= 7).

Clinical and treatment characteristics of patients with LF only, DF only and both LF and DF are shown in Table S1, S2 and S3, respectively.

Toxicity

The majority of patients (98.6%) developed acute toxicity. Thirty-eight (53.5%) had G≥ 2 acute toxicity and 5 (7%) had G≥ 3 acute toxicity. Most common G2 toxicities include nausea (21.1%), alopecia (22.5%) and radiation dermatitis (5.6%). G3 acute toxicity consisted of nausea (n=1), leukopenia (n=1), neutropenia (n=1) and thrombocytopenia (n= 2). Haematological G3 toxicities were only seen in patients that had received chemotherapy. No acute toxicity G4 or more was observed.

Overall, late toxicity was reported in 33 (46.5%) patients. Thirteen patients developed only toxicity G1 (18.3%) and 20 (28.2%) had toxicity G≥ 2 or more. G2 hearing impairment ocurred in 3 (4.2%) patients. G2 endocrinopathy was found in 17 (23.9%) patients (n=14 pituitary dysfunction, n=2 central hypothiroidism, n=1 primary hypothiroidism). Four (5.6%) had late G≥ 3 toxicity. G3 toxicity cases consisted of cataract (n=1), CNS radiation necrosis (n=1) a case of of a G3 stroke (n=1) developed in a patient with previous vascular disease (Moya Moya disease). There was one (1.4%) case of a G4 CNS radiation necrosis of the brainstem. Two-year freedom from G≥ 3 late toxicity was 92.6% (95% CI, 79.9% - 97.9%) (Fig. 2). No patient developed a secondary malignancy after PBSPT.

DISCUSSION

This study provides a detailed analysis of the early clinical outcomes of a cohort of C-AYAs with brain tumors referred to receive CSI with protons using a pencil beam scanning only delivery paradigm. Our 2-year LC, DC and OS rates of 86.3%, 80.5% and 84.7%, respectively, are consistent with recent reports investigating the use of CSI with protons among children and AYAs [3-8]. Of note, patients with recurrent or metastatic tumors at the start of PT were found to have a worse outcome. Our acute toxicity data points to an adequate tolerance of the treatment. It is noteworthy that at

two years, the reported actuarial freedom from G≥ 3 toxicity was greater than 90% (Fig.2). This data compares favorably with previous studies [3-8, 16] and supports the safety and efficacy of proton CSI for the control of CNS tumors.

Within our cohort, a predominance of patients with medulloblastoma (59.2%) was observed. An international survey among 40 proton centers investigating the patterns of care of the use of PT in pediatric patients in 2016 showed that median age was 10 years and 48% were delivered for CNS tumors. Of them, the most frequent indications were medulloblastoma (26.2%) and ependymoma (11.2%) [17]. This is not surprising, since it is the most frequent malignant brain tumor in children [18] and usually requires CSI as a key part of the treatment [19]. Other histologies that may require CSI in certain situations such as germ cell tumors, primitive neuroctodermal tumor, atypical teratoid rhabdoid tumor and high grade gliom [2, 9] were also included in our cohort. With an 85.9% of patients younger than 15 years of age, children also make up the majority of our population. Similar to a population-based study, we reported in our cohort a higher prevalence of male C-AYAS with brain tumors [18]. We therefore believe that our cohort is a good representation of the real clinical practice of a proton center treating children and AYA patients.

We observed a median time to local and distant failure of 24.2 and 10.7 months, respectively. Similar results were found in reported PT CSI for medulloblastoma patients with a median time to recurrence of around 15 – 30 months [3, 4, 6, 8]. Most data in the literature regarding patterns of failure after proton CSI are reported in patients with medulloblastoma. A phase II study including 59 patients with newly diagnosed medulloblastoma treated with PT showed that 71% of the failures were in the spine, 50% in the supratentorial region and 50% had diffuse leptomeningeal failure. Six (43%) had an out-of field failure in the posterior fossa [3]. Sethi et al.

investigated a cohort of 109 patients of which sixteen experienced a relapse. The majority of them involved the spinal (n= 8) and supratentorial compartment (n= 6) [4]. We observed that the majority of DFs in our cohort were not limited to one compartment, but were diffuse leptomeningeal metastases (n=7) (Table 2). We believe this might be explained due to a higher proportion of metastatic patients (47.9%), in comparison to the aforementioned studies in which this value ranges between 18 and 25% [3, 4]. A retrospective analysis in a small group (n=15) of infants with medulloblastoma showed encouraging results. With a median follow-up of 39 months, only 1 developed a failure [6]. Data on tumor control of AYAs receiving CSI with protons are scarcer. Liu et al. reported 4-year LC and DFS of a cohort of 15 AYAs with medulloblastoma of 90% and 90%, respectively [8]. Importantly, LC, DC and OS was 100% among AYAs in our cohort. Due to the small numbers, the difference of these outcome-metrics was not statistically different when compared to children (Table 2).

In our study, metastatic status before PBSPT was associated with a worse outcome in terms of DC and OS (Table 2). The prognostic impact of metastases among children and adults with brain tumors is well known [20- 23]. Most of the patients with brain tumors that develop distant metastases die due to progressive disease [23]. We observed a high percentage of patients with metastases (47.9%) and recurrent tumors (22.5%). Patients with recurrent tumors had significantly worse LC, DC and OS. However, our 2-year OS of 70% for patients with recurrent tumors compares favorably with the reported 51% 2-year OS among patients with recurrent medulloblastoma [24] and 74.9% in children with recurrent ependymoma [25].

In patients with medulloblastoma, results must also be interpreted in the context of their molecular analysis. Current consensus recognizes four molecular subgroups with

different demographics, genetics and prognosis (WNT, SHH, group 3 and group 4) [26]. Retrospective studies have shown that WNT has the best prognosis while group 3 has the worst [27]. Within our cohort, the majority corresponded to a group 3 or 4 and the lower prevalence of patients with WNT or SHH-group was similar to that published in a large meta-analysis [28].

Our low rates of G3 acute toxicity suggests a good tolerance. Few studies have analyzed acute toxicity of proton CSI. Three (5.6%) children developed acute G3 hematological toxicity. All of them received chemotherapy, which is known to increase hematologic toxicity [29]. Bearing in mind that this is a small cohort, our low haematological toxicity rates might be explained by a lower use of concomitant (8.5%) chemotherapy when compared to other proton studies that report a severe acute toxicity rate of 9-32% [3, 7]. PT CSI has been found to decrease acute hematological and gastrointestinal toxicity in comparison with photons [7]. Another strategy to reduce hematologic toxicity is vertebral sparing irradiation with protons. This is especially interesting in full-grown AYAs. Brown et al. showed a significant decrease in G2 gastrointestinal and hematological toxicity of proton vs. photon CSI [30]. Due to its steeper dose gradient, PBSPT might be able to reduce even more doses to vertebrae

Our actuarial 2-years freedom from G3 late toxicity of 92.6% is reassuring (Fig. 2). G2 hearing impairment occurred in 4.2% of the patients and no case of G≥ 3 was observed. Moeller et al. reported a 1-year severe ototoxicity rate of 5% in children treated with PT for medulloblastoma, but it is important to note that in this series all of the patients received platinum-based CT [16]. Our 23.9% rate of endocrinopathy requiring substitutive medication is aligned with data among C-AYA irradiated for brain tumors [31]. CNS radiation necrosis was observed in only 2 (2.8%) children. Similarly, Murphy et al. reported a 3.7% rate of radiation necrosis that appeared after a median

time of 4.8 months after photon radiotherapy for pediatric brain tumors [32]. After a median follow-up of 3 years, the experience of three reference centers in the United States showed a G≥ 2 radiation necrosis rate of 2.4% [33]. Vogel et al. observed a cumulative incidence of brainstem necrosis of 0.7% at 24 months after PBSPT for children with CNS turmors. [34]. We also observed 1 (1.4%) patient with a G3 stroke. Likewise, Yock et al. observed that 1 of 59 patients developed a stroke G4 after proton CSI [3]. No patient developed a secondary malignancy, notwithstanding that the follow-up time of our patients is very short. PT has been reported to decrease the estimated incidence of second tumors [35]. However, Paulino et al. reported recently a 5-year and 10-year secondary malignancy incidence rates of 1.0% and 6.9%, respectively after proton CSI, which did not differ from photon CSI [5]. The theorical benefit of PT in reducing second cancers might only be observed after PBSPT due to a reduced total body dose secondary to neutrons.[35]. Longer follow-up is needed to validate this hypothesis.

Data presented here must be cautiously interpreted due to its retrospective design and the fact that it reflects the experience of a single center. Additionally, the clinical outcomes are reported for a range of brain tumors. Longer follow-up is necessary to evaluate more mature clinical outcomes, especially regarding late toxicity and secondary tumors. We were not able to report on neurocognitive outcome or altered axial growth, for lack of systematically assessed information on that subject. We also included patients treated with a mixed photon-proton radiation treatment that could not be treated at our center as initially intended due to technical or geographical difficulties. This is a known issue: patients living far from a proton treatment facility are less likely to receive PT [36]. Today the use of PT for pediatric and some AYA patients

is worldwide accepted and is expected to continue and to increase in the following years [2, 36-38].

CONCLUSIONS

In conclusion, we report early clinical outcomes after CSI with PBSPT for C-AYAs with brains tumors that are in line with previous photon and proton CSI reports. Our low rates of severe acute and late toxicity reaffirm the use of PT as an appropriate treatment modality for such a vulnerable population, in which the sequelae of treatment can seriously affect their future life. A future analysis of quality of life, late toxicities and second malignancies would be of great interest to comprehend the long-term effects of PBSPT. Overall, our data contributes to the growing body of evidence supporting the safety and feasibility of PT CSI for C-AYAs with brain tumors and might help to better understand the patterns of care of the real clinical practice.

CONFLICTS OF INTEREST

The authors declare no conflict of interest

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LEGENDS

A) Figures:

- **FIGURE 1.** Kaplan-Meier curves showing actuarial LC (green), DC (blue) and OS (red)
- **FIGURE 2.** Kaplan-Meier curve showing actuarial freedom from grade 3 or more toxicity.
- **FIGURE S1.** Histogram showing the number of patients treated per year between 2004-2021

B) Tables:

- **TABLE 1**. Patient and treatment characteristics
- **TABLE 2.** Univariate analysis using log-rank to investigate variations in actuarial patterns of OS, LC and DC in 2 years after the start of the treatment
- **TABLE 3**. Site of local and distant failures
- **TABLE S1.** Clinical and treatment characteristics of patients that developed a LF only
- **TABLE S2**. Clinical and treatment characteristics of patients that developed a DF only
- **TABLE S3.** Clinical and treatment characteristics of patients that developed a LF and DF

TABLES

TABLE 1. Patient and treatment characteristics

		Median (range), n (%)
Age		7.4 (1.7 – 21.3)
Age group	Children (< 15 years)	61 (85.9)
	AYA (≥ 15 years)	10 (14.1)
Sex	Female	23 (32.4)
	Male	48 (67.6)
Lansky or KPS score	≥ 70	60 (84.5)
	< 70	11 (15.5)
Diagnosis	Medulloblastoma	42 (59.2)
	Ependymoma	8 (11.3)
	GCT	6 (8.5)
	PNET	5 (7)
	ATRT	3 (4.2)
	CPC	2 (2.8)
	HGG	2 (2.8)
	Pineoblastoma	2 (2.8)
	Lymphoma	1 (1.4)
Site of primary tumor	Supratentorial	26 (36.6)
	Infratentorial	43 (60.6)
	Spinal	2 (2.8)
WHO grade	WHO 1	2 (2.8)
	WHO 2	3 (4.2)
	WHO 3	7 (9.9)
	WHO 4	51 (71.8)
	NA	8 (11.3)
Tumor status	Primary	55 (77.5)
	Recurrent	16 (22.5)
Median tumor size (mm) at diagnosis		40 (4 -80)
Tumor size (mm) at diagnosis	< 40	22 (31)
	≥ 40	23 (32.4)
	NA	26 (36.6)
Metastasis site	No metastases	37 (52.1)
	CSF positive	8 (11.3)
	Intracranial	8 (11.3)
	Spinal	13 (18.3)
	Spinal and intracranial	5 (7)
Treatment according to a protocol	Yes	63 (88.7)
	No	8 (11.3)
Surgery	None	11 (15.5)
	Biopsy	4 (5.6)
	STR	18 (25.4)
	GTR	38 (53.5)
Chemotherapy	Induction	35 (49.3)[1]
	Concomitant	6 (8.5)[1]
	Maintenance	38 (53.5)[1]
RT dose (Gy_{RBE})	Dose per fraction	1.8 (1.2 – 2)
	Total dose	54 (18 – 60.4)
	CSI dose	24 (18 – 36.8)
	Boost dose	30.6 (0 – 36)
Photon combination	Yes	5 (7)
	No	66 (93)
Vertebral sparing	Yes	6 (8.5)
	No	65 (91.5)
Reirradiation	Yes	9 (12.7)
	No	62 (87.3)

[1]Absolute and relative values do not sum 71 and 100% respectively, since the same patient could receive induction, concomitant and maintenance chemotherapy. WHO: World Health Organisation; NA: Not available; CPC: Choroid Plexus Carcinoma; STR: Subtotal resection; GTR: Gross total resection.

TABLE 2. Univariate analysis using log-rank to investigate variations in actuarial patterns of OS, LC and DC in 2 years after the start of the treatment.

	n	2y-LC (95%CI)	*p*[a]	2y-DC (95%CI)	*p*[a]	2y-OS (95%CI)	*p*[a]
Sex	71		0.543		0.087		0.201
Female	23	95% (68 to 99)		90% (66 to 98)		90% (63 to 97)	
Male	48	81% (78 to 98)		76% (59 to 86)		83% (67 to 91)	
Age group	71		0.363		0.170		0.238
Children (< 15 years)	61	85% (81 to 97)		78% (64 to 87)		83% (69 to 91)	
AYA (15-39 years)	10	100%		100%		100%	
Lansky/KPS	71		0.191		0.702		0.119
≥ 70	60	84% (80 to 97)		100%		82% (68 to 90)	
< 70	11	100%		72% (62 to 86)		100%	
Initial tumor size	55		0.611		0.614		0.654
≥ 40 mm	23	82% (72 to 99)		81% (58 to 93)		86% (57 to 97)	
< 40 mm	22	93% (59 to 99)		82% (61 to 97)		88% (61 to 95)	
Primary or Recurrent	71		**<0.0001**		**0.004**		**0.003**
Primary	60	95% (80 to 99)		88% (74 to 94)		89% (76 to 95)	
Recurrent	11	44% (11 to 74)		54% (21 to 76)		70% (31 to 86)	
Metastases	71		0.187		**0.009**		**0.012**
Yes	34	75% (64 to 96)		66% (43 to 81)		74% (50 to 86)	
No	37	93% (82 to 100)		92% (76 to 97)		94% (78 to 98)	
Surgical resection	71		0.150		0.161		0.197
Yes	56	90% (88 to 99)		84% (71 to 92)		88% (73 to 94)	
No	15	69% (42 to 95)		67% (31 to 86)		74% (39 to 91)	

KPS: Karnofsy performance status. [a]p-value in bold for statistically significant values ($p < 0.05$)

TABLE 3. Site of local and distant failures

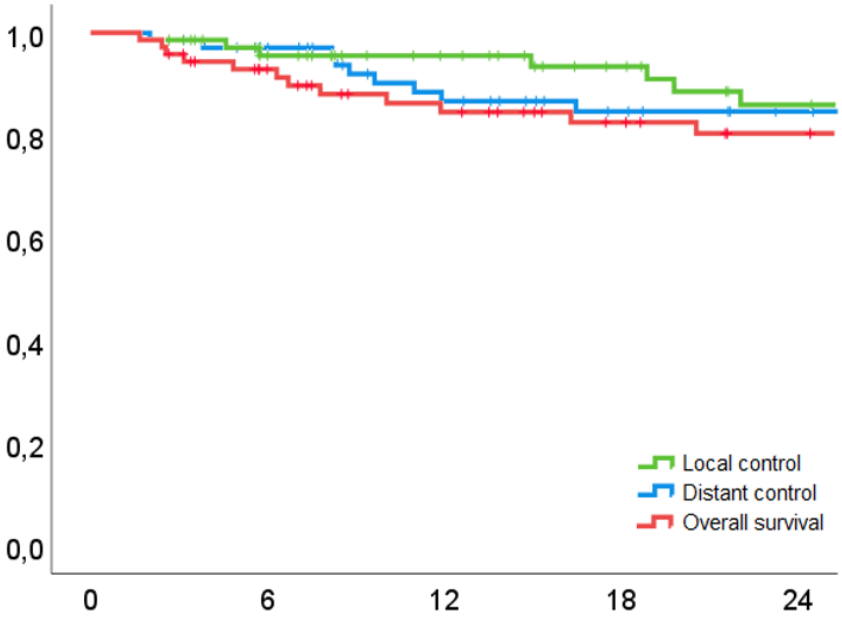
		n (%)
LFs	In-field	7 (87.5)
(n= 8)	Marginal	1 (12.5)
	Diffuse leptomeningeal	7 (46.6)
	Supratentorial	2 (13.3)
DFs	Infratentorial	2 (13.3)
(n= 15)	Brain[a]	1 (6.7)
	Spine	1 (6.7)
	Brain[a] and spine	1 (6.7)
	Extra-neural failure	1 (6.7)

[a]Not specified

FIGURES

- **FIGURE 1. Kaplan-Meier curves showing actuarial LC (green), DC (blue) and OS (red)**
- **FIGURE 2. Kaplan-Meier curve showing actuarial freedom from grade 3 or more toxicity.**

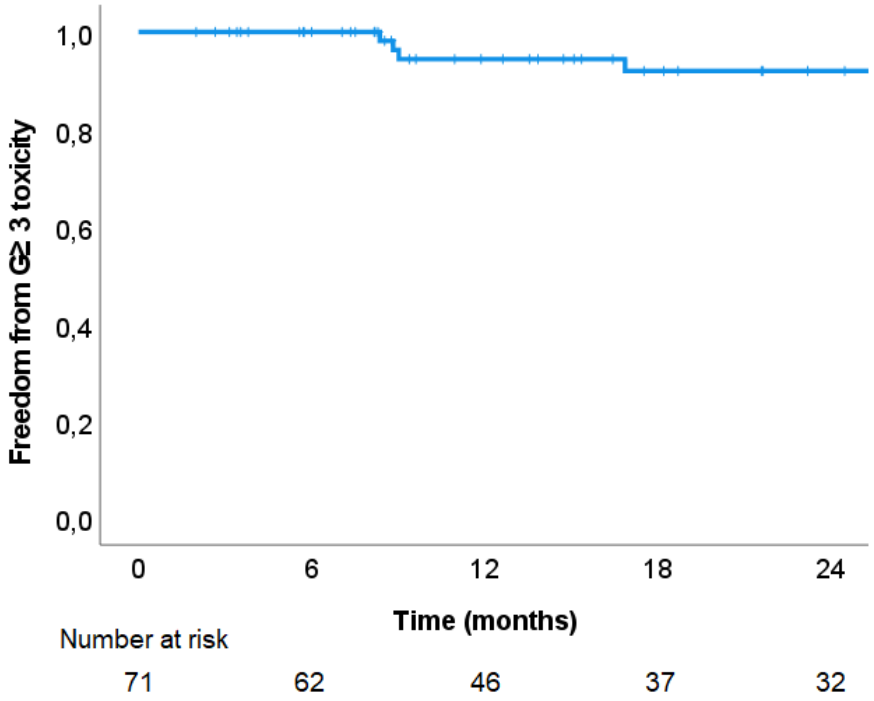
FIGURE 1. Kaplan-Meier curves showing actuarial LC (green), DC (blue) and OS (red)



Number at risk

Local control	71	60	49	40	33
Distant control	71	59	48	40	35
Overall survival	71	62	49	41	36

FIGURE 2. Kaplan-Meier curve showing actuarial freedom from grade 3 or more toxicity.



TABLES

- **TABLE S1.** Clinical and treatment characteristics of patients that developed a LF only
- **TABLE S2.** Clinical and treatment characteristics of patients that developed a DF only
- **TABLE S3.** Clinical and treatment characteristics of patients that developed a LF and DF

FIGURES

- **FIGURE S1.** Histogram showing the number of patients treated per year between 2004-2021

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TABLE S1. Clinical and treatment characteristics of patients that developed a LF only

n	Age	Sex	Diagnosis	Recurrent	M status	Surgery	CT protocol	CSI (D x Fr) Boost (D x Fr) (Gy RBE)	Mixed with photons	Re-RT	Time to LF (months)	Type of LF	Further treatment	Status (months)
1	4	F	PNET	Y	M0	STR	HIT2000	35.2 (1.6 x Fr) 55 (1.8 x Fr)	N	N	87	In-field	2nd LF: GTR 3rd LF: TMZ 4th LF: STR 5th LF: SRT (6 Gy x 5 Fr)	ANED (133)
2	5.2	M	CPC	N	M0	GTR	CPT-SIOP 2009	36 (1.8 x Fr) 54 (1.8 x Fr)	N	N	22	In-field	Surgery	D (68)
3	3.8	F	Ependymoma (WHO 3)	Y	M+	GTR	HIT2000	32 (1.6 x Fr) 53.6 (1.8 G x Fr) + TMZ	N	Y	19	Marginal	Surgery	D (43)
4	3.9	F	GBM	N	M+	STR	HIT-MED 2017	23.4 (1.8 x Fr) 59.4 (2 x Fr)	N	N	5	In-field	None	D (8)

F: Female; M: Male; M status: metastatic status; M+: metastatic; D x Fr: dose per fraction; TMZ: Temozolomide; Re-RT: reirradiation; ANED: No evidence of disease; D: Death

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TABLE S2. Clinical and treatment characteristics of patients that developed a DF only

n	Age	Sex	Diagnosis	Recurrent	M status	Surgery	CT protocol	CSI (D x Fr) Boost (D x Fr) (Gy RBE)	Mixed with photons	Re-RT	Time to DF (m)	Site of DF	Further treatment	Status (months)
1	2.4	M	MB	Y	M+	-	HIT2000	36.8 (1.6 x Fr) 54.4 (1.8 x Fr)	N	N	10	DLM	None	D (11)
2	9	M	MB	N	M+	STR	HIT2000	35.2 (1.6 x Fr) 55 (1.8 x Fr)	N	N	11	ST	Surgery and CT (HIT-REZ 2005)	D (16)
3	9.3	M	MB	N	M+	STR	Head Start II	23.4 (1.8 x Fr) 54 (1.8 x Fr)	Y*	N	32	ST	Surgery	AD (44)
4	4	F	MB	Y	M+	-	HIT2000	35.2 (1.6 x Fr) 55 (1.8 x Fr)	N	N	7	DLM	None	D (11)
5	10.1	M	MB	N	M0	GTR	HIT2000	36 (1.8 x Fr) 54 (1.8 x Fr)	N	N	8	DLM	TMZ	D (8)
6	1.9	M	ATRT	N	M+	STR	EU-RHAB 2016	24 (1.6 x Fr) 54.6 (1.8 x Fr)	N	N	2	Brain[a] + Spinal	None	D (3)
7	5.3	M	MB	N	M0	GTR	SIOP PNET 5-MB	23.4 (1.8 x Fr) 54 (1.8 x Fr)	N	N	3	DLM	None	AD (32)

8	9.5	M	ALCL	N	M+	GTR	NHL-BFM	18 (1.8 Gy/Fr)	N	N	16	Bone	VBL	ANED (40)
9	3.6	M	MB	N	M0	STR	SIOP PNET 5-MB	23.4 (1.8 x Fr) 54 (1.8 x Fr)	N	N	4	DLM	BVZ-TMZ-MTX-ara-C-CPT-11	AD (8)
10	6.3	M	MB	N	M+	GTR	I-HIT MED	35.2 (1.6 x Fr) 55 (1.8 x Fr)	N	N	2	DLM	NA	D (8)
11	2.9	F	MB	Y	M+	GTR	I-HIT MED	35.2 (1.6 x Fr) 55 (1.8 x Fr)	N	N	3	Spinal	CT (MEMMAT)	AD (6)

M: Male; F: Female; MB: Medulloblastoma; ALCL: Anaplastic Large Cell Lymphoma; M status: Metastatic status; Y: Yes, N: No; DLM: Difuse leptomeningeal; TMZ: Temozolomide; VBL: Vinblastine: BVZ: Bevacizumab; MTX: Metotrexate; ara-C: Citarabine; C-CPT-11: Irinotecan; D: Death; AD: Alive with disease; ANED: Alive with no evidence of disease.

[a]Not specified

TABLE S3. Clinical and treatment characteristics of patients that developed a LF and DF

n	**Age**	**Sex**	**Diagnosis**	**Recurrent**	**M status**	**Sx**	**CT protocol**	**CSI and total dose PRT (Gy RBE)**	**Ph-m**	**Re-RT**	**Time to LF (months)**	**Type of LF**	**Further treatment**	**Time to DF (months)**	**Site of DF**	**Status** (months)
1	8.3	M	PNET	Y	M+	STR	Head Start III	36 (1.8 x Fr) 54 (1.8 x Fr)	N	N	18	in-field	Sx	36	IT	D (38)
2	4.2	M	PNET	Y	M0	GTR	None	36 (1.8 x Fr) 54 (1.8 x Fr)	N	Y	4	in-field	None	6	Brain[a]	D (9)
3	9.9	M	Ependymoma (WHO 3)	Y	M+	-	None	35.2 (1.6 x Fr) 57.7 (4.5 Gy/Fr)	Y	Y	15	in-field	Sx + Laser ablation	20	IT	AD (22)
4	8.1	M	DIPG	Y	M+	-	None Fimepinostat	24 (1.6 x Fr)	N	Y	1	in-field	None	1	LM	D (2)

M: Male; F: Female; Y: Yes, N: No; M status: Metastatic status; M+: Metastatic; M0: Non-metastatic; Sx: Surgery; ST: Supratentorial; DLM: Difuse leptomeningeal; D: Death; AD: Alive with disease.

[a]Not specified

FIGURE S1. Histogram showing the number of patients treated per year between 2004-2021