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CLINICAL STUDY

# Pencil beam scanning proton therapy for pediatric intracranial ependymoma

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**Abstract** To assess the clinical outcome and late side effect profile of pencil beam scanning proton therapy (PT) delivered to children with intracranial ependymoma. Between July-2004 and March-2013, 50 patients with intracranial ependymoma (n = 46, grade 3) received involved-field PT at Paul Scherrer Institute (PSI). Median age at time of PT was 2.6 years (range 1.1–15.2). Thirty-six patients had infratentorial and 14 supratentorial ependymomas. Seventeen patients presented with macroscopic residual disease after subtotal resection before starting PT (8 with ≤1.5 cc and 9 with >1.5 cc residual tumor respectively). Forty-three (86 %) patients received post-operative chemotherapy before PT according to protocols; 44 (88 %) patients younger than 5 years required general anesthesia. Median prescribed dose was 59.4 Gy (RBE) (range 54–60) delivered in 1.8–2 Gy (RBE) per fraction. Late toxicity was assessed according to CTCAE v4.0. With a mean follow-up time of 43.4 months (range 8.5–113.7) seven patients experienced local failure (6 with infratentorial tumors and 1 with supratentorial tumor); four of the local failures were in patients with residual disease ≥1.5 cc at the time of PT and 3 without residual macroscopic disease. Five patients died from tumor progression. Actuarial 5-year Local Control rates were 78 ± 7.5 % and 5-year OS rates were 84 ± 6.8 %. Three patients developed grade ≥3 toxicity: 2 developed unilateral deafness (infratentorial tumors infiltrating into the internal acoustic canal), one patient developed a fatal brainstem necrosis. Repeated general anesthesia in children younger than 5 years was delivered without complications. Our data indicate the safety and the effectiveness of PT for pediatric ependymomas. Local control and survival rates are encouraging considering the high grade histology in 92 % of the patients and the number of patients with residual tumor ≥1.5 cc. The rates of late effects compare favorably with published photon-treated cohorts.

**Keywords** Central nervous system · Intracranial pediatric ependymoma · Pencil beam scanning proton therapy · Tumor local control · Radiotherapy

## Introduction

Intracranial ependymomas account for 5 to 8 % of pediatric brain tumors, the majority occurring in children younger than 4 years [1]. The best outcomes for localized disease are achieved combining maximal surgical resection followed by involved-field radiation therapy (RT) [2–12]. In such a young population having high chance of cure the late side effects of RT are of major concern. The possibility of delivering chemotherapy to avoid or delay RT in young children under the age of 3 years has been evaluated by different investigators, with inferior results [5, 8, 13–16]. In addition, in pediatric patients, the physical dose characteristics of protons translate on clinical advantages of reducing incidence and severity of late side effects.

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Several pediatric dose-comparative studies have demonstrated the dosimetric superiority of protons in comparison to external beam photon techniques including intensity modulated RT (IMRT), as proton have a finite range in tissue and optimally spare organs at risk in vicinity of the target volume, [17]. The most used method for the delivery of proton therapy (PT) is the passive-scattering technique [18]. In 1980, Kanai [19] proposed scanning a narrow pencil-beam in three-dimensions through the target volume. This concept of ''pencil beam scanning'' was further developed at Paul Scherrer Institute [20], where the first patient was treated on a pencil beam scanning gantry in 1996. The flexibility of the pencil beam scanning approach has been extended at PSI to deliver intensity-modulated proton therapy (IMPT) [21–23]. IMPT is the direct equivalent of IMRT with photons and has been successfully integrated into the clinical routine since its introduction in 1999. The pencil beam scanning method allows increasing the dose-conformation capabilities not only at the distal region of the target, but also to the proximal region of the target from a given field and allows to delivery IMPT efficiently. This increased conformation capabilities allows further sparing of the organs at risk located proximal to the target, compared with passive-scattering techniques. Up to now IMPT can be delivered efficiently only with pencil beam scanning methods.

This is the first report of the long-term results of the use of pencil beam scanning PT in a cohort of 50 patients treated with pencil beam scanning based PT for intracranial ependymoma.

## Methods and materials

### Patient characteristics

Between July 2004 and March 2013, 50 patients (36 male, 14 female) with histologically proven diagnosis of intracranial ependymoma WHO Grade 2 in 4 patients, Grade 3 in 46 patients were treated postoperatively with PT at PSI with curative intent. The tumors were infratentorial in 36 (72 %) patients and supratentorial in 14 (28 %) patients. Patients were referred from different Institutions from Switzerland and Europe. The majority (95 %) of the histological diagnosis were centrally reviewed according to HIT and COG protocols.

The median age of patients at the time of PT was 2.6 years (range 1.1–15.2), 44 patients (88 %) were <5 years requiring general anesthesia. Children were sedated with Propofol under spontaneous breathing [24].

The majority of patients have a performance status 0 prior to PT, only seven patients with posterior fossa tumors had some residual postoperative ataxia or cranial nerve palsy.

The mean follow-up (FU) time was 43.4 months (range 8.5–113.7 months). A summary of patient and tumor characteristics are summarized in Table 1.

### PT treatment planning and delivery

All patients were immobilized using a combination of body cast and a vacuum-assisted bite-block system or thermoplastic mask. Patients with infratentorial tumors were immobilized in general in prone position and patients with supratentorial tumors in supine position (Fig. 1). Patient positioning was checked before every fraction, as published previously [25]. All children underwent 3D planning with CT and MRI fusion.

The postoperative tumor bed and residual tumor were identified as gross tumor volume (GTV). The clinical target volume (CTV) was defined as a 0.5–1 cm extension of the GTV restricted for anatomical boundaries. Figure 2 shows a representative dose distribution for patients with infratentorial and supratentorial ependymoma respectively.

**Table 1** Patients and tumor characteristics and treatments details of 50 pediatric intracranial ependymomas treated with spot-scanning proton therapy

| | N (%) |
|---|---|
| Number of patients | 50 |
| Gender | |
| Male | 36 (72) |
| Female | 14 (28) |
| Age at time of PT (months) | |
| 12–24 | 13 (26) |
| 25–36 | 18 (36) |
| 37–48 | 10 (20) |
| 49–60 | 3 (6) |
| >60 | 6 (12) |
| Tumor location | |
| Infratentorial | 36 (72) |
| Supratentorial | 14 (28) |
| Type of surgery | |
| GTR | 33 (66) |
| STR ≤1.5 cc | 8 (16) |
| STR >1.5 cc | 9 (18) |
| Anesthesia | |
| Yes | 44 (88) |
| No | 6 (12) |
| Adjuvant Chemotherapy | |
| Yes | 43 (86) |
| No | 7 (14) |
| Median total dose [Gy (RBE)] | 59.4 (range 54–60) |

*GTR* gross total resection, *STR* subtotal tumor resection

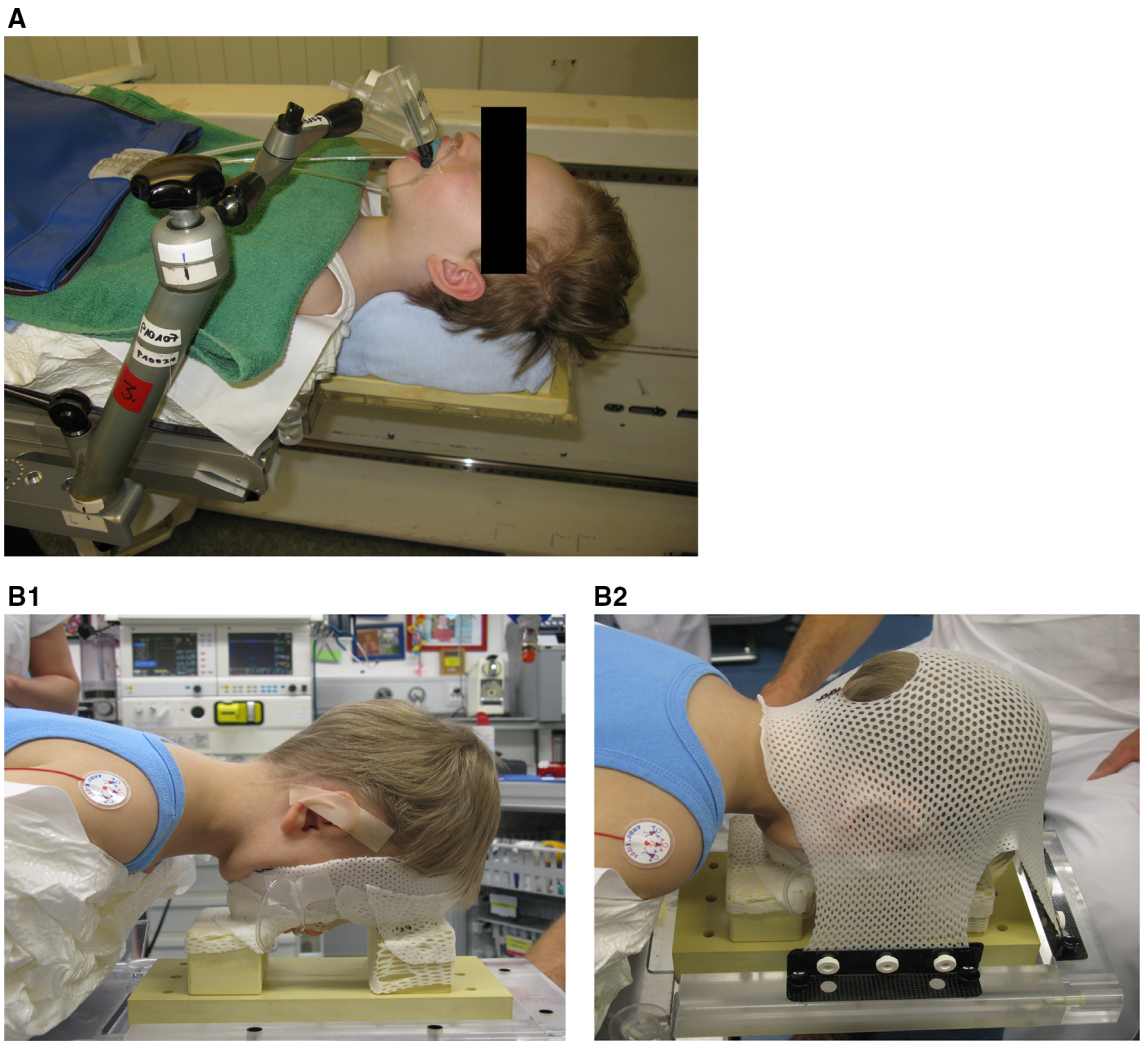


**Fig. 1** Immobilization examples for children under anesthesia for: **(A)** supratentorial tumors in supine with bite-block and **(B1, B2)** infratentoarial tumors in prone with thermoplastic masks

The relative biologic effectiveness (RBE) factor for protons of 1.1 (relative to that of Co-60) was used, and proton doses were expressed in terms of Gy (RBE) [Gy (RBE) = proton Gy × 1.1] [26]. Patients received a median PTV dose of 59.4 Gy (RBE) [range 54–60 Gy (RBE)], in fractions of 1.8–2 Gy (RBE).

Patients were treated using the pencil beam scanning technique at the scanning gantry by using energy-degraded beams from the 590-MeV cyclotron until 2005 [20] and subsequently the dedicated 250-MeV cyclotron.

Proton dose was computed using a 3-dimensional dose calculation algorithm developed at PSI [27, 28]. Single-field uniform dose (SFUD) plans or intensity modulated proton therapy (IMPT) plans were used [29].

Dose constraints to organs at risk (OARs) were determined as maximum dose (D2) of 59.4 Gy (RBE) to the brainstem, 50.4 Gy (RBE) to the spinal cord (for patients with infratentorial tumors with extension to the upper cervical spine), 54 Gy (RBE) to the optic chiasm and optic nerves and mean dose to at least one cochlea of 36 Gy (RBE). Treatment plans were optimized to maximize the coverage while observing OAR dose constraints.

## Surgery, chemotherapy and residual disease

Prior to PT, maximal feasible resection was performed for all patients. Patients were always evaluated for a second look surgical resection in case of residual tumor. Gross tumor resection (GTR) was defined as no evidence of disease on immediate postoperative MRI. The residual tumor at the time of PT was defined on the planning MRI with a threshold value of 1.5 cc.

Eleven (22 %) patients performed a second look surgery prior to PT. Seventeen (34 %) patients presented with

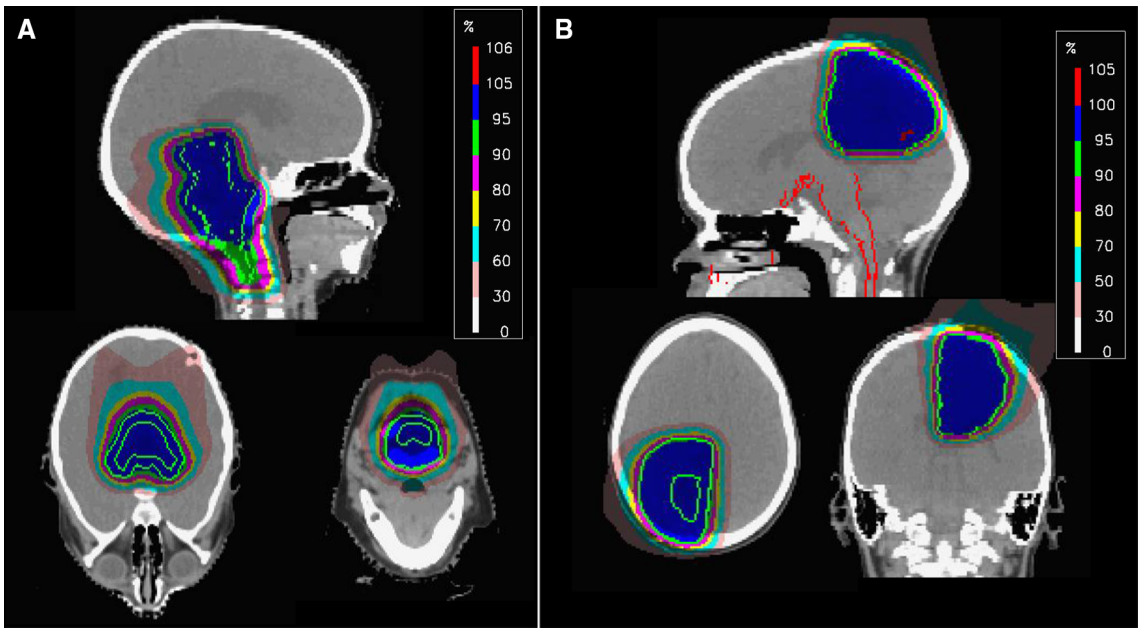


**Fig. 2** Representative spot-scanning PT plan for **a** infratentorial and **b** supratentorial epemdymoma

macroscopic residual disease after subtotal tumor resection before starting PT; 8 patients presented with residual tumor $\leq$1.5 cc and 9 patients presented with residual tumor $>$1.5 cc. Forty-three (86 %) patients received post-operative chemotherapy before starting PT according to international protocols, the mean interval time between initial diagnosis and initiation of PT was 7.5 months (range 2–25 months) due to this reason. The most common indications for chemotherapy were residual disease after resection and patient age under 3 years.

## Clinical data

Variables from demographic, tumor and treatment characteristics included the patient's gender, date of birth, date of pathological diagnosis, histological grade (the majority based on review by central board pathologists), receipt of chemotherapy before RT, dates of surgical procedures, extent of surgical resection, RT dose, dates of start and completion of RT, location of relapse if any, date of relapse and date of last follow-up.

## Follow-up evaluation

Patients were followed clinically and radiographically with serial brain and spine MRIs at regular intervals with neuroendocrinologic, ophthalmologic and auditory evaluations according to protocol recommendations. The neuroendocrinologic evaluation was systematically performed to all patients who received any dose of irradiation at the level of the hypothalamus or the pituitary gland. The radiological evaluations were performed all the 3–4 months during the first 2 years after end of treatment and all the 6 months thereafter. For the patients that were not seen locally at the Proton Center we received the referral medical reports, the MRI examinations for review as well as questionnaires answered from the parents. No patient was lost to follow-up and we have a 100 % compliance rate regarding answered questionnaires from the families. Not all the patients performed regular neuropsychological evaluations because patients were referred from different institutions around Europe not being possible to have follow-up on the cognitive assessment using standardized measures for all the patients.

Radiological criteria for local tumor control were defined as no evidence of macroscopic tumor on consecutive MRI.

Pituitary hormone deficiencies were defined as below-normal levels by gender and age, in addition to clinical diagnosis by a pediatric endocrinologist. Auditory and ophthalmologic evaluations were performed by an audiologist and an ophthalmologist respectively.

Late adverse events were prospectively defined as side effects observed after 90 days following completion of PT and classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.0, grading system [30].

## Statistical analysis

Local control (LC) was measured from the date of the start of PT to the date of local failure. Overall survival (OS) was

measured from the start of PT to the date of death. LC, and OS were censored for patients who had not failed or died at the date of their last follow-up, defined as the date of the most recent clinic note and/or MRI. LC and OS were estimated by the Kaplan–Meier method, using local recurrence and death as the respective failure endpoints. Two-sided p values for the potential impact of predictors on LC and OS were calculated using Fisher's exact test. All data analysis were carried out using the *StatSoft–Statistica* statistical package.

## Results

### Treatment outcomes

*Local and distant control*

With a mean follow-up time of 43.4 months (range 8.5–113.7), 7 patients (14 %) experienced in-field local failure; 6 with infratentorial tumors and 1 with a supratentorial tumor. This resulted in 5-year actuarial LC rates of 78.0 ± 7.5 % (Fig. 3). Four of the local failures were in patients presenting with residual disease ≥1.5 cc and 3 without residual macroscopic disease at the time of PT. Thirteen (76 %) out of the 17 patients presenting with macroscopic residual disease prior to irradiation responded completely to the irradiation; for a three (18 %) of these 17 patients a stabilization or a partial response of the disease was accomplished for several months with a mean interval time of 19 months (range 9–16 months) before progressing and 1 patient developed a progressive disease immediately after irradiation.

Two patients with local failure presented with synchronous microscopic CSF dissemination. One patient presenting with locally controlled infratentorial tumor developed supratentorial metastasis. All the patients presenting with local or distant failure in our cohort were patients having received postoperative chemotherapy prior to irradiation.

*Overall survival*

Five patients (10 %) died of progressive disease following local or distant failure at a median time of 33 months (range 24–48). Hence, this resulted in actuarial OS rates at 5 years of 84 ± 6.8 % (Fig. 4).

As a result of the limited number of events, we were not able to perform statistical analyses to identify prognostic factors for LC or OS.

### Late toxicity

Nineteen patients (38 %) developed 24 events of Grade 1 or Grade 2 late toxicities: 7 (14 %) patients developed permanent Grade 1 patchy alopecia or hair thinning. One patient (2 %) developed Grade 1 unilateral reduced hearing, 1 (2 %) patient developed Grade 1 concentration problems, and 9 (18 %) patients presented with a Grade 1 asymptomatic transient MRI changes of leukoencephalopathy. Three (6 %) patients presented with a permanent Grade 2 growth hormone deficiency requiring replacement and 3 (6 %) patients developed a permanent Grade 2 central hypothyroidism requiring replacement.

Three patients (6 %) developed grade ≥3 toxicity. Two patients with infratentorial tumors infiltrating into the internal acoustic canal developed definitive unilateral deafness as the ipsilateral cochlea was not spared due to the disease localization. One patient (3 years old girl) with an infratentorial ependymoma developed a fatal brainstem

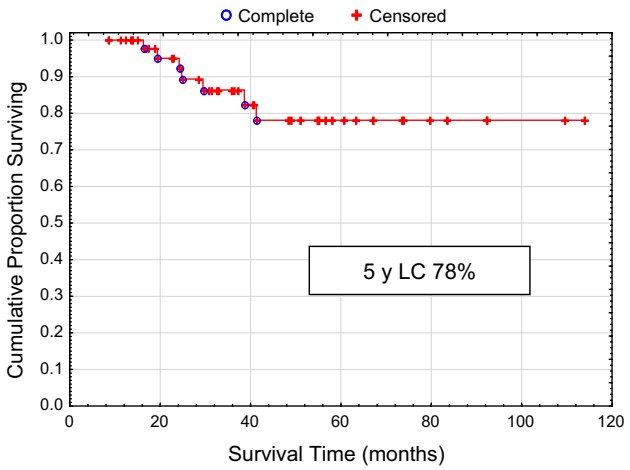


**Fig. 3** Actuarial local control rates

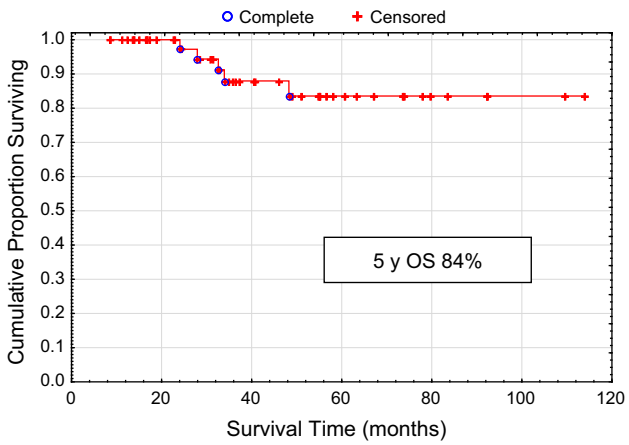


**Fig. 4** Actuarial overall survival rates

necrosis 7.5 months after starting PT, confirmed on autopsy. This patient was initially treated with GTR and adjuvant chemotherapy and presented with tumor relapse under chemotherapy; a second surgery was performed and complicated with brain stem infarct and meningitis. At the time of the PT the girl presented with some residual ataxia only and was treated to a total dose of 59.4 Gy (RBE).

No secondary malignancies were observed during the follow-up period.

## Discussion

Our results indicate the safety and the effectiveness of pencil beam scanning based postoperative PT for intracranial ependymomas. Estimates of 5-year PFS and OS from other retrospective photon series range from 41 to 58 and 54 to 71 %, respectively [2, 6–8, 31]. Merchant et al. [10] in their report on a prospective cohort of 153 patients with ependymoma found a 5-year PFS of 74 % and a 5-year OS of 85 %. MacDonald et al. [32] in their report on a cohort of 70 patients with localized ependymoma treated with passive scattering PT after 46 months of follow-up found a 3-year LC, progression free-survival and OS of 83, 76 and 95 % respectively. Our outcomes, are comparable to these reports, particularly considering that we had a lower rate of GTRs (66 vs. 81.7 % in the Merchant's series and 66 % in the MacDonald's series) and higher rate of WHO Grade 3 tumors (96 vs. 55 % in the Merchant series and 47 % in the MacDonald series) even if the issue of histology as prognostic factor in ependymoma is not resolved and there is some evidence from literature that European pathologist tend to have more Grade 3 tumors that their North American colleagues.

In our cohort 43 (86 %) patients received postoperative chemotherapy prior to irradiation according to protocols, prolonging the interval time between initial diagnosis and initiation of PT to a mean time of 7.5 months (range 2–25 months). Merchant et al. [9] reported a negative impact of prolonged chemotherapy prior to irradiation. In our cohort all the relapses were in patients having received chemotherapy but we cannot conclude that prolonged chemotherapy prior to radiotherapy has a negative impact on outcome as only seven patients in our series did not received postoperative chemotherapy.

We were not able to perform a failure analysis based on potential prognostic factors because of the small number of events observed. Cox proportional hazards regression requires at least ten events per risk factor to produce accurate estimates [33].

Many previous studies that have emphasized the importance of aggressive removal of the primary tumor [2, 6, 8, 10–12, 15]. We report a rate of GTR similar to other series, but not as high as that of Merchant et al., and MacDonald et al., mainly because of differences in the rate of second surgery. In the Merchant's 2009 series, 66 patients (43.1 %) underwent a second surgery, compared with 16 (23 %) in the MacDonald's series and 11 (22 %) in our series. The decision to recommend additional surgery remains challenging and is frequently limited by anatomical constraints and the level of morbidity considered acceptable by the parents and the physicians. Recently Morris et al. [34] established that more than one surgical procedure is safe for most patients. We advocate second-look surgery whenever required and feasible before PT.

The role of other prognostic factors is less clear. In some series anaplastic histology has been shown to worsen OS and PFS, including the large prospective cohort studied by Merchant et al. [4, 6, 8, 10–12]. Other series, similar to our report, did not find worse outcome [7, 35]. These differences may result from variation in the pathological interpretation of anaplasia and lack of statistical power. The evaluation of genetic profiles may better characterize prognostic subgroups [12, 36] in the future.

The average age of the patients in our cohort is relatively young. The reason is that patients were referred from different Institutions around Switzerland and Europe and due to our limited capacity the younger patients were given priority. Some studies, with the exception of Merchant's study [2, 7, 8, 31], found worse survival outcomes among patients under 3 years of age. This finding is probably related to the former common practice of delaying or omitting RT for this population. The benefit of RT in children under 3 years of age and the limited efficacy of chemotherapy to delay RT is well established, and postoperative conformal RT should continue as the standard of care for all ages [10, 11, 15, 16].

Opposite to Merchant et al., we did not detect that the incidence of distant failures increases relatively to the incidence of local failure. Modern series report a cumulative incidence of distant failures between 10 and 15 % over 3–5 years (6 % in our series) [3, 4, 6].

We report low rates of overall toxicities. Concerning the endocrinologic toxicity, in our series only three patients (6 %) developed laboratory evidence of growth hormone deficiency or central hypothyroidism requiring hormonal replacement, both of which are common complications of focal photon radiotherapy [37–39] Merchant et al., in a prospective study of pediatric patients receiving focal photon RT for localized brain tumors, found a correlation of dose to the hypothalamus and growth hormone deficiency. A mean dose below 16.1 and 5 Gy limited the risk to 50 % and to below 20 % respectively [40]. In the MacDonald et al. series 1 out of 32 patients (3 %) with thyroid hormone follow-up developed laboratory evidence of central hypothyroidism and 2 out of 25 patients (8 %)

with growth hormone follow-up were diagnosed of growth hormone deficiency.

Relative cognitive stability after conformal photon therapy for patients with ependymoma has already been established [41–43]. In addition, theoretical quantitative modeling predicted a benefit for protons from the decreased volume of temporal lobes and cerebrum receiving intermediate and high doses [44]. In our series concerning the cognitive outcomes we preferred not to describe the data available for only a part of the cohort as not the full cohort performed regular neuropsychological evaluation, and so far into the partial cohort who has already performed regular testing there are not significant changes and the will be part of future updated analysis with a larger cohort. That happens because patients were referred from different institutions around Europe not being possible to have follow-up on the cognitive assessment using standardized measures for all the patients. In the other hand all the children were schooled and only one patient treated for a supratentorial tumor reported concentration problems described by parents and teachers.

We had no cases of secondary malignancies.

Although several prior studies have described imaging changes after PT in the brain of adult patients treated for skull base tumors [45–48], description of PT-related imaging findings in the brain in pediatric patients is limited. In our series 9 (18 %) patients developed asymptomatic transient MRI changes (signal abnormalities and enhancement) between 2 and 11 months after completion of PT. Sabin et at [49] described that 8 of 17 young children (47 %) with localized brain tumors treated with PT as part of a prospective protocol developed transient MRI changes at a median time of 3.9 months after the completion of PT. Those were mostly transient signal abnormalities and enhancement in brain parenchyma consistent with radiation-induced effects on normal-appearing tissue. The median time to resolution or the beginning of resolution of the imaging changes was 2.3 months. Correlation with PT planning data revealed that the areas of imaging abnormality were located within or adjacent to the volume that received the highest radiation dose. Radiologists should be aware of these findings as these signal changes and enhancement may resemble the imaging findings of tumor pseudoprogression.

In our cohort with a mean follow-up time of 43.4 months, 27 patients (54 %) were followed for more than 36 months and only 14 patients (28 %) were followed for less that 18 months. Longer follow-up is still required to provide more mature data concerning the outcome of pencil beam scanning PT, especially concerning the long term outcome on toxicities, as one of the major potential benefits of proton therapy compared with standard conformal techniques with photons is the improvement of the long term quality of life reducing the incidence and the severity of the toxicities on long survivors.

The distinct physical properties of protons allow for complete sparing of normal tissues beyond the end range of the proton beam. The use of pencil beam scanning and the use of IMPT as available for clinical use at PSI further improves the conformality and sparing of normal tissues upon that which can be achieved with passive scattering proton radiotherapy obtaining further sparing of normal tissues and the entrance of the pencil beams translating in potential further reduction of rates of toxicity [17].

The present study represents the largest clinical series of pediatric intracranial ependymomas treated with pencil beam scanning PT. The treatment was very well tolerated, with minimal acute toxicity, low morbidity profile and excellent LC and OS rates.

## Conclusions

Our study contributes to the small but growing body of evidence demonstrating the safety and the effectiveness of pencil beam scanning based PT for treating pediatric intracranial ependymomas. Pencil beam scanning technology was applied routinely and without technical difficulties or complications in this young patient population.

Local control and survival rates are encouraging considering the high grade histology in 92 % of the patients and the number of patients with residual tumor $\geq$1.5 cc (18 %). Furthermore, rates of late effects from PT compare favorably to published reports of photon-treated cohorts and comparable to published report of passive scattering PT treated cohort. We have established outcome data for a cohort of patients treated homogeneously.

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