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CLINICAL STUDY – PATIENT STUDY

Intensity modulated radiation therapy or stereotactic fractionated radiotherapy for infratentorial ependymoma in children: a multicentric study

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Abstract This study was to evaluate the treatment dosimetry, efficacy and toxicity of intensity modulated radiation therapy (IMRT) and fractionated stereotactic radiotherapy (FSRT) in the management of infratentorial ependymoma. Between 1999 and 2007, seven children (median age, 3.1 years) with infratentorial ependymoma were planned with either IMRT (3 patients) or SFRT (4 patients), the latter after conventional posterior fossa irradiation. Two children underwent gross total resection. Median prescribed dose was 59.4 Gy (range, 55.8–60). The median follow-up for surviving patients was 4.8 years (range, 1.3–8). IMRT (median dose, 59.4 Gy) and FSRT (median dose, 55.8 Gy) achieved similar optimal target coverage. Percentages of maximum doses delivered to the cochleae (59.5 vs 85.0% Gy; $P = 0.05$) were significantly inferior with IMRT, when compared to FSRT planning. Percentages of maximum doses administered to the pituitary gland (38.2 vs 20.1%; $P = 0.05$) and optic chiasm (38.1 vs 14.1%; $P = 0.001$) were, however, significantly higher with IMRT, when compared to FSRT planning. No recurrences were observed at the last follow-up. The estimated 3-year progression-free survival and overall survival were 87.5 and 100%, respectively. No grade >1 acute toxicity was observed. Two patients presented late adverse events (grade 2 hypoacousia) during follow-up, without cognitive impairment. IMRT or FSRT for infratentorial ependymomas is effective and associated with a tolerable toxicity level. Both treatment techniques were able to capitalize their intrinsic conformal ability to deliver high-dose radiation. Larger series of patients treated with these two modalities will be necessary to more fully evaluate these delivery techniques.

Keywords Pediatric tumor · Infratentorial ependymoma · Intensity modulated radiotherapy · Fractionated stereotactic radiotherapy

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Introduction

Ependymomas accounts approximately for 8–10% of all childhood CNS tumors and the mean age at diagnosis ranges from 50 to 70 months [1–4]. They are of neuroectodermal origin arising from ependymal cells in the obliterated central canal of the spinal cord, the filum terminale, choroid plexus or white matter adjacent to the highly angulated ventricular surface [5]. The majority of these tumors are of infratentorial location, particularly in the fourth ventricle [6].

Ependymoma is a rare tumor with fewer than 170 new cases diagnosed in the United States each year [7] and its treatment is somewhat controversial, including a multimodality approach, consisting of surgery, radiotherapy and chemotherapy.

Complete surgical resection appears to be the most important factor for children with ependymoma [8–11].

Craniospinal irradiation has been utilized in the past as standard approach in the management of infratentorial ependymomas [12], but has been progressively replaced by a more localized radiation fields, including the posterior fossa [13] or volumes limited to pre-surgical tumor bed with an added margin of 1–2 cm [14]. Reducing the dose of radiation administered to the organs at risks (OARs) and to the normal developing brain is a logical approach for treating pediatric ependymomas. As such, the use of non-conventional radiation therapy (RT), including intensity-modulated RT (IMRT) or fractionated stereotactic RT (FSRT), allows one to achieve significant improvements in dose distributions when compared to 3D conformal RT. No comparative study has assessed the dose distribution of IMRT compared to FSRT techniques.

In this study, we first analyzed the dose deposition of these two delivery techniques. Secondly, we assessed the acute and late toxicity of IMRT and FSRT. Lastly, we analyzed the outcome of these patients.

Materials and methods

From 1999 to 2007, a total of seven patients with resected infratentorial ependymoma were planned at the University Hospital of Geneva (3 patients) and Lausanne (4 patients) with postoperative IMRT and FSRT boost after posterior fossa irradiation, respectively. The patients' characteristics are detailed in Table 1.

Presenting symptoms and signs were nausea and vomiting in seven, ataxia in four, headache in two, and nystagmus and vertigo in one patient. Visual disturbance associated with memory and cognitive impairment was found in one patient. The majority of patients were neurologically unimpaired.

Staging consisted of magnetic resonance imaging (MRI) of the entire central nervous system. Cytological examination of the cerebrospinal fluid (preoperative, $n = 2$; postoperative, $n = 5$) was done in all patients. No patients had M+ disease during the time of diagnosis. One patient, however, presented with a metastatic progression before the start of IMRT, documented on a spinal MRI. Based on the operative reports and postoperative MRI, two and five patients had gross total resection and subtotal resection, respectively. Pathology was World Health Organization (WHO) grade II and III in six and one patients, respectively. Two patients received chemotherapy according to the institutional open protocols. No concomitant chemotherapy was delivered during RT.

Target volume consisted on the preoperative gross tumor volume (GTV) delineated on the preoperative MRI, which was fused with the planning CT. For FRST boost, a 4-mm 3D anisotropic margin was added to the GTV, defining the planning target volume (PTV). For IMRT, the CTV was defined by the GTV + 15-mm margin and the PTV was and additional 5-mm margin beyond the CTV. Three patients were planned at University of Geneva for IMRT using a 6-MV dedicated multileaf collimator linear accelerator (CLINAC 2100-C; Varian Medical System, Palo Alto, CA). An IMRT technique employing five or seven coplanar fields was adopted to deliver a median dose of 59.4 Gy (range, 59.4–60) in 1.8 or 2 Gy/daily fraction.

Four patients were planned at University of Lausanne for FSRT boost after conventional PF irradiation. A BrainLAB multileaf collimator linac (BrainLAB, Fieldkirchen, Germany) was utilized for treatment delivery. Four or five isocentric non-coplanar fields were utilized as a boost to

Table 1 Patient demographics and tumor characteristics ($n = 7$)

	n	%
Age (years)		
Median	3.1	
Range	1.5–9.9	
Age (years)		
<4	5	71
≥4	2	29
Gender		
Male	4	57
Female	3	43
KPS		
100	3	43
90	2	29
80	1	14
50	1	14
NFS		
0	2	28
1	3	43
2	1	14
4	1	14
Histology type (WHO)		
II	6	86
III	1	14
Surgery		
GTR	2	29
STR	5	71
Chemotherapy		
Yes	2	29
No	5	71
Follow-up after RT (years)		
Median	4.8	
Range	1.3–8	

KPS Karnofsky Performance Index, *NFS* Neurological Function Scale, *WHO* World Health Organization, *GTR* gross total resection, *STR* subtotal resection

deliver to target volume a total dose ranged from 55.8 to 59.4 Gy (median, 55.8). PF was treated with conventional 3D external beam radiotherapy (EBRT) using two lateral opposed fields with a median dose of 46.8 cGy (range, 36–50.4) in 1.8 Gy daily fractions delivered with 6- or 18-MV photons of a multileaf standard accelerator. Median FSRT boost dose to the local field was 9 Gy (range, 5.4–23.4).

Median time to radiation treatment start was 38 days. Five patients <4 years old (2 and 3 in IMRT and FSRT groups, respectively) required general anaesthesia during simulation and the RT delivery. Daily setup position was verified using portal images matched with digitally reconstructed radiographs for patients treated with IMRT, while for those treated with FSRT, the stereotactic setup was based on an infrared guided repositioning device with the patient immobilized in a customized mask attached to a non-invasive stereotactic localization frame with an overall geometrical uncertainity of 1–2 mm.

Patients were followed weekly during the treatment course and with a visit at 6 weeks after completion of RT, then regularly every at 3- or 6-month intervals with clinical examination and MRI of the brain every 4 months during the first 2 years and every 6 months successively. The median follow-up for surviving patients was 4.8 years (range, 1.3–8) after RT start.

Acute and late side effects were evaluated using the Common Toxicity Criteria (CTCAE) Version 3.0 grading system (http://www.ctep.cancer.gov). Acute toxicity was defined as side effects occurring during treatment or within 90 days after NCRT completion. Neurocognitive testing was performed at the baseline and then regularly after the start of RT.

Progression-free survival (PFS) and overall survival (OS) were calculated from the date of the first day of RT using Kaplan–Meier estimates. The events were death (all causes of death included) for OS and progressive disease or death for PFS. Progressive disease was defined as treatment failure occurring locally (PF) and/or distantly (spine or/and brain). Differences between the FSRT and IMRT percentages of prescribed doses were calculated using the two-sided Student-*t* test. The statistical analysis was performed on the SAS system (Ver. 5.0; SAS, Chicago, IL).

Results

Dosimetric characteristics

Treatment characteristics and dosimetric results of IMRT and FSRT are summarized in Tables 2 and 3. Optimal target volume coverage was obtained with both techniques. The percentage of the prescribed GTV mean dose was similar with IMRT and FSRT (100.5 and 100.3%, respectively). Patients planned with IMRT received however significantly ($P = 0.05$) more monitor units (MU) for treatment delivery (median, 594 MU) than those planned with FSRT (median, 498 MU).

Comparing IMRT and FSRT, the mean percentage of maximum dose delivered to OARs was significantly lower with FSRT for the pituitary gland and optic chiasm (Table 3). Conversely, a lower mean percentage of maximum dose to the cochleae was observed with IMRT when compared to SFRT planning (Table 3). Likewise, the mean percentage of maximum dose delivered to the BS was significantly lower with IMRT when compared to FSRT planning (Table 3). When assessing the percentage of mean dose received by 50% of the volume of this critical structure or the mean percentage of the minimum dose, the computed doses to the BS were however not significantly different with IMRT and FSRT planning (Table 3; 77.1 vs 85.6%; $P = 0.13$ and 38.7 vs 67.4%; $P = 0.10$, respectively). The supratentorial brain received an inferior percentage of mean and minimum doses using IMRT when compared to FSRT (Table 3). The percentage of maximum doses delivered to the brain were however not different (mean, 84.4 vs 84.1%; $P = 0.97$; Table 3).

Table 2 Treatment characteristics of non-conventional radiation therapy

	IMRT	FSRT[a]
Patient (*n*)	3	4
Total dose (Gy)		
Median	59.4	55.8
Range	59.4–60	55.8–59.4
Fractions (*n*)		
Median	33	31
Range	30–33	31–33
Treatment duration (days)		
Median	48	48
Range	46–50	46–52
Monitor units		
Median	594	498
Range	532–880	451–544
Mean dose ± SD delivered to target volume (Gy)		
D_{max}	63.1 ± 1.1	58.8 ± 2.6
D_{min}	51.3 ± 2.7	55.1 ± 1.1
D_{50}	59.9 ± 0.5	56.9 ± 2.0

IMRT Intensity modulated radiotherapy, *EBRT* external beam radiotherapy, *FSRT* fractionated stereotactic radiotherapy, D_{max} mean maximum dose, D_{min} mean minimum dose, D_{50} mean dose for 50% of tissue volume

[a] FSRT is delivered with external beam therapy (see text)

Table 3 Comparison between IMRT and EBRT + FSRT boost for mean maximum, minimum, and 50% of tissue volume doses (% of the total prescribed dose) for organs at risk

	IMRT			FSRT[a]			P[b]
	D_{max}	D_{min}	$D_{50\%}$	D_{max}	D_{min}	$D_{50\%}$	
Brainstem (Gy)	58.1 (97.5%)	23.1 (38.7%)	46.0 (77.1%)	58.9 (103.9%)	48.5 (67.4%)	48.5 (85.6%)	0.04
Cochleae (Gy)	35.4 (59.5%)	25.3 (42.5%)	29.0 (48.6%)	48.1 (85.0%)	45.2 (80.0%)	45.9 (81.2%)	0.05
Pituitary gland (Gy)	22.8 (38.2%)	13.3 (22.4%)	16.7 (28.2%)	11.3 (20.1%)	1.9 (3.3%)	3.6 (6.3%)	0.05
Optic chiasm (Gy)	22.7 (38.1%)	11.0 (18.5%)	14.0 (23.5%)	8.0 (14.1%)	2.3 (4.0%)	3.7 (6.6%)	0.001
Supratentorial brain (Gy)	50.3 (84.4%)	0 (0.0%)	6.2 (10.3%)	47.5 (84.1%)	0.2 (0.0%)	12.3 (21.7%)	0.97

IMRT Intensity modulated radiotherapy, *EBRT* external beam radiotherapy, *FSRT* fractionated stereotactic radiotherapy, D_{max} mean maximum dose, D_{min} mean minimum dose, and $D_{50\%}$ mean dose to 50% of tissue volume

[a] FSRT is delivered with external beam therapy (see text)

[b] Student's t test, D_{max}

Tumor control

One patient with a Grade III ependymoma who underwent sub-total resection died before the start of IMRT because of spinal metastatic spread of disease not diagnosed at the moment of IMRT planning. At the last follow-up, no patient presented a local or distant progression. The estimated 3-year progression-free and OS rates were 85.7 and 100%, respectively. No second malignancies were observed at last follow-up.

Toxicity

Intensity modulated radiation therapy and SFRT were well tolerated during treatment. One patient could, however, not start radiotherapy, as a result of her declining NFS. She subsequently died shortly afterwards of uncontrolled metastatic disease. All other patients completed the prescribed course of RT without treatment interruptions and with a median treatment time inferior than 50 days. The most common acute side effects were grade 1 alopecia or retro-auricular erythema. Stable KPS and NFS were observed for all treated patients. No patient developed acute grade 1 nausea and vomiting at the start of RT. No acute grade >1 adverse events were observed for the six treated patients.

During the follow-up, two patients presented hypoacousia, of which one bilateral hearing dysfunction (grade 2) was attributed to cisplatinum chemotherapy. Another patient, not receiving chemotherapy, presented a unilateral right hearing impairment (grade 2) after IMRT, despite the absence of difference between the mean dose delivered to right and left cochlea (D mean: 25 vs 25.5 Gy for right and left cochlea, respectively). No radiation-induced hormone deficiency, brain necrosis, myelitis, visual loss or neurocognitive impairment were observed at the last follow-up.

Discussion

The estimated 3-year PFS rate of >85% compared favorably with conventional RT series [15–17]. These data are also in line with the IMRT study of Schroeder et al. [8], reporting an identical outcome showed that IMRT can help to improve local control without an increased risk of marginal failure.

Current US protocols aim at delivering high dose (i.e., 60 Gy) RT using conventional RT techniques only. These techniques have been associated with substantial late radiation-induced adverse events in malignant brain tumor children at young ages. A recent series from Brazil has shown undisputedly that the majority (>80%) of children with brain tumors present a compromise speech, language and hearing function, as a result of their illness and treatment [18]. It is axiomatic that the less non-target brain tissue is irradiated, such as the cochleae and pituitary gland, the better the neuro-cognitive or endocrinological function will be. Controlled use of IMRT and FSRT allows one to achieve significant improvement in dose distribution while sparing OARs, when compared to conventional RT. We do not have the prescience to compare these two radiation modalities with our limited number of patients, although all published ependymoma series contain a restricted number of subjects. There are unquestionably several limitations of our study. First, the study design was retrospective in nature and thus lacked complete data for certain variables such as neurocognitive or quality of live data. The small sample size of seven children limited the statistical power to detect significant differences between IMRT and FSRT parameters. Additionally, the differential institutional treatment strategies and delivery techniques limits the applicability of these data to patients treated with non-conventional RT. This being said, and notwithstanding these limitations, it is reasonable to make two observations.

First, both techniques presented equivalent optimal target volume coverage but correlated with a different dose distribution at OARs. While FSRT used after conventional PF irradiation delivered less radiation to the OARs located in the floor of the middle cranial fossa, such as the optic chiasm and the pituitary gland, IMRT capitalized the conformal ability to 'paint' the dose in the vicinity of the brainstem and the cochleae (Table 3). However, the increased cochlear irradiation in the FSRT group must be considered with caution, as it results essentially from the posterior fossa conventional RT course and not from the FSRT contribution. Moreover, it has been suggested that smaller radiation fields, when compared to more comprehensive irradiation, are equi-effective in ependymoma [19], suggesting that the irradiation of the entire posterior fossa may not be warranted for non-metastatic, low-grade infratentorial ependymoma [20]. Thus, the decision to irradiate the cerebellum before the FSRT boost can bias the final dose distribution in this subgroup of patients, allowing to a less optimal sparing of OARs than that expected using FSRT alone.

Second, the number of MU necessary for the delivery of 55–60 Gy was significantly higher with IMRT than with FSRT (Table 2). The number of MU in IMRT is function of the plan complexity. In essence, the more complex the plan is, the longer the beam has to be turned on, so as to optimally conform the dose to the target volume by various delivery modalities (dynamic sequential arc or 'step and shoot' sliding windows techniques). Using small, non-intensity modulated stereotactic fields does not require, by definition, this photon-fluence modulation and thus a consequential increased number of MU. Although the integral dose (i.e., dose outside the target volume) increase is not solely due to the MU output but also to the beam energy and machine collimator design, it is a major concern in the pediatric population [21]. Using pediatric-size anthropomorphic phantom, a dose comparative study has shown that IMRT delivery resulted in higher doses to distant points to the target when compared to non-IMRT [22]. Consequently, using an IMRT delivery in a pediatric population, an increased risk to develop second radiation-induced malignancies is expected, although no reports in this regard have been published in the recent literature [23, 24]. The limited follow-up period of the present series should caution us to develop any zealotry about the lack of observed radiation-induced tumors. During the carcinogenesis period, there is a latency time between exposure to radiation and cancer onset. Thus, longer observation time may be necessary to observe these secondary malignancies.

Recently, different authors investigated the clinical outcome and the evident dosimetric advantage of proton beam radiation over photons in the treatment of intracranial ependymoma [25, 26]. Nevertheless, it is important to underline that the accessibility to proton centers is limited worldwide and that IMRT and FSRT remain actually the most widely diffused and accessible non-conventional radiation techniques able to offer excellent results in the treatment of pediatric tumors.

Conclusions

In conclusion, the clinical outcomes obtained with either IMRT or FSRT compared favorably with the data of conventional RT reported in the literature. These treatment techniques are feasible and well tolerated, even in a very young population. Dosimetrically, they appear to be similar in terms of tumor coverage. The acute and late toxicities were tolerable and comparable between IMRT and FSRT despite a differential OARs irradiation. Further research regarding radiation delivery with these techniques is justified in the framework of future dose-comparative and clinical studies.

Conflict of interest None.

References

1. Arndt V, Kaatsch P, Steliarova-Foucher E, Peris-Bonet R, Brenner H (2007) Up-to-date monitoring of childhood cancer long-term survival in Europe: central nervous system tumours. Ann Oncol 18:1734–1742
2. Foreman NK, Love S, Thorne R (1996) Intracranial ependymomas: analysis of prognostic factors in a population-based series. Pediatr Neurosurg 24:119–125
3. Horn B, Heideman R, Geyer R, Pollack I, Packer R, Goldwein J, Tomita T, Schomberg P, Ater J, Luchtman-Jones L, Rivlin K, Lamborn K, Prados M, Bollen A, Berger M, Dahl G, McNeil E, Patterson K, Shaw D, Kubalik M, Russo C (1999) A multi-institutional retrospective study of intracranial ependymoma in children: identification of risk factors. J Pediatr Hematol Oncol 21:203–211
4. Perilongo G, Massimino M, Sotti G, Belfontali T, Masiero L, Rigobello L, Garre L, Carli M, Lombardi F, Solero C, Sainati L, Canale V, del Prever AB, Giangaspero F, Andreussi L, Mazza C, Madon E (1997) Analyses of prognostic factors in a retrospective review of 92 children with ependymoma: Italian Pediatric Neuro-oncology Group. Med Pediatr Oncol 29:79–85
5. Centeno RS, Lee AA, Winter J, Barba D (1986) Supratentorial ependymomas. Neuroimaging and clinicopathological correlation. J Neurosurg 64:209–215
6. Reni M, Gatta G, Mazza E, Vecht C (2007) Ependymoma. Crit Rev Oncol Hematol 63:81–89
7. Allen JC, Siffert J, Hukin J (1998) Clinical manifestations of childhood ependymoma: a multitude of syndromes. Pediatr Neurosurg 28:49–55
8. Pollack IF, Gerszten PC, Martinez AJ, Lo KH, Shultz B, Albright AL, Janosky J, Deutsch M (1995) Intracranial ependymomas of childhood: long-term outcome and prognostic factors. Neurosurgery 37:655–666, discussion 666–657

9. Robertson PL, Zeltzer PM, Boyett JM, Rorke LB, Allen JC, Geyer JR, Stanley P, Li H, Albright AL, McGuire-Cullen P, Finlay JL, Stevens KR Jr, Milstein JM, Packer RJ, Wisoff J (1998) Survival and prognostic factors following radiation therapy and chemotherapy for ependymomas in children: a report of the Children's Cancer Group. J Neurosurg 88:695–703
10. Rousseau P, Habrand JL, Sarrazin D, Kalifa C, Terrier-Lacombe MJ, Rekacewicz C, Rey A (1994) Treatment of intracranial ependymomas of children: review of a 15-year experience. Int J Radiat Oncol Biol Phys 28:381–386
11. Schroeder TM, Chintagumpala M, Okcu MF, Chiu JK, Teh BS, Woo SY, Paulino AC (2008) Intensity-modulated radiation therapy in childhood ependymoma. Int J Radiat Oncol Biol Phys 71:987–993
12. Bloom HJ, Glees J, Bell J, Ashley SE, Gorman C (1990) The treatment and long-term prognosis of children with intracranial tumors: a study of 610 cases, 1950–1981. Int J Radiat Oncol Biol Phys 18:723–745
13. Nazar GB, Hoffman HJ, Becker LE, Jenkin D, Humphreys RP, Hendrick EB (1990) Infratentorial ependymomas in childhood: prognostic factors and treatment. J Neurosurg 72:408–417
14. Timmermann B, Kortmann RD, Kuhl J, Meisner C, Slavc I, Pietsch T, Bamberg M (2000) Combined postoperative irradiation and chemotherapy for anaplastic ependymomas in childhood: results of the German prospective trials HIT 88/89 and HIT 91. Int J Radiat Oncol Biol Phys 46:287–295
15. Mansur DB, Perry A, Rajaram V, Michalski JM, Park TS, Leonard JR, Luchtman-Jones L, Rich KM, Grigsby PW, Lockett MA, Wahab SH, Simpson JR (2005) Postoperative radiation therapy for grade II and III intracranial ependymoma. Int J Radiat Oncol Biol Phys 61:387–391
16. Merchant TE, Mulhern RK, Krasin MJ, Kun LE, Williams T, Li C, Xiong X, Khan RB, Lustig RH, Boop FA, Sanford RA (2004) Preliminary results from a phase II trial of conformal radiation therapy and evaluation of radiation-related CNS effects for pediatric patients with localized ependymoma. J Clin Oncol 22:3156–3162
17. Paulino AC, Wen BC, Buatti JM, Hussey DH, Zhen WK, Mayr NA, Menezes AH (2002) Intracranial ependymomas: an analysis of prognostic factors and patterns of failure. Am J Clin Oncol 25:117–122
18. Goncalves MI, Radzinsky TC, da Silva NS, Chiari BM, Consonni D (2008) Speech-language and hearing complaints of children and adolescents with brain tumors. Pediatr Blood Cancer 50:706–708
19. Combs SE, Kelter V, Welzel T, Behnisch W, Kulozik AE, Bischof M, Hof H, Debus J, Schulz-Ertner D (2008) Influence of radiotherapy treatment concept on the outcome of patients with localized ependymomas. Int J Radiat Oncol Biol Phys 71: 972–978
20. Paulino AC (2001) The local field in infratentorial ependymoma: does the entire posterior fossa need to be treated? Int J Radiat Oncol Biol Phys 49:757–761
21. Hall EJ (2006) Intensity-modulated radiation therapy, protons, and the risk of second cancers. Int J Radiat Oncol Biol Phys 65:1–7
22. Mansur DB, Klein EE, Maserang BP (2007) Measured peripheral dose in pediatric radiation therapy: a comparison of intensity-modulated and conformal techniques. Radiother Oncol 82: 179–184
23. Miralbell R, Lomax A, Cella L, Schneider U (2002) Potential reduction of the incidence of radiation-induced second cancers by using proton beams in the treatment of pediatric tumors. Int J Radiat Oncol Biol Phys 54:824–829
24. Hall EJ, Wuu CS (2003) Radiation-induced second cancers: the impact of 3D-CRT and IMRT. Int J Radiat Oncol Biol Phys 56:83–88
25. MacDonald SM, Safai S, Trofimov A, Wolfgang J, Fullerton B, Yeap BY, Bortfeld T, Tarbell NJ, Yock T (2008) Proton radiotherapy for childhood ependymoma: initial clinical outcomes and dose comparisons. Int J Radiat Oncol Biol Phys 71:979–986
26. Merchant TE, Hua CH, Shukla H, Ying X, Nill S, Oelfke U (2008) Proton versus photon radiotherapy for common pediatric brain tumors: comparison of models of dose characteristics and their relationship to cognitive function. Pediatr Blood Cancer 51:110–117