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ORIGINAL ARTICLE

Treatment tolerance of particle therapy in pediatric patients

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ABSTRACT

Curative treatment of pediatric cancer not only focuses on long-term survival, but also on reducing treatment-related side effects. Advantages of particle therapy are mainly due to their physical ability of significantly reducing integral dose.

Methods. Between January 2009 and December 2012, we treated 83 pediatric patients (aged 21 and younger) at the Heidelberg Ion Therapy Center at University Hospital of Heidelberg (HIT). In total 56 patients (67%) received proton irradiation, while 25 (30%) patients were treated with carbon ions (C12). Two patients received both treatments (3%). Treatment toxicity was analyzed retrospectively and documented according to the CTCAE/RTOG classification. In a second step, treatment toxicity from ion therapy was analyzed in comparison to treatment toxicity during photon irradiation of a comparable historical group of 19 pediatric patients.

Results. In all patients, particle therapy was tolerated well (median follow-up time 3.7 months), children (20 patients) with at least two follow-up visits showed a median follow-up time of 10.2 months. During the first two months patients mainly suffered from radiogenic skin reaction (63%), mucositis (30%), headache and dizziness (35%) as well as nausea and vomiting (13%). Severe toxicity reaction (grade II–IV) was only seen in patients who had intensive simultaneous chemotherapy or who had undergone several operations in the irradiated area before radiotherapy (18%). Treatment toxicity during ion therapy was comparable to treatment toxicity from photon irradiation of a historical group.

Conclusions. In comparison to conventional therapy, patients with particle therapy do not suffer from increased acute treatment-related toxicity during the first months. More experience with particle therapy will be needed during the next years to help to thoroughly evaluate the high potential of ion therapy.

During the last few decades, treatment concepts in pediatric oncology have improved significantly with many long-term survivors. Today, treatment not only focuses on tumor control and cure, but also on reducing treatment-related side effects. However, many children still suffer from long-term sequelae, e.g. neurocognitive deficits and growth retardation. Late toxicity may also lead to abnormal endocrine function, hearing loss, as well as secondary malignancies. These treatment-related side effects significantly reduce quality of life and cause high rates of morbidity among survivors [1–4]. Radiation oncologists aim at minimizing treatment-related toxicity by reducing integral dose and by sparing normal tissue. Progress has been made by the introduction of three-dimensional (3D) radiation therapy, followed by high-precision stereotactic radiotherapy and further development with the establishment of intensity-modulated radiotherapy (IMRT). Nevertheless, treatment-related side effects still remain an issue and are of strong focus regarding the treatment of children.

Particle therapy is characterized by the unique physical and biological ability to significantly reduce integral dose and thereby potentially minimize side effects [5]. Due to the distinct energy deposition profile of ion irradiation, a high local dose (Bragg Peak) can be applied in the defined target volume, while a

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low dose is deposited in the entry and exit channel. Therefore, optimal doses of radiation can be delivered to the tumor site, while surrounding healthy tissue is spared [6]. Thus, particle therapy and its promising abilities might be the next therapeutic step for further reducing long-term toxicity and improving tumor control.

Up to now, only little data can be found about side effects in children having received ion therapy. During the last years, multiple centers have started treating children with ion therapy for reducing toxicity. Experiences have been gained mainly in pediatric tumors in the central nervous system, such as ependymoma, neuroblastoma, medulloblastoma, craniopharyngeoma, low-grade astrocytoma, and germ cell tumors. Not many studies have been conducted regarding side effects in children undergoing particle therapy, especially not based on larger patient numbers [7–12]. Prospective and ideally randomized trials are still lacking. To our knowledge we are the first center to analyze such a large number of patients (n = 83) receiving particle therapy for acute and intermediate toxicity reaction.

Table I. Patients' characteristic of 83 children and young adults treated with proton and carbon ion irradiation.

Histology	N (%)
Primary brain tumors	28 (34%)
Pilocytic astrocytoma	n = 15
Astrocytoma (WHO II-III)	n = 4
Glioblastoma	n = 3
Others (ATRT, PNET, medulloblatoma, atypical menigeoma)	n = 4
Neurocytoma/ pituaray adenoma/ craniopharyngeoma	*3 (4%)*
Chordoma/chondrosarcoma	*12 (14%)*
Skull base chordoma	n = 9
Skull base chordosarcoma	n = 3
Osteosarcoma	7 (8%)
Skull base	n = 3
Pelvic	n = 4
Rhabdomyosarcoma	*14 (17%)*
ACC	*5 (6%)*
Other sarcoma	*4 (5%)*
Angiofibroma/arteriovenous hemangioma	*4 (5%)*
Germ cell tumors	*3 (4%)*
Aggressive fibromatosis/desmoid tumor	*3 (4%)*
Gender	
Male	49 (59%)
Female	34 (41%)
Treatment conceps	
Protons	58 (70%)
Carbon ions	27 (33%)
Photons and proton boost	4 (31%)
Photons and carbon ion boost	9 (69%)

Material and methods

From January 2009 to December 2012, we treated 83 pediatric patients with particle therapy at the Heidelberg Ion Therapy Center (HIT) at the University Hospital of Heidelberg. The median age was 14 years and ranged from 1 to 21 years. In total 34 patients were female (41%) and 49 were male (59%). Main indications were brain or head and neck tumors (92%). Histological types encompassed the typical pediatric spectrum. Patients' characteristics are summarized in Table I. In seven patients, radiotherapy was performed as re-irradiation treatment. Diagnoses for patients with re-irradiation treatment were osteosarcoma, aggressive fibromatosis, glioblastoma and rhabdomyosarcoma.

Patients were seen several times during and after primary treatment. Acute toxicity reaction (first two months), toxicity reaction after six months and toxicity reaction after 12 months were investigated retrospectively. Treatment-related side effects were documented according to CTCAE/RTOG classification. Data was collected retrospectively from our institutional documentation database and databases from other departments involved in treatment [13]. If patients had shown disorders and symptoms in the same intensity before radiotherapy, these symptoms were not regarded as toxicity due to radiotherapy. If symptoms intensified during treatment and no progression of disease or other treatment was reported, the aggravation was seen as toxicity reaction. Progression of disease was not taken as toxicity reaction. One child died due to progression of disease.

Children were treated according to the guidelines of the Society for Paediatric Oncology and Haematology (GPOH) in most cases, for the other cases an individual therapy was decided by an interdisciplinary team in a tumorboard conference. In total 56 patients received proton irradiation (67%), while 25 patients (30%) were treated with carbon ions (C12). Two children received a combined treatment with protons and a carbon ion boost (3%). Median radiation doses and range for each tumor entity are shown in Table II. Median dose for only proton irradiation was 54.0 GyE (range 20–80 GyE) and for carbon ion treatment was 60 GyE (range 39–66 GyE). Proton irradiation was mostly used for pediatric patients, while carbon ion treatment was generally applied for young adults with skull base tumors in otherwise difficult-to-control tumors. Of the patients treated with carbon ions, histologies included glioblastoma, atypical meningioma, chordoma, chondrosarcoma, adenoid-cystic carcinoma; the median age of these patients was 19 years (range 11–21), so only adolescent patients were treated with carbon and purely pediatric patients with protons.

Thirteen patients (16%) with radiation resistant tumors or recurrent tumors [such as osteosarcoma,

Table II. Radiation doses of the different tumors.

	IMRT (median dose; range)	Proton therapy (median dose; range)	Carbon ion therapy (median dose; range)
Brain tumors			
Pilocytic astrocytoma		*54 GyE (50.4–54.0 GyE)*	
Astrocytoma (WHO II–III)		*54 GyE (45–55.8 GyE)*	
Glioblastoma	50 Gy	*10 GyE (boost after IMRT)*	*18 GyE (boost after IMRT)*
Glioblastoma (relapse)			*39 GyE*
ATRT		*50.4 GyE*	
PNET		*54 GyE*	
Medulloblastoma (relapse)		*39.6 GyE*	
Atypical meningeoma			*51 GyE*
Neurocytoma/		*59.4 GyE*	
Pituary adenoma		*54 GyE*	
Craniopharyngeoma		*50.4 GyE*	
Sarcoma/chordoma			
Skull base chordoma		*72 GyE*	*66 GyE (60.0–66.0 GyE)*
Skull base chordosarcoma		*70 GyE*	*60 GyE*
Skull base osteosarcoma	42 Gy		*24 GyE (boost after IMRT) 61.5 GyE (60.0–63.0 GyE)*
Pelvic osteosarcoma	50 Gy (50–54 Gy)	*54 GyE*	*18 GyE(18–24 GyE) (boost after IMRT or proton irradiation)*
Rhabdomyosarcoma nasopharynx	*41.6 Gy*	*9 GyE*	
Rhabdomyosarcoma		*50.4 GyE (41.4–52.2 GyE)*	*45 GyE*
ACC	*50 Gy (50–56 Gy)*	*24 GyE (boost)*	*24 GyE (18–24 GyE) (boost)*
Other sarcoma	*56 Gy (54–58 Gy)*	*54 GyE*	*16 GyE (15–18 GyE) (boost after IMRT or proton irradiation)*
Others			
Angiofibroma		*45 GyE*	
Arteriovenous hemangioma		*20 GyE (SBRT)*	
Germ cell tumor		*54 GyE*	
Germinoma	*24 Gy (CSI)*	*16 GyE (boost); 24 GyE*	
Aggressive fibromatosis/Desmoid tumor		*58 GyE (56–66 GyE)*	

synovial sarcoma, glioblastoma and adenoid cystic carcinoma (ACC)], which require high-local dose as a definitive treatment, received photon IMRT combined with particle boost irradiation. Thirteen patients also received simultaneous chemotherapy according to the guidelines of the GPOH.

Treatment planning, patient positioning and anesthesia was done as described previously [9].

In a second step, we compared the patients with head-and-neck rhabdomyosarcoma to a previously published group of children (19 children) diagnosed with the same tumor entity for acute toxicity reaction. Patients' characteristics have been previously described [14]. These children were treated with IMRT or fractionated stereotactic radiotherapy (FSRT) and simultaneous chemotherapy according to the German Soft Tissue Sarcoma Study protocols between August 1995 and November 2005.

Results

In all patients, particle therapy was well tolerated. The median follow-up time was 3.7 months (range 0.9–28.9 months) for all patients. Patients (20 children) who had at least two follow-up visits showed a median follow-up time of 10.2 months (range 2.4–28.9 months).

In the first two months after radiotherapy, patients mainly suffered from grade I toxicity reaction: radiogenic skin reaction (49%), reduced Karnfosky performance score (37%), neurological disorders (29%), mucositis (16%), nausea (11%), pharyngitis/dyphagia (10%), conjunctivitis (10%), bone marrow toxicity (8%), xerostomia (8%), otitis externa (6%). Grade II toxicity reaction was found in 21 patients (25%): radiogenic skin reaction (12%), mucositis (11%), bone marrow toxicity (10%) and neurological disorders (5%). Further grade I and II toxicity reaction was detected in less than 5% of patients (Figure 1). Severe toxicity reaction (CTCAE/RTOG classification grade III–IV) was very rare (Figure 1). Four percent of patients suffered from grade III bone marrow toxicity, while 2% and 1% of patients were diagnosed with grade III mucositis and radiogenic skin reaction, respectively. Grade IV acute toxicity reaction (bone marrow) was only detected in patients receiving simultaneous chemotherapy (12%). Nearly all mild side effects disappeared within the first six months or remained at a very low level.

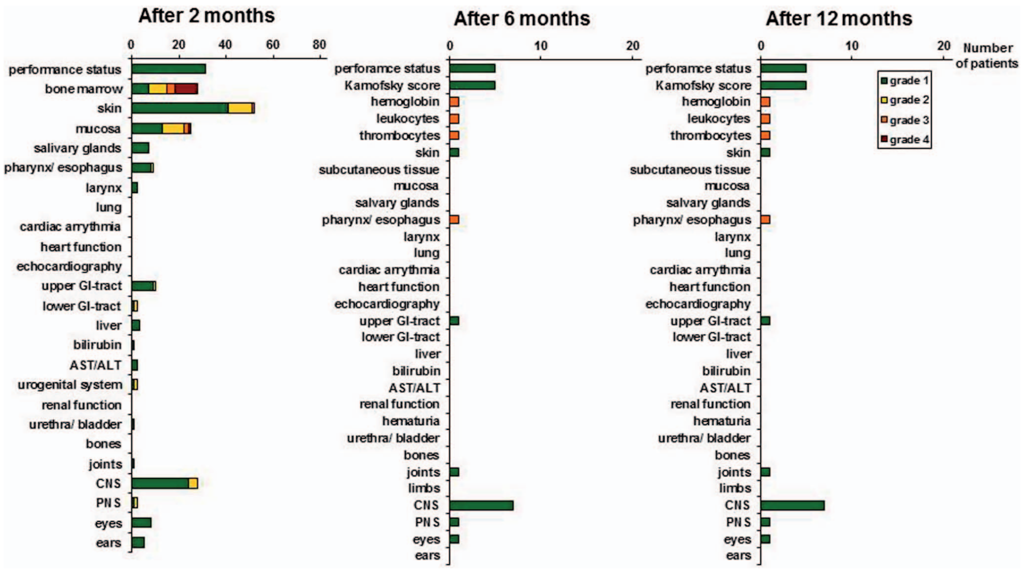

Figure 1. Toxicity reaction after 2 months, 6 months and 1 year: nearly all side effects disappeared quickly.

After six months data was only available for 43 patients. Grade I toxicity was detected in few patients: neurological disorders (28%), reduced Karnofsky performance score (11%), radiogenic skin reaction (7%), mucositis (7%). Further grade I toxicity reaction was detected in less than 5% of patients. Grade II toxicity reaction occurred mainly as bone marrow toxicity (5%) and reduced Karnofsky performance score (2%) and mucositis (2%). Only one patient (2%) showed grade III bone marrow toxicity, while another patient (2%) was diagnosed with grade III dysphagia. A further patient complained about grade II fibrosis of the facial region. This patient had received several operations in the irradiated area before the start of treatment. Grade IV toxicity was not detected.

After 12 months only 21 patients were available for analysis. Grade I neurological disorders (33%) and Karnofsky performance score (24%) were detected besides other grade I toxicity reactions only shown by one patient each time. Grade II toxicity reaction was not detected in any patient. Grade III bone marrow toxicity reaction was found in one patient who had received intensive chemotherapy treatment (2%). The patient who showed grade III dysphagia six months after treatment still suffered from dysphagia (grade III). This patient had received several re-operations in the irradiated area.

Overall, severe toxicity reaction (grade III–IV) was only seen in patients who had simultaneous chemotherapy or who had undergone several operations previously in the irradiated area. Patients receiving simultaneous chemotherapy mainly suffered from hematologic side effects. Leukopenia was mostly reported, while some patients also showed anemia and thrombocytopenia. Not all patients receiving simultaneous chemotherapy suffered from hematologic side effects. Patients, who were only treated with vincristine monotherapy during radiation, did not show any severe hematologic toxicity (Supplementary Table I, to be found online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.998273). Only patients with chemotherapeutic regimes containing several chemotherapeutic drugs, such as ifosfamide, doxorubicin, etoposide and methotrexate, suffered from severe hematologic side effects.

Furthermore, we compared acute toxicity reaction of patients treated with proton irradiation to patients treated with carbon therapy (Figure 2). Patients treated with carbon irradiation suffered from a higher level of mucositis (48%), xerostomia (16%) and dysphagia/odynophagia (20%). Patients who received proton irradiation showed higher levels of skin toxicity (68%), nausea and vomiting (16%) and bone marrow toxicity (38%).

In a second step, we compared the detected toxicity profile of particle therapy to the toxicity of photon irradiation in head and neck rhabdomyosarcoma patients (Table III). On the whole, we detected a slightly higher level of toxicity in the proton therapy group which was mainly only grade I–II toxicity level. However, the photon irradiation group was treated with a median dose of 45.0 Gy, while the proton irradiation group received a median dose of 50.4 Gy. In the proton irradiation group, one patient developed skin erythema grade III, this patient was also treated with simultaneous chemotherapy leading to grade III bone marrow

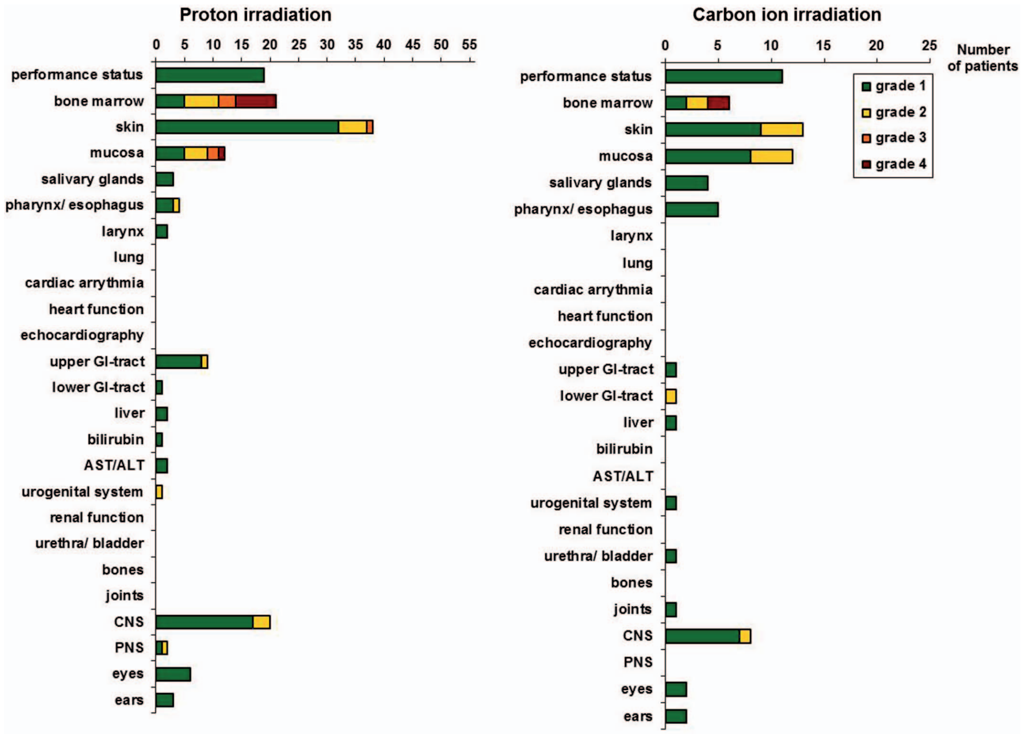

Figure 2. Comparison of acute toxicity reaction after proton irradiation and carbon ion irradiation.

toxicity. Another patient suffered from grade III mucositis. However, this patient was diagnosed with a T4 alveolar rhabdomoysarcoma of the sinuses and received a simultaneous radiochemotherapy according to the CWS protocol. The patient was treated with a hyperfractionated and accelerated proton irradiation.

Discussion

The aim of this analysis was to examine detailed acute and intermediate toxicity reaction in pediatric patients undergoing particle therapy. In terms of clinical characteristics, histological subtype of CNS malignancy, median age and gender, our study cohort seemed to be comparable to population-level databases [15].

Regarding our 83 patients, toxicity from particle therapy was relatively mild and severe side effects were rare. Hattangandi et al. also only detected mild skin erythema and anorexia as acute side effects analyzing nine pediatric patients suffering from high-risk pediatric neuroblastoma treated with proton therapy [10]. Moeller et al. analyzed 23 children diagnosed with medulloblastoma and treated with proton radiotherapy for ototoxicity and also discovered low rates of early post-radiation toxicity [16]. Our 83 pediatric patients mainly complained about radiogenic skin reaction, mucositis, headache and dizziness during the first two months of treatment. Supportive treatment with dexapanthenol containing lotion and analgetic medication for radiogenic skin reaction, as well as medical mouthwashes for mucositis mostly led to a fast improvement of adverse effects.

Table III. Comparison of acute side effects between particle and photon therapy in head- and neck rhabdomyosarcoma patients.

	Particle therapy (N = 13)	Photon therapy (N = 19)
Skin erythema	92%	42%
Mucositis	46%	42%
Nausea and vomiting	15%	11%
Conjunctivitis	38%	16%
Toxicity > 2°	15%	none

In another study, 10 pediatric patients diagnosed with ATRT tumors and treated with proton radiation after surgery and chemotherapy mainly showed nausea and vomiting, followed by central hypothyroidism and growth hormone deficiency in rare cases [17]. In several studies, MacDonald et al. analyzed proton radiotherapy in pediatric patients with ependymoma and could also only show mild toxicity reactions [12]. Regarding other tumor entities treated with ion therapy, only mild side effects were detected as well [7–11,18,19].

In our patients, nearly all mild side effects disappeared within the first few months or remained at a very low level. Severe toxicity reaction (grade III–IV) was only seen in patients undergoing simultaneous chemotherapy or who had received several operations in the irradiated area. Patients with simultaneous chemotherapy often suffered from hematologic side effects. Leukopenia was mostly reported, while some patients also showed anemia and thrombocytopenia. Patients who had received multi-modal therapies including several re-operations in the irradiated area, suffered from fibrosis of the former tumor region during the follow-up visits. Often re-operations were needed.

Comparing the two different particle therapies with each other in terms of acute toxicity, we detected different patterns of toxicity reactions. While patients treated with carbon ion irradiation suffered from higher level of mucositis, xerostomia and dysphagia/odynophagia, patients treated with proton irradiation showed higher levels of skin toxicity, nausea and vomiting and bone marrow toxicity. The carbon ion irradiation group mainly consisted of head- and neck sarcoma, chordoma and ACC patients. All these tumor entities are found in close proximity to the oral cavity. Therefore, irradiation of these tumors is known to lead to higher levels of the above mentioned side effects. Jensen et al. found similar patterns of acute toxicity examining 103 patients with malignant salivary gland tumors who were treated with IMRT and a carbon ion boost irradiation [20].

Regarding the patients treated with proton irradiation, more patients received simultaneous chemotherapy probably leading to a higher level of bone marrow toxicity in this group. Furthermore, patients of the proton irradiation group suffered from higher levels of nausea and vomiting. Brain tumors were primarily treated with proton irradiation, therefore higher levels of nausea and vomiting might be found in this subgroup. For the patients treated with carbon ion, generally, higher local doses were given in critical location, thus toxicity patterns seem to be slightly different than in photon or proton patients.

Comparing the rhabdomyosarcoma patients treated with photon irradiation to the patients having received proton therapy, we detected a slightly higher rate of toxicity in the proton irradiation group which was probably partly due to the intensified simultaneous chemotherapy. Furthermore, the photon irradiation group received a lower median dose of 45.0 Gy, while the proton group was irradiated with a median dose of 50.4 Gy. Interestingly, Ladra et al. recently also detected low toxicity rates analyzing 57 children with rhabdomyosarcoma who received proton irradiation [21]. They examined pediatric rhabdomyosarcoma of any locations, while we mainly focused on orbital and head and neck rhabdomyosarcoma which led to different toxicity profiles.

However, taken together, no significant differences in rates of side effects can be observed between treatment regimens, and differences in toxicity patterns are most likely due to variation in location, tumor volumes, clinical situation or tumor and normal tissue anatomy. With particle therapy, the long-term benefit could be a reduction in long-term side effects, such as secondary malignancies, thus, of course, long-term follow-up will provide the necessary basis for this hypothesis.

A study similar to ours was conducted by Suneja et al. In their clinical study, 48 children with pediatric central nervous system malignancies were treated with proton beam radiation, and were analyzed for acute toxicity reaction. Only mild toxicity reaction was detected, most commonly fatigue, alopecia and dermatitis were reported [22]. However, up to now only little data is known about long-term and prospectively acquired data on toxicity after particle therapy. Nearly all studies are conducted retrospectively. To our knowledge, there is only one prospective trial examining acute toxicity reaction in children after ion therapy. Kuhlthau et al. analyzed 142 pediatric patients with brain tumors for health-related quality of life [23]. They found that proton radiation significantly affected morbidity and quality of life for children. However, overall health-related quality of life three years after treatment significantly improved to a level comparable to a general population of children with non-cancer chronic health conditions.

Nevertheless, radiation is not only known to cause acute side effects, but also late toxicity reaction. Due to the curative intent of most pediatric treatment regimens these are the most feared toxicities, and all techniques are aiming to reduce and minimize long-term sequelae. In radiation, this can be achieved specifically by the reduction of integral dose, which is a main characteristic of particle therapy due to the inverse dose profile. The major concern is an increased risk of second malignancies after irradiation [24]. Chung et al. reported a comparison of 558 patients treated with proton therapy matched to 558 who received photon therapy to analyze the incidence of second malignancies. Interestingly, proton therapy was associated with a lower risk of secondary malignancies compared to photon therapy [25].

In summary, we analyzed 83 pediatric patients and adolescents for acute toxicity after ion therapy and found only mild and manageable side effects. However, further larger prospective studies are needed to evaluate the true potential of proton radiotherapy. Improved knowledge about early and late toxicity is required to provide severe advice to pediatric patients and families.

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References

[1] Armstrong FD. Proton-beam radiation therapy and health-related quality of life in children with CNS tumors. J Clin Oncol 2012;30:2028–9.
[2] Bhat SR, Goodwin TL, Burwinkle TM, Lansdale MF, Dahl GV, Huhn SL, et al. Profile of daily life in children with brain tumors: an assessment of health-related quality of life. J Clin Oncol 2005;23:5493–500.
[3] Duffner PK. Long-term effects of radiation therapy on cognitive and endocrine function in children with leukemia and brain tumors. Neurologist 2004;10:293–310.
[4] Geenen MM, Cardous-Ubbink MC, Kremer LC, van den Bos C, van der Pal HJ, Heinen RC, et al. Medical assessment of adverse health outcomes in long-term survivors of childhood cancer. JAMA 2007;297:2705–15.
[5] Krejcarek SC, Grant PE, Henson JW, Tarbell NJ, Yock TI. Physiologic and radiographic evidence of the distal edge of the proton beam in craniospinal irradiation. Int J Radiat Oncol Biol Phys 2007;68:646–9.
[6] Glimelius B, Isacsson U, Blomquist E, Grusell E, Jung B, Montelius A. Potential gains using high-energy protons for therapy of malignant tumours. Acta Oncol 1999;38:137–45.
[7] Beltran C, Roca M, Merchant TE. On the benefits and risks of proton therapy in pediatric craniopharyngioma. Int J Radiat Oncol Biol Phys 2012;82:e281–7.
[8] Childs SK, Kozak KR, Friedmann AM, Yeap BY, Adams J, MacDonald SM, et al. Proton radiotherapy for parameningeal rhabdomyosarcoma: clinical outcomes and late effects. Int J Radiat Oncol Biol Phys 2012;82:635–42.
[9] Combs S, Kessel K, Herfarth K, Jensen A, Oertel S, Blattmann C, et al. Treatment of pediatric patients and young adults with particle therapy at the Heidelberg Ion Therapy Center (HIT): Establishment of workflow and initial clinical data. Radiat Oncol 2012;7:170.
[10] Hattangadi JA, Rombi B, Yock TI, Broussard G, Friedmann AM, Huang M, et al. Proton radiotherapy for high-risk pediatric neuroblastoma: Early outcomes and dose comparison. Int J Radiat Oncol Biol Phys 2012;83:1015–22.
[11] Hauswald H, Rieken S, Ecker S, Kessel K, Herfarth K, Debus J, et al. First experiences in treatment of low-grade glioma grade I and II with proton therapy. Radiat Oncol 2012;7:189.
[12] MacDonald SM, Sethi R, Lavally B, Yeap BY, Marcus KJ, Caruso P, et al. Proton radiotherapy for pediatric central nervous system ependymoma: Clinical outcomes for 70 patients. Neurooncology 2013;15:1552–9.
[13] Kessel K, Bougatf N, Bohn C, Habermehl D, Oetzel D, Bendl R, et al. Connection of European particle therapy centers and generation of a common particle database system within the European ULICE-framework. Radiat Oncol 2012;7:115.
[14] Combs S, Behnisch W, Kulozik A, Huber P, Debus J, Schulz-Ertner D. Intensity modulated radiotherapy (IMRT) and fractionated stereotactic radiotherapy (FSRT) for children with head-and-neck-rhabdomyosarcoma. BMC Cancer 2007;7:177.
[15] Patel S, Bhatnagar A, Wear C, Osiro S, Gabriel A, Kimball D, et al. Are pediatric brain tumors on the rise in the USA? Significant incidence and survival findings from the SEER database analysis. Child's Nervous System 2014;30:147–54.
[16] Moeller B, Chintagumpala M, Philip J, Grosshans D, McAleer M, Woo S, et al. Low early ototoxicity rates for pediatric medulloblastoma patients treated with proton radiotherapy. Radiat Oncol 2011;6:58.
[17] De Amorim Bernstein K, Sethi R, Trofimov A, Zeng C, Fullerton B, Yeap BY, et al. Early clinical outcomes using proton radiation for children with central nervous system atypical teratoid rhabdoid tumors. Int J Radiat Oncol Biol Phys 2013;86:114–20.
[18] MacDonald SM, Trofimov A, Safai S, Adams J, Fullerton B, Ebb D, et al. Proton radiotherapy for pediatric central nervous system germ cell tumors: Early clinical outcomes. Int J Radiat Oncol Biol Phys 2011;79:121–9.
[19] Merchant TE. Clinical controversies: Proton therapy for pediatric tumors. Semin Radiat Oncol 2013;23:97–108.
[20] Jensen A, Nikoghosyan A, Hinke A, Debus J, Munter M. Combined treatment of adenoid cystic carcinoma with cetuximab and IMRT plus C12 heavy ion boost: ACCEPT [ACC, Erbitux(R) and particle therapy]. BMC Cancer 2011;11:70.
[21] Ladra MM, Szymonifka JD, Mahajan A, Friedmann AM, Yong Yeap B, Goebel CP, et al. Preliminary results of a phase II trial of proton radiotherapy for pediatric rhabdomyosarcoma. J Clin Oncol 2014;32:3762–70.
[22] Suneja G, Poorvu PD, Hill-Kayser C, Lustig RA. Acute toxicity of proton beam radiation for pediatric central nervous system malignancies. Pediatr Blood Cancer 2013;60:1431–6.
[23] Kuhlthau KA, Pulsifer MB, Yeap BY, Rivera Morales D, Delahaye J, Hill KS, et al. Prospective study of health-related quality of life for children with brain tumors treated with proton radiotherapy. J Clin Oncol 2012;30:2079–86.
[24] Suit H, Goldberg S, Niemierko A, Ancukiewicz M, Hall E, Goitein M, et al. Secondary carcinogenesis in patients treated with radiation: A review of data on radiation-induced cancers in human, non-human primate, canine and rodent subjects. Radiat Res 2007;167:12–42.
[25] Chung CS, Yock TI, Nelson K, Xu Y, Keating NL, Tarbell NJ. Incidence of second malignancies among patients treated with proton versus photon radiation. International J Radiat Oncol Biol Phys 2013;87:46–52.

Supplementary material available online

Supplementary Table I to be found online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.998273