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SHORT COMMUNICATION

Hypofractionated stereotactic body radiation therapy (SBRT) in pediatric patients: preliminary toxicity results of a national prospective multicenter study

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Objectives: While hypofractionated stereotactic body radiotherapy (SBRT) has been largely adopted in the adult setting, its use remains limited in pediatric patients. This is due, among other factors, to fear of potential toxicities of hypofractionated regimens at a young age. In this context, we report the preliminary acute (<3 months from SBRT) and middle-term (3–24 months) toxicity results of a national prospective study investigating SBRT in pediatric patients.

Methods: Between 2013 and 2019, 61 patients were included. The first 40 patients (median age: 12 y, range: 3–20) who completed a 2-year-follow-up were included in the present analysis. SBRT was used for treating lung, brain or (para)spinal lesions, either as first irradiation (35%) or in the reirradiation setting (65%).

Results: Acute and middle-term grade ≥2 toxicities occurred in 12.5 and 7.5% of the patients, respectively. No grade ≥4 toxicities occurred. Almost all toxicities occurred in the reirradiation setting.

Conclusion: SBRT showed a favorable safety profile in young patients treated for lung, brain, and (para)spinal lesions.

Advances in knowledge: SBRT appeared to be safe in pediatric patients treated for multiple oncology indications. These results support further evaluation of SBRT, which may have a role to play in this patient population in the future.

INTRODUCTION

Hypofractionated stereotactic body radiotherapy (SBRT) was demonstrated to be safe and efficient in multiple indications in adult patients,[1] including primary and secondary tumors in the lung, spine, and brain, as well as in the reirradiation setting. Consequently, SBRT was widely adopted in this population.

In contrast, high-dose-per-fraction radiotherapy is barely used in pediatric patients. Current clinical experience is mainly limited to the use of radiosurgery or hypofractionated SBRT in the treatment of brain lesions (*e.g.* gliomas, medulloblastomas, ependymoma, or metastases[2–6]). Regarding extra cranial tumors, available data are scarce, mainly consisting of case-reports or retrospective series of SBRT in lung,[7,8] bone/soft tissue,[2,9] or liver lesions.[10] Altogether, these data show promising local control results (in the order of >75%).[2,5,9] Theoretically, the steep-dose gradient and tighter margins used in SBRT could also allow for better preservation of the healthy surrounding tissues. Nevertheless, significant toxicities have been reported, *e.g.* brain radionecrosis (RN),[4,6] myositis,[8,9,11] neuropathy,[8,9,11] bone fracture,[8] and enteritis.[11] Concerns about these potential toxicities hinder a widespread use of SBRT in children.

SBRT could however be useful in many pediatric situations. On one hand, it is expected to yield high rates of local control, which is of interest in the curative setting (*e.g.* in case of local relapse or in the oligometastatic setting). On the other hand, it could be useful in palliative situations, aiming at relieving symptoms and improving quality of life, in place of more protracted RT schedules or invasive procedures.

In order to assess the toxicity and efficiency of SBRT in the pediatric setting, a national prospective multicenter study was opened in France in 2013. We report here the acute and middle-term toxicity results for the first 40 patients included, with a 2-year-follow-up.

METHODS AND MATERIALS

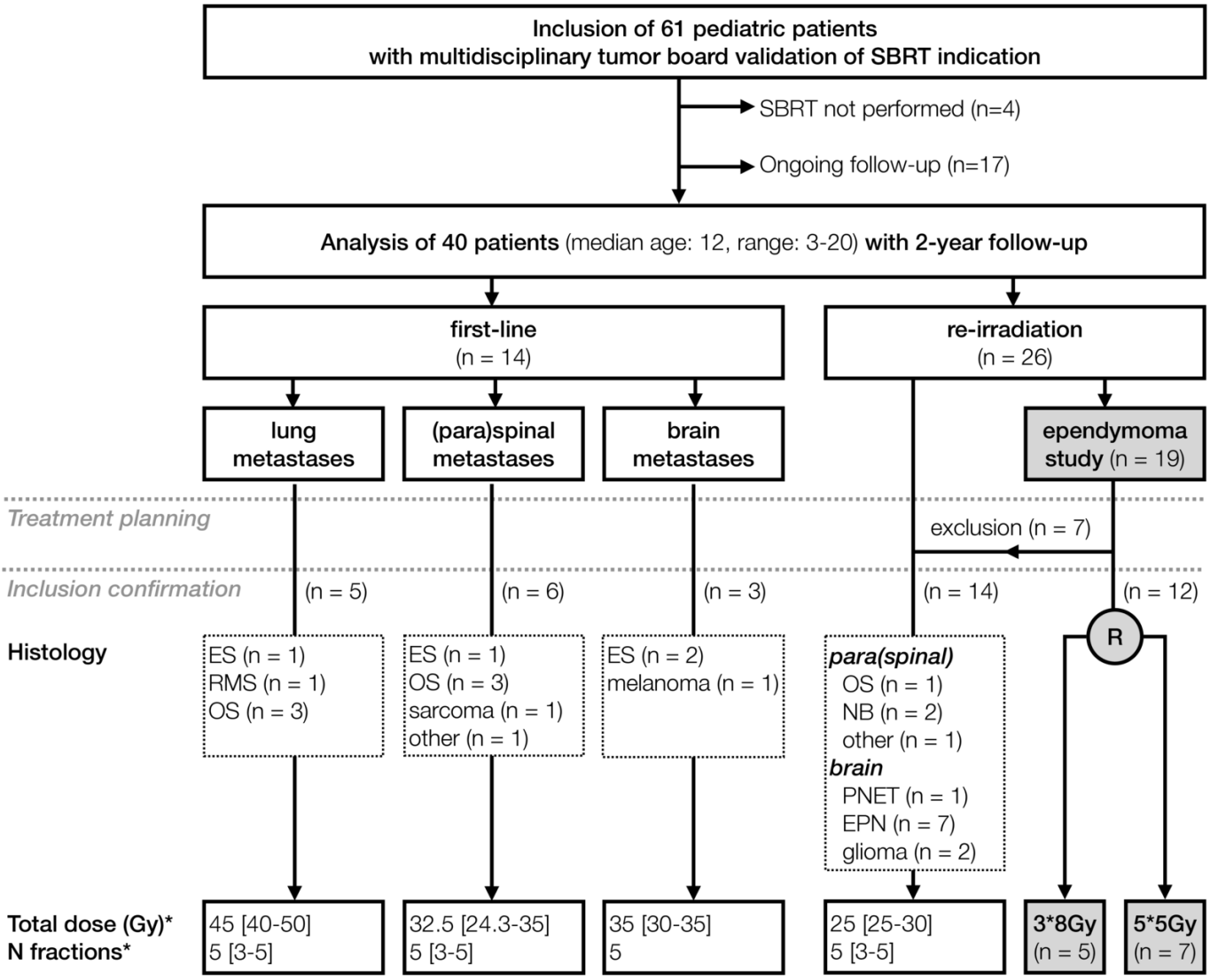
Study design and participants

This study was gradually opened between December 2013 and December 2019 in 14 French radiotherapy departments, both equipped to perform SBRT and with expertise in pediatric RT (as defined by the French National Cancer Institute).

Patients aged between 18 months and 20 years with proven malignancy were eligible. For each patient, the decision to perform SBRT was validated by the regional pediatric multidisciplinary tumor board. Full inclusion criteria are available on https://clinicaltrials.gov/ct2/show/NCT02013297.

The study population consisted of five patient groups (Figure 1). In the first three groups, SBRT was used for the first irradiation (hereafter referred as *first-line*) of: (1) primary or secondary lung tumors, (2) primary or secondary (para)spinal tumors, and (3) secondary brain tumors. In the last two groups, SBRT was used for the reirradiation of (4) tumors in the lung, spine/paraspinal, or brain, or (5) ependymomas. In this last group (hereafter referred as *ependymoma study*), patients with locally relapsing intracranial ependymoma were randomized between

Figure 1. Patients and treatments characteristics *expressed as median and range – Dose was prescribed to the isodose 80%/ N: number of fractions; EPN: ependymoma; ES, Ewing's sarcoma; NB, neuroblastoma; OS, osteosarcoma; PNET, primitive neuroectodermal tumor; RMS, rhabdomyosarcoma.



two regimens: 24 Gy in 3 fractions (24 Gy/3#) and 25 Gy/5#. Patients could only be randomized if treatment planning showed that both treatment plans were acceptable according to organ at risk (OAR) constraints. Otherwise, patients were included in the fourth treatment group, with other reirradiation cases.

SBRT procedure

Treatment was allowed with any equipment adequate for stereotactic treatment delivery (*e.g.* Linac-based SBRT, Tomotherapy®, or Cyberknife®). Immobilization was ensured using a thermoplastic mask for brain or head and neck tumors, and using a vacuum bag for extra cranial tumors. General anesthesia could be performed if necessary. Treatment plans were reviewed online by at least one external pediatric radiotherapy expert. SBRT dose regimen was selected based on the number, location, and size of the lesion(s), as well as cumulative radiation dose to the normal tissues in case of reirradiation. The radiation dose was not adapted based on histology. The following dose regimens were allowed (prescribed to the 80%-isodose):

- *first-line*:
  - lung: 45 Gy/3# or 50 Gy/5# (peripheral lesions), 40 Gy/5# (central lesions)
  - (para)spinal: 27 Gy/3# or 35 Gy/5#
  - brain: 18 Gy/1#, 24 Gy/3#, or 35 Gy/5#
- reirradiation:
  - 25 Gy/5# to 40 Gy/8# (except *ependymoma study*: 24 Gy/3# or 25 Gy/5#) depending on cumulative dose to critical organs.

Given the absence of recommendations specific to pediatric patients, normal tissue dose constraints for SBRT proposed by Timmerman et al[12] were used.

Follow-up schedule, toxicity endpoints, and statistics

Clinical follow-up examinations were carried out 3, 6, 12, and 24 months after SBRT. Toxicity was scored according to the Common Terminology Criteria for Adverse Events (CTCAE) v. 4.0. Radiological assessment was performed after 3, 6, 12, and 24 months. Acute and middle-term toxicities were defined as toxicities occurring within 3 months, or between 3 and 24 months after SBRT, respectively.

With regard to toxicity, no explicit stopping rules were defined beforehand. The study was monitored by an independent expert committee which was in charge of analyzing the yearly toxicity report and allowing for continuation of the study in case of favorable benefit-risk balance. Any severe (Grade 4 or 5) toxicity would trigger an emergency meeting of this committee.

Data management and descriptive statistics were performed using the SAS software (v. 9.4, SAS Institute Inc., Carry, NC). The variables examined included age, gender, tumor histology, dosimetric parameters, and observed adverse events.

RESULTS

Patients' characteristics

61 patients were included in 10 centers. Four out of them were eventually not treated using SBRT within the study due to: patient's refusal (n = 1), early disease progression (n = 1), physician's decision to treat the patient outside the study (n = 1) or to change the treatment strategy (n = 1). 40 patients with at least 2 years of follow-up were included in the current toxicity analysis. Among these 40 patients, 25 were male (62.5%) and median age was 12 years (range: 3–20). SBRT was used in *first-line* in 14 patients and in the reirradiation setting in 26 patients. Tumor types and dose regimens are described in Figure 1. 25 patients (62.5%) received SBRT with a curative intent (*i.e.* in case of local relapse or in the oligometastatic setting).

Radiotherapy

36 out of the 40 patients (90%) were treated according to the protocol. Three patients undergoing *first-line* SBRT received 30 Gy/5# instead of 35 Gy/5# due to critical OAR dose limitation. One patient undergoing reirradiation (spinal lesion) received 27 Gy/3# instead of being treated using five fractions (protocol violation).

Treatment was delivered using Cyberknife® (n = 21, 52.5%), Novalis TrueBeam® (n = 13, 32.5%), Tomotherapy® (n = 2, 5%), or another Linac (n = 4, 10%). None of the 40 patients required general anesthesia.

Toxicity

Of the 40 patients, 16 were still alive 24 months after SBRT. As regards toxicity assessment, 36, 32, 23, and 16 patients were evaluable at 3, 6, 12, and 24 months after SBRT, respectively.

Six serious adverse events were reported in four patients (Table 1). None of these were related to SBRT.

Concerning acute toxicities, four patients (10%) experienced Grade 2 toxicity (asthenia, hyperacusis, diarrhea, radiation pneumonitis) (Table 1) and one patient (2.5%) experienced Grade 3 toxicity (epilepsy). This occurred in a 13-year-old girl reirradiated (25 Gy/5#) for a relapsing high-grade glioma, 2 years after having received 54 Gy/30# as initial treatment. Cumulative equivalent dose in 2Gy-fractions assuming an α/β ratio of 3 Gy ($EQD2_{3Gy}$) was 91.8 Gy. She developed a partial seizure on the last day of SBRT, received anti-epileptic medication for six months, and was seizure-free afterwards. Noteworthy, four of the five grade ≥2 toxicities occurred in the reirradiation setting.

With regard to middle-term toxicities, three grade ≥2 toxicities occurred in three patients (7.5%), two of which had undergone reirradiation (Table 1). Only one grade >2 toxicity was observed, namely Grade 3 brain RN in a 5-year-old boy with a history of supratentorial ependymoma. The first symptom of the disease was right lower limb paresis. He was initially treated with complete resection followed by adjuvant radiotherapy (59.4 Gy/33#). 1 year later, he experienced isolated local relapse and underwent a second complete resection, followed by SBRT on the resection cavity (25 Gy/5#, cumulative $EQD2_{3Gy}$: 97.0 Gy). Local relapse

Table 1. Serious adverse events, short-, and middle-term toxicities after SBRT

Patient			Patient group		SBRT site	Previous RT dose	SBRT dose	Cumulative $EQD2_{3Gy}$	Toxicity					
Age	Gender	Primary tumor							Type	Grade^	Imputability	Beginning	Duration	Management
Serious adverse events														
19	F	Rhabdoid	Reirradiation	(Para)spinal	T11-T12	35 Gy/5#	25 Gy/5#		Device-related infection	3	Non-related	D44	18 days	
11	F	Glioma	Reirradiation	Brain	R thalamus	54 Gy/30#	25 Gy/5#		Dehydration	3	Non-related	M12	6 days	
									Renal colic	3	Non-related	M9	1.5 months	
									Venous thrombosis	2	Non-related	M11	8 days	
7	M	Ependymoma	Reirradiation	Brain	R frontal	54 Gy/30#	25 Gy/5#		Lung infection	3	Non-related	M10	1 month	
7	M	Ependymoma	Reirradiation	Brain	R Luschka	59.4 Gy/33#	25 Gy/5#		Deglutition disorder	3	Non-related	M7.5	3 months	
Short-term grade ≥2 toxicities (within 3 months of SBRT)														
17	F	Ependymoma	Reirradiation	Ependymoma study	R parietal	59.4 Gy/33#	25 Gy/5#	97.0 Gy	Asthenia	2	Related	D8	113 days, resolved	No treatment
11	F	Glioma	Reirradiation	Brain	R thalamus	54 Gy/30#	25 Gy/5#	91.8 Gy	Epilepsy	3	Related	D5	144 days, resolved	Antiepileptic medication
19	F	Ewing's sarcoma	First line	Lung	L lower lobe	0	50 Gy/5#	N/A	Radiation pneumonitis	2	Related	D89	*	No treatment
11	M	Ependymoma	Reirradiation	Brain	R occipital	≃ 50 Gy	30 Gy/5#	102 Gy	Hyperacusis	2	Related	D25	*	No treatment
8	M	Neuroblastoma	Reirradiation	(Para)spinal	lumbar	21 Gy/14#	25 Gy/5#	58.9 Gy	Diarrhea	2	Related	D2	1 day, resolved	No treatment
Middle-term grade ≥2 toxicities (3 to 24 months after SBRT)														
18	F	Osteosarcoma	First line	Lung	R lower lobe	0	45 Gy/3#	N/A	Radiation pneumonitis	2	Related	M7	Present at M24	No treatment
4	M	Ependymoma	Reirradiation	Ependymoma study	R occipital	59.4 Gy/33#	25 Gy/5#	97.0 Gy	Radiation necrosis	3	Related	M8.5	Present at M24	See manuscript for details
14	M	Ependymoma	Reirradiation	(Para)spinal	L2	20 Gy/5#	27 Gy/3#	92.8 Gy	Pyloric spasm	2	Related	M5	4 days, resolved	Antalgic medication

Symbol: #: fraction; ^: maximum toxicity grade; *: ongoing at the time of death or at the end of the study follow-up (2 years)F: female; M: male; R: right; L: left; Dxx / Mxx: xx days (D) or months (M) after SBRT, N/A: not applicable

was suspected on MRI 9 months after SBRT. At this time, the limb paresis had worsened. He was administered chemotherapy (vincristine-etoposide-cyclophosphamide), ending 19 months after SBRT. Paresis remained stable afterwards, and successive MRI showed stability then minor response. Considering both clinical and radiological evolution, the diagnosis of RN was eventually retained.

Both for acute and middle-term toxicities, no Grade 4 or 5 toxicity occurred.

DISCUSSION

We report here the preliminary results of a national prospective multicenter cohort study investigating SBRT in young patients. This study is, to our knowledge, the first to prospectively evaluate SBRT in a wide range of pediatric indications, *i.e.* lung, (para)spinal, and brain tumors, both for initial irradiation and for reirradiation.

Alcorn et al recently reported the results of an international survey evaluating patterns of pediatric SBRT.[13] Among patients under 21 years of age undergoing hypofractionated SBRT, 42% were treated with definitive intent, 46% with palliative intent, and 12% in the reirradiation setting. Interestingly, the present study included more patients treated with definitive intent (62.5%), as well as more patients in the reirradiation setting (65%). Physicians were possibly more inclined to treat patients in the definitive or in the reirradiation setting in comparison with the published pattern of practice thanks to the radiotherapy guidelines and quality control provided within the study.

For the first 40 patients included in the present study, SBRT was feasible and safe with regard to acute and middle-term toxicities. All but four patients were treated according to the dose regimens recommended in the study protocol, and none of them required anesthesia.

Concerning acute toxicities, four Grade 2 (asthenia, hyperacusis, diarrhea, and radiation pneumonitis) and one Grade 3 (epilepsy after brain reirradiation) toxicities were observed. To our knowledge, hyperacusis was never described after SBRT, neither in children nor in adults. One radiation pneumonitis (Grade 2) was previously reported in a 14-year-old boy undergoing SBRT (36 Gy/3#) for a lung metastasis (Ewing's sarcoma) and was successfully treated with high-dose corticoids.[7] We found one report of epilepsia after brain SBRT in a 20-year-old male with recurrent medulloblastoma.[2] He was reirradiated using SBRT (35 Gy/5#) 34.5 months after initial RT. He developed epilepsy and brain RN approximately 1 year after SBRT, and received anticonvulsant medication. In most adult series, epilepsy occurs in less than 5% of the patients, in concordance with our results.[14]

Concerning middle-term toxicities, two Grade 2 (radiation pneumonitis, pyloric spasm) and one Grade 3 (brain RN) toxicities were observed. Two out of these three toxicities occurred after reirradiation. While pyloric spasm was not previously described in children after SBRT, Lazarev et al[11] reported two cases of Grade 4 enteritis resulting in small-bowel obstruction requiring surgery. Both patients had previously received abdominal or pelvic RT. On the contrary, brain RN was already well described in pediatric patients receiving radiosurgery or hypofractionated RT to the brain, in particular in cases of reirradiation. Merchant et al[4] reported that six out of six patients receiving reirradiation using RS (15–20 Gy/1#) for recurrent ependymoma developed RN (among which one died and one required surgery and hyperbaric oxygen therapy). Waxweiler et al[6] observed brainstem RN in 5 out of 11 patients undergoing reirradiation (24 Gy/3#) for tumors in or around the brainstem. Kano et al[3] found more reassuring results in a series of 89 patients undergoing RS (9–24 Gy/1#) for recurrent ependymoma, with 7% symptomatic adverse radiation effects.

Definitive acute and middle toxicity results, as well as local control results on the whole series are expected in 2022. Longer follow-up will be necessary to evaluate the long-term toxicity of this treatment strategy, *e.g.* stroke, bone fracture, or secondary tumors in high-dose regions. Results of ongoing or future prospective studies are also awaited to clarify the role of SBRT in children. In that respect, SBRT is currently being considered to treat metastatic sites in Ewing's sarcoma (AEWS1221 (NCT02306161)) and in rhabdomyosarcoma (FaR-RMS (2018-000515-24)), as well as to boost residual disease in ependymoma (SIOP Ependymoma II (2013-002766-39)).

Pediatric malignancies consist in a wide range of diseases, each affecting a limited number of patients, only some of which are eligible for SBRT. Due to this, the main limitations of the present study are its non-randomized design and the fact that various tumor types were included.

CONCLUSION

In summary, SBRT was safe regarding acute and middle-term toxicity in pediatric patients treated for lung, brain or (para) spinal lesions. These results support further evaluation of SBRT, which may have a role to play in this patient population in the future.

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CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest.

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ETHICAL APPROVAL

This study was performed in line with the principles of the Declaration of Helsinki. Ethical approval was granted by the Comité de Protection des Personnes (CPP) Sud-Est IV (Ref.: 13/055). Written informed consent was obtained from all individual participants included in the study, and from their legal guardians for patients under the age of 18.

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