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## Original Research

# Radical radiotherapy for paediatric solid tumour metastases: An overview of current European protocols and outcomes of a SIOPE multicenter survey



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**KEYWORDS**

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Soft-tissue sarcoma;  
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Neuroblastoma;  
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**Abstract Purpose/objective:** About 20% of children with solid tumours (ST) present with distant metastases (DM). Evidence regarding the use of radical radiotherapy of these DM is sparse and open for personal interpretation.

The aim of this survey was to review European protocols and to map current practice regarding the irradiation of DM across SIOPE-affiliated countries.

**Materials/methods:** Radiotherapy guidelines for metastatic sites (bone, brain, distant lymph nodes, lung and liver) in eight European protocols for rhabdomyosarcoma, non-rhabdomyosarcoma soft-tissue sarcoma, Ewing sarcoma, neuroblastoma and renal tumours were reviewed. SIOPE centres irradiating  $\geq 50$  children annually were invited to participate in an online survey.

**Results:** Radiotherapy to at least one metastatic site was recommended in all protocols, except for high-risk neuroblastoma. Per protocol, dose prescription varied per site, and information on delineation and treatment planning/delivery was generally missing.

Between July and September 2019, 20/27 centres completed the survey. Around 14% of patients were deemed to have DM from ST at diagnosis, of which half were treated with curative intent. A clear cut-off for a maximum number of DM was not used in half of the centres. Regardless of the tumour type and site, conventional radiotherapy regimens were most commonly used to treat DM. When stereotactic radiotherapy was used, a wide range of fractionation regimens were applied.

**Conclusion:** Current radiotherapy guidelines for DM do not allow a consistent approach in a multi-centre setting. Prospective (randomised) trials are needed to define the role of radical irradiation of DM from paediatric ST.

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## 1. Introduction

Advanced treatment strategies for localised paediatric solid tumours (ST) result in overall survival rates between 60% and 95% [1–5]. However, around 20% of children present with distant metastases. Improvement in outcomes for these patients has been limited and achieving cure remains challenging. Depending on histology, survival rates are around 35% (range 5–95%) and are mainly obtained by advances in systemic therapy [4–9].

Whole lung irradiation has been included in protocols for Ewing sarcoma (ES), rhabdomyosarcoma (RMS) and unfavourable renal tumours [8,9]. However, there is little evidence supporting radiotherapy to other metastatic sites: only a few papers have shown radiotherapy to be effective for local control [10–15].

Offering patients with oligometastases a potentially curative treatment, aiming to delay progression and improve quality of life, is gaining importance in adult radiation oncology [16–19]. In contrast to common adult cancers, intensified systemic regimens without radiotherapy offer some chance of cure for children and adolescents with distant metastasis due to the increased sensitivity of paediatric tumours and the plasticity of normal tissues to recover easily from high-dose therapy [4,5,8,9].

Stereotactic ablative body radiotherapy is increasingly used in adult patients with oligometastatic disease, producing good local control with limited toxicity [16,17]. This technique requires accurate immobilization, localization imaging and precise treatment

planning and delivery systems. It enables hypofractionation with highly conformal dose distributions and sparing of adjacent normal tissues. This approach allows smaller margin sizes and larger doses in fewer fractions compared to conventionally fractionated radiotherapy [20]. In paediatrics, concomitant irradiation of the primary tumour and all metastatic sites with a conventional fractionation regimen becomes challenging with an increasing number of metastatic sites since a prolonged treatment session demands enormous compliance of the child, as well as enough machine and anaesthesia capacity. On the other hand, hypofractionation radiotherapy on metastatic sites allows irradiation of a larger number of metastases within a daily acceptable time slot while respecting the overall treatment time, making it a more attractive alternative to conventional radiotherapy.

The literature on the use of a stereotactic approach with hypofractionation in paediatrics is limited to a small number of retrospective reports, which demonstrate feasibility and good local control [21–27]. However, the radiobiological effect of a higher dose per fraction and the associated late effects are still unclear.

The purpose of this study is to map the recommended practice on metastatic site irradiation in ongoing European protocols and to report the outcome of a survey across SIOPE-affiliated countries of the current practice of radiotherapy for metastases from paediatric ST.

## 2. Materials and methods

### 2.1. European protocols applied across SIOPE-affiliated countries

To evaluate the current radiotherapy guidelines for children presenting with metastatic disease, European protocols for RMS and non-rhabdomyosarcoma soft-tissue sarcoma (STS), ES, neuroblastoma (NBL) and renal tumours were analyzed. Details regarding the recommended radiotherapy procedures for metastatic sites within these protocols were evaluated and stratified by anatomical site (bone, brain, distant lymph nodes, lung and liver). The total dose (Gy), dose per fraction, number of fractions (fx) and the calculated equivalent dose in 2 Gy fractions (EQD2) using an  $\alpha/\beta$  ratio of 3 for late effects and 10 for tumour tissue [28] were evaluated. Recommendations on delineation and margins for the metastatic sites were collected.

### 2.2. Survey

To document the current practice of radiotherapy for metastases from paediatric ST across SIOPE-affiliated countries (<https://www.siope.eu/about-siope/members/>), an online survey with 44 questions was designed with SurveyMonkey (SurveyMonkey Inc., San Mateo, California, USA). The survey included multiple-choice, dichotomous and open-ended questions.

#### 2.2.1. Participants

The European Union Joint Action on Rare Cancer (JARC) project mapped more than 230 paediatric radiotherapy centres [29]. Centres irradiating at least 50 children annually were invited to complete the study-related survey sent by email with a web link.

#### 2.2.2. Population and tumour characteristics

Each department was asked to estimate the number of children irradiated annually and the number presenting with metastatic disease from RMS, STS, ES, NBL and renal tumours. The treatment intent was categorised as either palliative or curative (aiming to cure the patient by giving a radical radiotherapy dose at the metastatic site(s)). Metastatic disease was further stratified by the treatment site: bone (spine and non-spine), brain, distant lymph nodes, lung and liver. Numbers and information on radiotherapy with curative intent for each site were collected.

#### 2.2.3. Imaging characteristics

For delineation and planning purposes, participants were asked to indicate the imaging modalities used per tumour type and site. As computed tomography (CT) imaging is always needed for planning, the question focussed on magnetic resonance imaging (MRI) and positron emission tomography (PET), and specifically

for NBL patients iodine-123-metaiodobenzylguanidine/single-photon emission computed tomography (mIBG/SPECT).

#### 2.2.4. RT characteristics

Questions on radiotherapy planning for metastatic sites paid special attention to the use of a conventional or a stereotactic technique. A conventional technique was described according to ICRU 62/83 guidelines [30,31], using a  $D_{max} < 107\%$  and  $V_{95\%} > 99\%$  for the planning target volume (PTV) and fraction doses  $\leq 2.0$  Gy. For stereotactic techniques,  $D_{max}$  doses up to 140% were commonly used with fraction doses above 2.0 Gy [32]. No distinction between conventional and stereotactic techniques was made for the use of clinical target volume (CTV) margins. Participants indicated whether this patient cohort was treated within a local, national or international protocol. Additionally, specific doses and fractionation schemes were collected and stratified by the primary tumour site. Questions on immobilization and position verification were asked.

#### 2.2.5. Future steps

A request was made for future ideas concerning radiotherapy with curative intent to metastatic sites from ST.

## 3. Results

### 3.1. Protocols

Eight European protocols on paediatric ST and their radiotherapy procedures for primary metastatic disease are listed in Table 1.

For RMS, the European paediatric Soft-tissue Sarcoma Study Group (EpSSG) FaR-RMS (Frontline and Relapsed RhabdoMyoSarcoma) protocol [33] is due to open in 2020. In this protocol (version 1.0; dd 10-2019), patients with unfavourable metastatic disease will be randomised to receive, or not to receive, radiotherapy to all sites of metastases, where feasible. Site-specific dose and delineation guidelines for metastatic disease were described.

For non-rhabdomyosarcoma STS, the EpSSG NRSTS-2005 protocol (version 1.1; dd 09-2009) was evaluated [34]. Although primarily for non-metastatic patients, radiotherapy for bone, brain, lymph nodes, lung and liver metastases at diagnosis in patients with extra-renal rhabdoid tumours was included.

For ES, the 'Radiotherapy Guidelines' document (version 2.0; dd 01-2017) from the Euro Ewing-2012 protocol [35] described whole lung irradiation for pulmonary metastatic disease. In contrast to the Euro-Ewing-2008 protocol, Euro-Ewing 2012 gave no further guidelines for brain and other extrapulmonary sites.

For metastatic NBL, the SIOPEN (International Society of Paediatric Oncology European Neuroblastoma Group) HR-NBL2 protocol, opened in 2020, did not

Table 1

Recent and current clinical protocols describing radiotherapy procedures for primary metastatic disease from solid tumours with curative intent.

Site	Tumour type	Protocol	Case	Dose in Gy (+boost)	Fx	Dose/Fx	EQD2 $\alpha/\beta$ (3)	EQD2 $\alpha/\beta$ (10)	Margin	Note
Bone	RMS	RMS-2005	—	30	±20	1.5–1.8	27–34.6	28.8–35.4		Depending on the site, age and volume
		Far-RMS-2019	Favourable metastatic disease (Modified Oberlin Prognostic Score of ≤1) [46]	41.4	23	1.8	39.7	40.7	GTV-CTV 5–10 mm + CTV-PTV local standard of care	Single phase
			Exceptional cases of bulky macroscopic residual metastatic disease	41.4 (+9)	23 (+5)	1.8	48.4	49.6		Two phase or SIB
	STS	NRSTS-2005	—	25.2	14	1.8	24.2	24.8	GTV-CTV 2 cm + appropriate margin for PTV	Entire bone (APPA)
	ES	Ewing-2008	—	≥45	—	—	—	—		If available and feasible: ESRT
	NBL	Ewing-2012	—	—	—	—	—	—		
		HR-NBL1	—	—	—	—	—	—		
	Renal	HR-NBL2	—	—	—	—	—	—		
		Umbrella-2016	—	30–30.6	10–17	1.8–3	29.4–36	30.1–32.5		
Brain	RMS	RMS-2005	—	—	—	—	—	—		
		Far-RMS-2019	Pre-treatment tumour volume ≤20 cc and diameter <3 cm	18–20	1	18–20	75.6	42	Target volume delineation according to local standard of care	SRT
				24	3	8	52.8	36		SRT
				30	5	6	54	40		SRT
	STS	NRSTS-2005	Pre-treatment tumour volume >20 cc and diameter >3 cm	30	10	3	36	32.5		Whole brain
			Boost in patients ≤ 3 lesions < 3 years	21.6 (+10.8)	12 (+6)	1.8	20.7–31.1	21.2–31.9	Boost margin 0–1 cm	Whole brain (boost with IMRT or SRT)
	ES	Ewing-2008	Isolated metastases (+boost if 1 or 2 lesions with maximum diameter 2–3 cm)	30 (+20)	15 (+10)	2	30–50	30–50		Whole brain (+SRT)
	NBL	Ewing-2012	—	—	—	—	—	—		
		HR-NBL1	—	—	—	—	—	—		
	Renal	HR-NBL2	—	—	—	—	—	—		
		Umbrella-2016	IM (+boost for macroscopic residual disease)	15 (+10.8)	10 (+6)	1.5–1.8	13.5–27.6	14.4–28.3		Whole brain (+SIB)
			HI (+boost for macroscopic residual disease)	25 (+10.8)	14 (+6)	1.8	24.2–34.6	24.8–35.4		Whole brain (+SIB)
Distant lymph nodes	RMS	RMS-2005	—	30	±20	1.5–1.8	27–34.6	28.8–35.4		Depending on the site, age and volume
		Far-RMS-2019	—	41.4	23	1.8	39.7	40.7	Target volume delineation according to local standard of care	Single phase
	STS	NRSTS-2005	—	19.8	11	1.8	19	19.5	GTV-CTV 1 cm + appropriate margin for PTV	
	ES	Ewing-2008	—	—	—	—	—	—		
	NBL	Ewing-2012	—	—	—	—	—	—		
		HR-NBL1	—	—	—	—	—	—		

	Renal	HR-NBL2	—	—	—	—	—	—		
	Renal	Renal	—	—	—	—	—	—		
Lung	RMS	RMS-2005	—	15	10	1.5	13.5	14.4	Target volume delineation according to local standard of care CTV-PTV 1–2 mm	Whole lung
		Far-RMS-2019	—	15	10	1.5	13.5	14.4		Whole lung (APPA)
	STS	NRSTS-2005	<12 months	10.5	7	1.5	9.5	10.1		Whole lung
			≥12 months	15	10	1.5	13.5	14.4		Whole lung
	ES	Ewing-2008	≤14 years	15	2 Fx/day	1.25	12.8	14.1	CTV-PTV 1 cm	Whole lung (APPA)
			> 14 years	18	12	1.5	16.2	17.3		Whole lung (APPA)
		Ewing-2012	≤ 14 years	15	10	1.25	12.8	14.1		Whole lung (APPA)
			> 14 years	18	12	1.5	16.2	17.3		Respiratory-gated radiotherapy can be used
	NBL	HR-NBL1	—	—	—	—	—	—		
		HR-NBL2	—	—	—	—	—	—		
	Renal	Renal	IM (+boost for macroscopic residual disease)	12 (+10-13)	8	1.5	10.8	11.5		Whole lung (+SBRT boost)
			HI (+boost for macroscopic residual disease)	15 (+15-20)	10	1.5	13.5	14.4		Whole lung (+SBRT boost)
Liver	RMS	RMS-2005	—	30	±20	1.5–1.8	27–34.6	28.8–35.4		Depending on the site, age and volume
		Far-RMS-2019	—	—	—	—	—	—		
	STS	NRSTS-2005	<12 months	15	10	1.5	13.5	14.4		Whole liver (if diffusely involved)
			≥12 months	19.8	11	1.8	19	19.5		Whole liver (if diffusely involved)
	ES	Ewing-2008	—	-	-	-	-	-		
		Ewing-2012	—	-	-	-	-	-		
	NBL	HR-NBL1	—	—	—	—	—	—		
		HR-NBL2	—	—	—	—	—	—		
	Renal	Renal	IM (+boost for macroscopic residual disease)	14.4 (+10.8)	8 (+6)	1.8	13.8–24.2	14.2–24.8		Whole liver (+SIB/SBRT)
			HI (+boost for macroscopic residual disease)	20–25.2 (+16.2)	11 (+9)	1.8	19.0–34.6	19.5–35.4		Whole liver (+SIB/SBRT)

Details adapted from recent and current clinical protocols for Rhabdomyosarcoma (RMS, EpSSG-RMS-2005 and Far-RMS-2019), Soft Tissue Sarcoma (STS, EpSSG-NRSTS-2005), Ewing Sarcoma (ES, EWING-2008 and 2012), Neuroblastoma (NBL, HRNBL-1 and 2 QUARTET), Renal tumours (SIOP-RTSG UMBRELLA 2016).

Other abbreviations: IM: intermediate risk histology, HI: High risk histology, (E)SRT: (extracranial) stereotactic radiotherapy, SIB: simultaneous integrated boost, SBRT: stereotactic body radiotherapy.

recommend systematic radiotherapy of distant metastatic sites [36], in line with the earlier HR-NBL1 protocol.

Since June 2019, paediatric renal tumour patients are registered in the SIOP-Renal Tumour Study Group UMBRELLA protocol (SIOP-RTSG-UMRELLA-2016) [37]. For both intermediate- and high-risk histology subgroups, radiotherapy is advocated for bone, brain, lung and liver metastases. Unresected residual metastases or the area of macroscopic incomplete resection of metastases may be boosted by a stereotactic technique or by using a simultaneous integrated boost (SIB).

In summary, radiotherapy to at least one metastatic site was recommended in all protocols, except for HR-NBL2. Dose prescription varied per site. Recommendations for treatment planning and delivery techniques were sporadic. Protocols mentioned that metastatic site radiotherapy can be considered by local multidisciplinary teams and treated according to local expertise and practice. Discussion with the study coordinator is recommended for complex cases.

### 3.2. Survey

#### 3.2.1. Participants

Twenty-one of 27 centres (78%) from nine countries responded. One did not complete the survey and was excluded (resulting  $N = 20$ ).

#### 3.2.2. Patient selection

Within the twenty radiotherapy departments, an estimated number of 2524 paediatric patients (median per centre 90, range 50–450) were treated annually. Approximately 14% ( $N = 357$ ) presented with metastatic disease, of which half ( $N = 181$ ) were treated with curative intent (Fig. 1). Regardless of the tumour type, over 65% of the radiotherapy centres agreed that primary metastatic disease could be irradiated with curative intent. Poor prognosis was the major reason not to offer potentially curative radiotherapy (Fig. 2). Half of the centres did not define a maximum number of metastatic lesions, while 13% of the centres did not irradiate with curative intent when more than one lesion is present. If the number of sites would be a limiting factor at presentation, reconsideration of radiotherapy after neoadjuvant chemotherapy was mentioned by 75%.

#### 3.2.3. Imaging characteristics

MRI-guided metastatic target volume delineation was done nearly exclusively for CNS lesions, and commonly for bone, distant lymph nodes and liver lesions (Fig. 3). Lung lesions are defined by a CT-scan often combined with a PET-scan. For NBL, the mIBG/SPECT is used to define all kind of metastases. Five centres (25%) reported an MRI-scanner within the radiotherapy department and scanned patients in the radiotherapy treatment position. Fifteen centres perform their MRI-scans within the radiology departments and usually

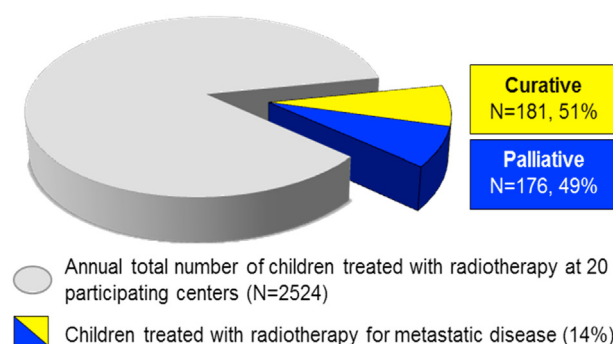


Fig. 1. Overview of the estimated annual numbers of paediatric patients receiving radiotherapy at the 20 participating centres, categorized as either non-metastatic (grey) or metastatic (blue/yellow). From the latter category, around 50% is treated with palliative (blue) or curative (yellow) intent. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

not (12 out of 15 centres) in the radiotherapy treatment position.

#### 3.2.4. Treatment planning

As illustrated in Fig. 4, all photon radiotherapy departments ( $N = 19$ ) use at least a conventional planning technique. Twelve radiotherapy departments (63%) also use stereotactic planning techniques and fractionation schemes, in particular for brain metastases. Deciding between conventional and stereotactic approaches depended on reasons including the number of lesions, volume size and dose constraints for organs at risk. Six out of 20 departments, four in France, used a stereotactic technique according to an institutional or a national protocol [38,39], yielding varying dose prescriptions (16–50 Gy) and fractionation schemes (1–7 fractions), depending on the primary tumour type, metastatic site, as well as radiotherapy department.

#### 3.2.5. Treatment delivery

A thermoplastic mask and vacuum mattress were routinely used by all centres depending on the anatomical location (Fig. 5). Position verification was done either by correcting for rotation and translation (>70% for both conventional and stereotactic techniques) or translation only (approximately 20%). Offline corrections were used in a limited number of departments for conventional techniques only (Fig. 5).

For photon delivery, rotational intensity-modulated radiation therapy (IMRT) was most commonly used ( $\geq 85\%$  of the centres, regardless of the lesion site), followed by conventional IMRT (on average 41%). For proton delivery, a pencil beam scanning technique, with either a uniform dose beam or intensity-modulated proton therapy was equally reported by the four proton centres.



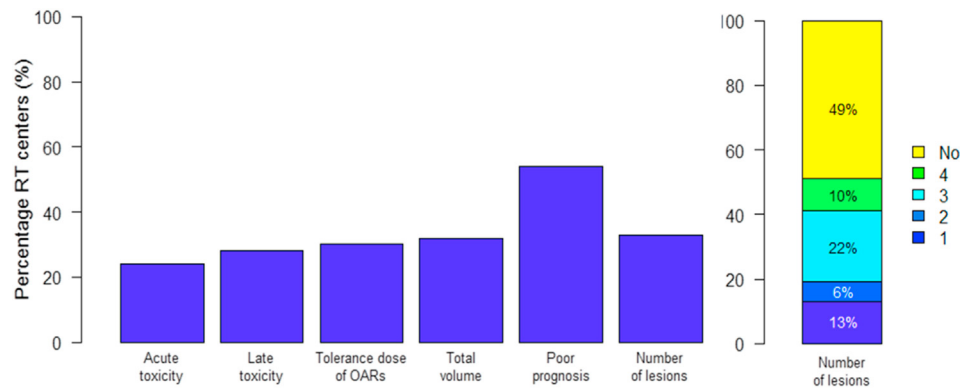


Fig. 2. Potential limiting factors for radiotherapy with curative intent on metastatic sites (x-axis) (left). Focussing on the number of metastatic sites, centres indicated whether they use a maximum number of candidate lesions or not (right).

### 3.2.6. Future steps

All participants expressed concerns about the current lack of well-defined guidelines in protocols for metastatic disease, in particular selection criteria for hypofractionation, and dose prescription per tumour type, margin size and metastatic site. Furthermore, all participants are in favour of cooperative research groups conducting (randomised) trials for irradiation of metastatic sites.

## 4. Discussion

This study describes a subset of European protocols and clinical practice of radical radiotherapy for metastatic sites in childhood ST across twenty major European departments. It shows significant variation in protocol recommendations and reported practice.

The overall survival of metastatic paediatric ST can range between 5% and 95%, mainly depending on histology, site and number of metastases [40,41]. In contrast to adults with stage IV disease, no randomised trials have been completed to demonstrate the role of radiotherapy to metastases in children [16–18]. However, the current FaR-RMS trial includes a randomisation to evaluate this. Patients with unfavourable metastatic disease will be randomised to receive loco-regional radiotherapy only versus radiotherapy to all metastatic sites where feasible. However, further details or criteria for this feasibility are lacking in the protocol. So far, evidence for radiotherapy is limited to a small number of retrospective analyses [10–14]. Nevertheless, most survey respondents are in favour of potentially curative metastatic radiotherapy, with some disagreement on the maximum number of metastatic sites, taking into account that with an increasing number of metastases, prognosis worsens [40–42]. The exact number of lesions does not play a key role in current European protocols [33–37]. Whether the number should be used as a cut-off for curative radiotherapy is uncertain, as high-resolution imaging techniques are of higher possibility to demonstrate more smaller lesions. With an increasing number of visible

metastases, the feasibility of conventional radiotherapy will become more challenging. On the other hand, a stereotactic technique with a limited number of fractions may facilitate full treatment respecting the overall treatment time.

In adults, the current radiotherapy approach for multifocal metastatic disease has a strong focus on stereotactic techniques with hypofractionation [16–18]. In general, carcinomas require a much higher biological dose than paediatric embryonal tumours to achieve local control. Given the higher incidence and the longer experience of biologically effective dose calculations, dose and fractionation schemes are well developed for the vast majority of adult tumours [43]. Similar radiobiological data for children, balancing the lower doses needed to obtain disease control and the higher age-dependent risk of normal tissue toxicity by the use of hypofractionation regimens, are lacking. The latter becomes even more important when thinking of hypofractionation with protons [44].

This survey shows that conventionally fractionated rotational IMRT is currently the main technique for the radical irradiation of metastatic disease in children regardless of any tumour type. Also in the literature, evidence for hypofractionated stereotactic radiotherapy in children is limited. Some studies showed the feasibility of a stereotactic technique, with varying dose and fractionation schemes [26,39,45]. Local control rates ranged from 50 to 85% at a median follow-up of 2 years, with no acute or severe late toxicities observed [26,39,44]. Casey *et al.* retrospectively evaluated the indications for a radiotherapy dose and fractionation schedule with curative intent of 49 bone metastases in RMS and ES patients [12]. Hypofractionation with 3.0–8.0 Gy per fraction was utilized in 10/49 bone lesions only, conventional normofractionation in 34/49 bones and hyperfractionation with 1.5 Gy twice per day in 5/49 bones. The use of mild hypofractionation resulted in a similar local control.

All respondents mentioned that large prospective registration studies are needed to understand tumour

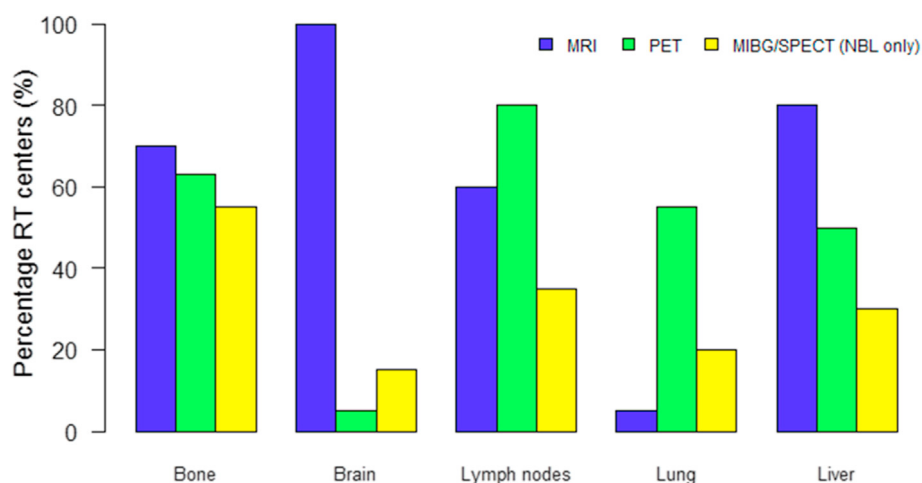


Fig. 3. Percentages of centres indicating which imaging modalities were used to define (and delineate) the target volume for a metastatic site, such as bone, brain, lymph nodes, lung and liver. Abbreviations: PET, Positron Emission Tomography; MRI, Magnetic Resonance Imaging and MIBG/SPECT: iodine-123-metaiodobenzylguanidine/single-photon emission computed tomography.

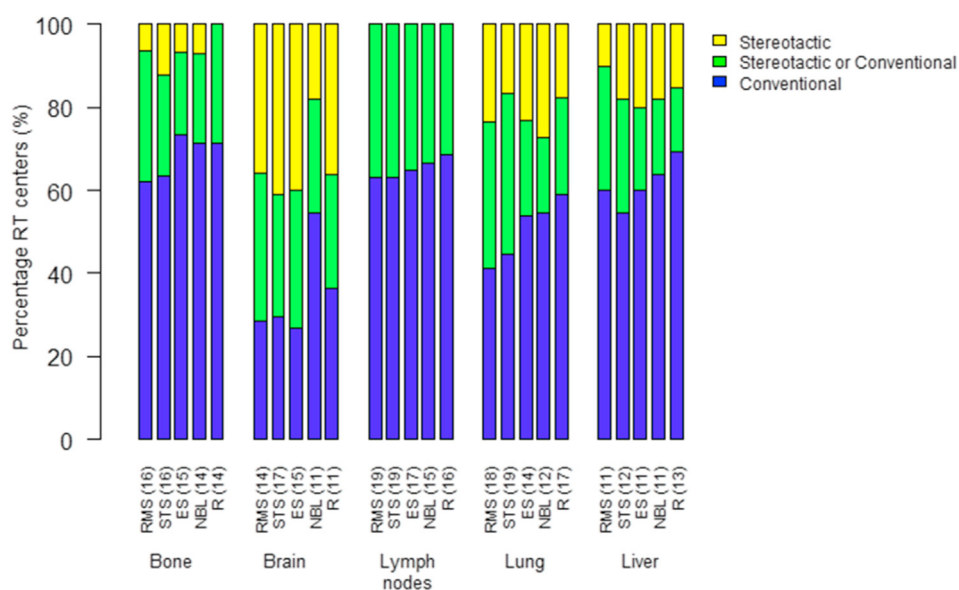


Fig. 4. Percentages of departments using conventional only (in blue), stereotactic only (in yellow) or both techniques (in green) for metastatic disease categorised by site and per primary tumour (between brackets ( $N$ ) = number of centres that indicated to irradiate with curative intent) Abbreviations: RMS, rhabdomyosarcoma; STS, soft-tissue sarcoma; ES, Ewing sarcoma; NBL, neuroblastoma and R, renal tumours. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

control and side-effects on different tissues after non-conventional fractionation regimens. In France, a national prospective study considering a stereotactic approach in children was started in 2013 and included 48 patients so far [38]. Fifteen patients underwent hypofractionation radiotherapy for brain, lung or spinal lesions during first-line treatment. The stereotactic approach was feasible and safe for all patients, but more follow-up is needed to evaluate middle-term and long-term toxicity [38]. Without any further results from these prospective trials, prescribed doses to metastases in the biologic range of the primary tumour dose are recommended [12]. In addition to registration studies,

dosimetric studies investigating a range of dose and fractionation schedules for different metastatic sites and related constraints could lead to a better understanding of the feasibility of hypofractionation and the dose distribution in healthy surrounding tissues in children.

Our survey has certain limitations. It relied on respondents' knowledge and experience, and questions were answered on how participating radiation oncologists (would) act in specific situations. Since some of the cases described in this survey are relatively rare, to ensure a minimum of clinical experience, only centres irradiating at least 50 children annually were invited to participate [29]. All participants irradiated at least one



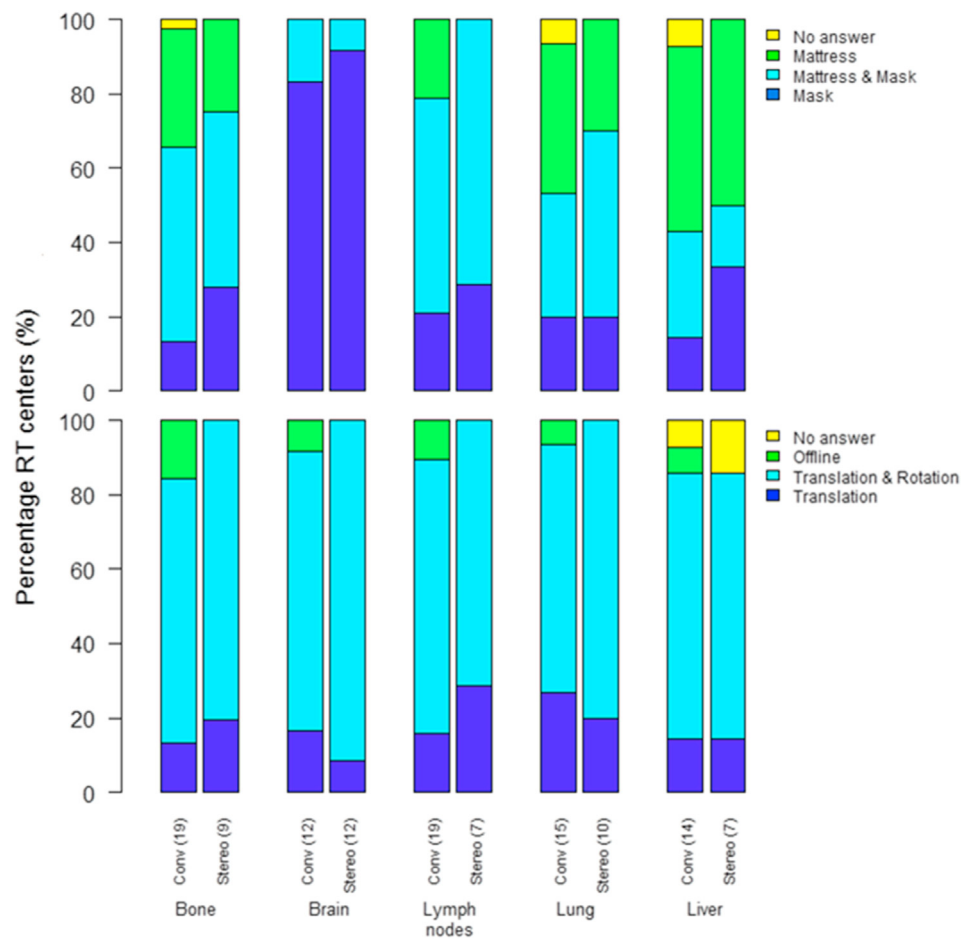


Fig. 5. Details regarding immobilization devices (upper panel) and position verification methods (lower panel) used for conventional (left bar) and stereotactic (right bar) planning techniques indicated per metastatic site. The number between the brackets indicates the number of centres reporting the use of conventional and/or stereotactic planning techniques.

patient of the type being surveyed (median 6, range 1–37), annually. Although smaller centres were not invited for the survey, this study reflects on current radiotherapy practices applicable to the whole paediatric radiotherapy community.

In addition, our protocol review and survey focussed on radiotherapy procedures with curative intent for metastatic disease at primary diagnosis and makes no recommendations for radiotherapy on metastatic sites in the context of salvage or palliation. The role of radiotherapy to metastatic sites as part of a salvage approach at the time of disease relapse is best discussed on an individual basis within a multidisciplinary team or by contacting experts in the field. In the context of palliation, hypofractionation radiotherapy with a variety of fractions and doses can easily be applied mainly depending on the tumour type, site and life expectancy.

The next step towards further consensus is to set up a radiotherapy working group for ST with primary metastatic disease to discuss the total- and fraction dose-related issues per site, age group and per disease category, and tackling issues like normal tissue tolerance and biologically effective dose calculations. To

understand tumour control and side-effects, taking into account the potential variables, large registries are needed.

In conclusion, the present study reviewed the radiotherapeutic approach for metastatic sites in current European paediatric ST study protocols. A survey across SIOPE-affiliated centres unveiled consistencies and differences regarding patient selection and treatment characteristics. A collaboration of experts from leading paediatric radiotherapy departments is needed to reach consensus on the local approach of metastatic sites. This is essential to set up prospective (randomised) trials to generate more evidence on the first-line radiotherapy to metastatic sites in stage IV disease.

#### Authors contributions

Study concepts: P.S. Kroon, E. Seravalli, G.O. Janssens.

Study design: P.S. Kroon, E. Seravalli, G.O. Janssens.

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Quality control of data and algorithms: S.C. Huijskens, P.S. Kroon, G.O. Janssens.

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Statistical analysis: NA.

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Manuscript editing: All co-authors.

Manuscript review: All co-authors.

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### Conflict of interest statement

None declared.

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