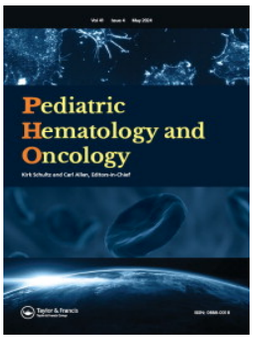

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The significance of surveillance imaging in children with Ewing sarcoma and osteosarcoma

Scott Greve Brekke[a], Arne Lucke[b], Henrik Hasle[a] and Thomas Baad-Hansen[c]

[a]Department of Pediatrics, Aarhus University Hospital, Aarhus N, Denmark; [b]Department of Radiology, Aarhus University Hospital, Aarhus N, Denmark; [c]Department of Orthopedic Surgery, Aarhus University Hospital, Aarhus N, Denmark

ABSTRACT

Primary bone tumors in children and adolescents, while rare, pose significant challenges in diagnosis and management. Children treated for Ewing sarcoma and osteosarcoma are offered a 5-year follow-up program after end of treatment, including radiological surveillance of primary location of tumor and the lungs. There is no consensus regarding how often and how the children should be followed with radiological imaging. This retrospective descriptive study of 69 patients (34 with Ewing sarcoma and 35 with osteosarcoma) investigated the consequences of abnormal findings in 1279 follow-up images. Nine relapses were detected, 4 in the Ewing group (3 local and 1 pulmonary) and 5 in the osteosarcoma group (1 local and 4 pulmonary). Of these, only two patients exhibited symptomatic relapses, with the remainder identified through imaging. The positive predictive value for relapse detection was 0.44 in the Ewing group, and 0.5 in the osteosarcoma group. In the Ewing sarcoma patient image follow-up program, the probability of anomaly detection was 12% (95% CI, 10–15). For osteosarcoma patients, the likelihood was 6% (95% CI, 4–8). Our data indicates that abnormal findings on follow-up images rarely represents relapse of tumor. As the surveillance protocol differs between the patient groups, wherein Ewing sarcoma patients primarily are monitored through MRI while osteosarcoma patients are predominantly tracked via X-rays, there is an increased occurrence of incidental findings in the first group. However, it is imperative to interpret imaging data in conjunction with clinical information, avoiding isolated reliance on imaging results when making treatment decisions.

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Ewing sarcoma; follow-up; osteosarcoma; surveillance imaging

1. Introduction

Primary bone tumors are rare, accounting for 5% of all malignant neoplasms in children and adolescents each year.[1–3] Osteosarcoma (OS) represents the most common bone tumor in children (incidence ca. 0.3 per 100,000 per year), followed by Ewing sarcoma (EWS) (incidence ca 0.2 per 100,000 per year).[2–4] 5-year survival of both malignancies has improved dramatically since the introduction of chemotherapy,

CONTACT Scott Greve Brekke scott.g.brekke@gmail.com Department of Pediatrics, Aarhus University Hospital, Aarhus N, Denmark.

radiation therapy (RT) and improved limb saving surgery.[5] Unfortunately, overall survival after local relapse of tumor and relapse with metastases is still poor.[5–9] To detect relapse in an early stage, patients with EWS and OS are enrolled in a 5-year follow-up (FU) program consisting of clinical examinations and radiological imaging.

Previous studies claim that there is no evidence to suggest that a structured follow-up imaging protocol (FUIP) improves overall survival after relapse compared to a 'watch and wait for symptoms".[10–12] A recent study concludes that FUIP improves overall survival in EWS, but this is still a topic of debate.[12–14] FU-imaging comes with great costs; increased risk of psychological stress in patients and their families, increased exposure to contrast agents and for young children anesthetics, economic cost to the health care system, as well as a risk of secondary malignancies due to increased exposure to radiation.[10,12,15]

There is consensus that patients should be followed at the end of treatment.[16] Though, the consensus regarding how often, and how the patients should be followed is more unclear. Current FUIP is mainly empirical and vary from center to center.[17]. At Aarhus University Hospital (AUH), the FUIP is according to ESMO guidelines.[18] In the absence of any formal prospective studies, the guidelines do not provide strict rules regarding surveillance imaging.[18] Hence, the FUIP differs between EWS and OS regarding image modality, but not in time interval. EWS FU is performed using mainly magnetic resonance imaging (MRI) of the primary location and chest X-ray, while FU of OS is performed mainly using X-ray of primary location and the chest. The difference in FUIP between the two patient groups may lead to different findings, and the consequences of abnormal findings may differ as well. The objective of this study is to review all the radiological anomalies during routine follow-up in children treated for EWS and OS between 2005 and 2019, along with the clinical decisions made in response to these findings.

2. Materials and methods

2.1. Study population

We conducted a retrospective longitudinal analysis of prospectively collected data. All patients diagnosed with EWS or OS from 2005 to 2019, treated in the Department of Pediatrics AUH, between the age of 0–17 years of age were identified and crosschecked with the Danish Childhood Cancer Register.[19] Patients with EWS were treated according to EuroEwing99,[20] and OS patients were treated according to the EURAMOS-1[21] protocol which states:" For the purposes of the study, patients will be followed-up for a minimum of five years after the end of the trial. The baseline was set at the time of status examination, approximately one month after the last cycle of chemotherapy. The FUIP consists of imaging every 3rd month during year 1–3 and every 6th month during year 4–5. Permission to collect and analyze data was given from the Danish Patient Safety Authority, case number 31-1521-373.

2.2. Characteristics of patients and disease

We included all patients ($n = 69$) diagnosed with histologically proven EWS ($n = 34$) or OS ($n = 35$) at the Department of Pediatrics at AUH between January 2005 and December 2019. Figure 1 presents the inclusion and exclusion criteria for the study.

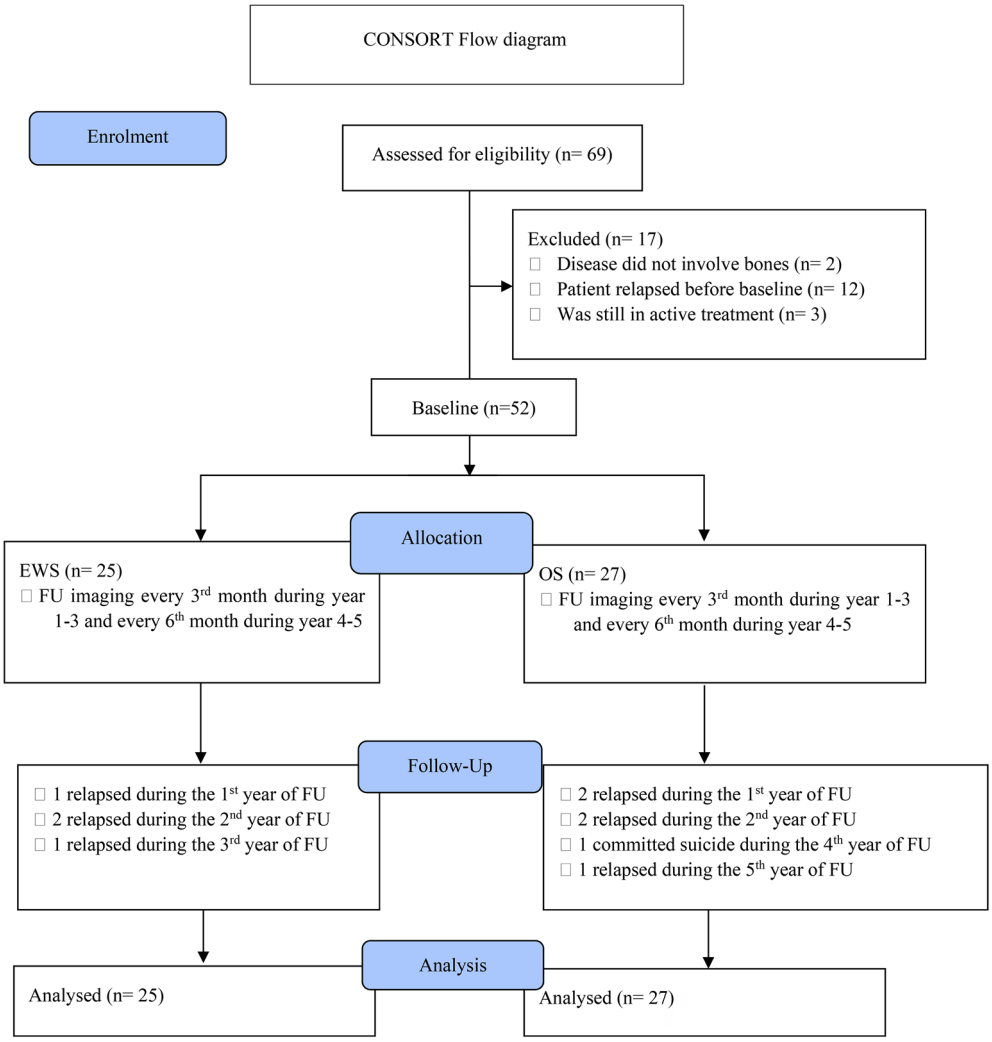

Figure 1. CONSORT diagram. A total of 69 patients with histologically proven Ewing sarcoma ($n = 34$) or osteosarcoma ($n = 35$) were included. The final data set for analysis included 52 patients, 25 Ewing sarcomas and 27 osteosarcomas.

Relevant information regarding type of surgery, radiation, anatomical location of tumor and whether the tumor had metastasized were determined (see Table 1). Radiological follow-up images as part of the FUIP were systematically reviewed. We recorded the date, image modality (MRI, X-ray, ultrasound, CT, or PET-CT), anatomical location pictured, abnormalities found in the skeleton or soft tissue, consequences of abnormal findings, and finally whether the malignancy was confirmed or refuted. Abnormalities were categorized as either suggestive of malignancy, benign or unclear based upon the radiological description and multidisciplinary conference. To be classified as suspect of malignancy, the radiological description had to indicate clear signs of malignancy. If the changes were described as seemingly benign, it was classified as benign. If the description presumed that the abnormality was benign, but relapse,

Table 1. Disease characteristics, treatment and follow up of the 25 patients with Ewing sarcoma (EWS) and the 27 patients with osteosarcoma (OS).

	EWS [%]	OS [%]
Tumor location		
Face or skull	2 [8]	1 [4]
Chest region	4 [16]	0
Spine	3 [12]	0
Upper extremities	3 [12]	1 [4]
Pelvic region	5 [20]	1 [4]
Lower extremities	8 [32]	24 [89]
Metastases present at the time of diagnosis.	6 [24]	3 [11]
Type of surgery (primary site)		
Local excision	14 [56]	0
Amputation	4 [16]	7 [26]
Rotational plastic	0	5 [18.5]
Biological reconstruction	3 [12]	4 [15]
Internal prosthesis	1 [4]	10 [37]
None	3 [12]	1 [4]
Radiation dose (Gy)		
Number of patients	10	1
Median [range]	55 [45-72]	72
FU without relapse [months]		
<12	3 [12]	4 [15]
12–24	4 [16]	4 [15]
>24	18 [72]	19 [70]
Median FU time without relapse [months]	15	13
Recurrence pattern		
Local relapse	3	1
Lung	1	4
No relapse	21	22

metastases, or another genesis could not be excluded, it was classified as unclear. Radiological follow-up ended 5 years after baseline, if the patient relapsed, or on September 30, 2020, whichever came first.

2.3. Data analysis

Descriptive statistics on demographic and cancer information are presented. Total numbers of scans, image modality used, number of abnormal findings, location of abnormal findings and consequences of abnormal findings in the EWS and OS groups were described. Sensitivity, specificity, and positive predictive value (PPV) were calculated for both groups. A true positive image refers to an image initially considered suspicious for malignancy, subsequently confirmed as a relapse of tumor. Conversely, a false positive image is one initially deemed suspicious for malignancy but later refuted. A true negative image is one without suspicion for malignancy (benign or unclear) that never later proved to be malignant. Lastly, a false negative image is one initially without suspicion for malignancy but later confirmed as a relapse of tumor (see Table 2).

3. Results

Fifteen patients were excluded due to relapse before the end of treatment or if they still were in active cancer treatment. Two patients were excluded due to only extra

Table 2. Number of scans suspect and not suspect for malignancy (column), and if the malignancy were confirmed or refuted (row).

	EWS			*OS*		
	Malignancy confirmed	Malignancy refuted	Total	Malignancy confirmed	Malignancy refuted	Total
FU-images suspect for malignancy	4 = TP	5 = FP	9	5 = TP	4 = FP	9
FU-images not suspect for malignancy	0 = FN	599 = TN	599	0 = FN	663 = TN	663
Total	4	604	608	5	667	671
Sensitivity (TP/total number of confirmed) = 1				Sensitivity (TP/total number of confirmed) = 1		
Specificity (TN/total number of refuted) = 0.99				Specificity (TN/total number of refuted) = 0.99		
PPV (TP/total number of suspect for malignancy) = 0.44				PPV (TP/total number of suspect for malignancy) = 0.5		

True positive (TP), True negative (TN), False positive (FP) and False negative (FN).

skeletal location of the tumor (see Figure 1). Thus, 15 boys and 10 girls diagnosed with EWS, with a median age of 9 years (range 3–16) at primary diagnosis were included. Furthermore, 14 boys and 13 girls with OS with a median age of 12 years (range 6–17) at primary diagnosis were included. At the end of FU, 21 patients with EWS and 21 patients with OS were alive without disease. During the follow-up period, one patient diagnosed with OS passed away due to reasons unrelated to the disease. Seventeen patients were still in the follow-up period by September 30, and therefor had not completed 5 years of follow-up.

This study included a total of 608 imaging studies for EWS patients and 671 imaging studies for OS patients. The number of local imaging studies were 327 in EWS (220 MRIs, 75 X-rays, 22 ultrasounds, 4 CT scans, and 6 PET-CT scans) and 328 in OS (56 MRIs, 265 X-rays, 2 ultrasounds, 3 CT scans, and 2 PET-CT scans). Pulmonary images comprised 269 for EWS patients (0 MRIs, 240 X-rays, 0 ultrasounds, 29 CT scans, and 0 PET-CT scans) and 334 for OS patients (0 MRIs, 302 X-rays, 0 ultrasounds, 32 CT scans, and 0 PET-CT scans). False positive findings were found in 5 images from EWS patients, and 4 in OS patients. True positive findings were found in 4 images from EWS patients and 5 OS patients. Abnormal findings were confirmed as relapse of tumor by a combination of biopsies, additional scans and/or of image-modality. The rate of confirmed incidental findings were 70/608 = 11.5% for EWS patients and 36/671 = 5.4% for OS patients. In response to abnormal findings 63 extra procedures were done in EWS patients (6 biopsies, 34 additional images, and 23 changes of image modality). For OS patients, 45 extra procedures were performed (6 biopsies, 25 additional images, and 14 changes of image modality). The consequences of abnormal findings are presented in Table 3. Nine patients relapsed during the FU period (4 EWS and 5 OS). In the cohort, four relapses occurred locally, two of them (one EWS and one OS) were diagnosed on routine imaging whereas two were diagnosed due to imaging made because of local pain. Five relapses occurred in the lungs by routine chest X-ray, none of these patients had pulmonary symptoms.

3.1.1. Ewing sarcoma

Of all abnormalities found ($n = 74$), 22% were found to be reactive changes, 19% were changes related to treatment, 19% were unspecific (none of them relapsed), 9% were

Table 3. Abnormalities identified through imaging and the subsequent clinical decisions.

	EWS	OS
Malignancy suspected	9	9
Further investigation:	9	9
Biopsy	5	1
Change of follow up protocol	3	8
Change of imaging modality	4	6
Observation only	0	0
Benign condition suspected	32	11
Further investigation:	9	2
Biopsy	0	0
Change of follow up protocol	6	2
Change of imaging modality	3	1
Observation only	23	9
Unclear	32	21
Further investigation:	27	20
Biopsy	1	5
Change of follow up protocol	25	15
Change of picture modality	16	7
Observation only	5	1

Overall counts.

infections, and 5% proved to be relapse of tumor. The remaining 25% of abnormalities represented other abnormalities (pseudoarthrosis, osteoporosis, overlying bones etc.)

Out of a total of 327 images featuring the primary tumor location, 52% ($n = 169$) included the opposite extremity. Among these, 130 were obtained using MRI, 29 with X-ray, 1with ultrasound, 3 with CT-scans and 6 with PET-CT. There were identified 10 abnormalities in a contralateral bone, and all 10 were located to the lower extremities, in a total of 5 patients. For 3 patients, the contralateral abnormality turned out to be reactive changes to increased physical activity. In one patient, the irregularity was determined to be a blood vessel. In the fifth patient, the precise nature of the anomaly could not be definitively established. This patient had undergone treatment for EWS in the left proximal fibula; however, the observed changes on MRI were situated in the right tibia. Despite this uncertainty, comprehensive investigations were undertaken, leading to the contribution of six out of the ten abnormal images from contralateral extremities. This comprehensive assessment culminated in a biopsy, which ultimately proved to be unspecific reactive changes. Nine abnormalities were found in other locations of which 7 were found on MRI and 2 on X-ray (see Table 4). The 10 abnormalities found contralaterally, and 9 abnormalities found in other locations resulted in 3 biopsies (50% of all biopsies in EWS patients) and 6 changes of image modalities/regime.

Four tumor relapses were identified, with three occurring locally, detected through MRI, and one pulmonary relapse, detected via chest X-ray. To discover one relapse, 152 images were performed among EWS patients. In EWS patients, all abnormal contralateral findings were incidental findings on MRI.

3.1.2. Osteosarcoma

Of all abnormalities found ($n = 41$), 20% proved to be sequela to treatment, 20% was unaccounted for, 12% was relapse of tumor, 7% were infections, and 5% proved to

Table 4. Location, and type of abnormalities found in other locations.

Patient number	Primary location of tumor (side)	Location of abnormality	What abnormality
14 (EWS)	Calcaneus (left)	Proximal tibia (left)	Fissure
14 (EWS)	Calcaneus (left)	Distal femur (left)	Fracture due to trauma
17 (EWS)	Proximal tibia (left)	Distal tibia (left)	Aseptic osteomyelitis
20 (EWS)	3rd metatarsal (right)	Trochlea tali (left)	Edema
21 (EWS)	Distal tibia (left)	Proximal tibia (left)	Edema
42 (EWS)	Distal radius (right)	Distal tibia (right)	Inflammation
42 (EWS)	Distal radius (right)	Distal tibia (right)	Reactive changes
69 (EWS)	Os pubis	Acetabulum (left)	Change of bone-structure
69 (EWS)	Os pubis	Collum femoris (left)	Epifysiolysis
31 (OS)	Proximal tibia (left)	Ilium (right)	Stool overlap.
50 (OS)	Calcaneus (right)	Elbow (right)	Reactive lymph node
55 (OS)	Distal femur (left)	Calcaneus (left).	Osteoporosis

represent reactive changes. The remaining 36% represented other abnormalities (pseudoarthrosis, osteoporosis, overlying bones etc.)

Out of a total of 328 images featuring the primary location, 13% ($n=42$) of the primary location included the contralateral extremity of which 40 studies were taken with MRI and 2 with PET-CT. All abnormalities found in a contralateral bone ($n=2$) were in the lower limbs. One of the abnormalities turned out to be a reaction to increased physical activity, the other could not be accounted for. Three abnormalities were found in other locations, of which 2 were found on MRIs and 1 on X-ray. The two abnormalities found contralaterally, and three abnormalities found in other locations resulted in two biopsies (1/3 of all biopsies in OS patients) and two scans earlier than scheduled.

Five tumor relapses were identified, with one local detected through MRI and four pulmonary relapses detected by chest X-ray. To discover one relapse, 134 images were performed among OS patients. In contrast to the EWS group, abnormalities found contralaterally in OS patients were associated with patient complaints leading to additional imaging.

4. Discussion

Justifying more than 1.200 radiological images of 52 patients in the FUIP is to detect a relapse as early as possible, allowing for earlier or less intensive treatment with an increased chance of survival.[10] The cost–benefit of such a surveillance program is debated in patients undergoing follow up due to other malignant diseases such as breast cancer and bladder cancer.[22–24] This study sought to investigate the number and types of abnormalities found during FU imaging, what consequences abnormal findings had in EWS and OS.

Abnormalities mimicking relapse were seen in both groups, but benign changes were found more commonly among EWS than OS patients, as FU-imaging of primary location among EWS patients were mainly performed using MRI, providing more detailed information than X-ray. Thus, treatment-related structural changes, as well as other abnormalities may be easier detectable using MRI. EWS is more sensitive to RT, and 40% of EWS patients indeed received RT. Some of the abnormalities seen were later confirmed to be benign changes after RT. Nevertheless, there were no difference in number of abnormalities found among EWS patients receiving RT compared to those with non-RT (2,9 per RT-patient, and 3,0 per non-RT patient).

Furthermore, MRI, as compared to X-ray, involves a larger part of the body, often including the contralateral extremity. The increased volume investigated could lead to an increased risk of incidental findings and may explain why 25% of abnormalities were located outside the primary location and the lungs in the EWS group and only 12% in the OS-group.

Findings of other suspected malignancy sites other than primary tumor location and the lungs resulted in 5 biopsies out of the total of 12 biopsies performed, of which none were found to be malignant – illustrating the dilemma clinicians face when finding abnormalities. In our data, relapse never occurred outside primary location or lungs confirming the low risk of malignancy outside the primary site and the lung.[3,4]

A total of 76 images led to further investigation. Further investigation may also cause great amount of concern and anxiety for both patients and their relatives.[15] Nine patients were found to present a relapse. A PPV of 0.47 indicates that a scan suspect for malignancy is far from always predictive of relapse. In particular, MRI, but also CT and PET-CT scans incur substantial costs.[25,26] CT scans contribute with a considerable dose of irradiation, and Pearce and colleagues found increased incidence of secondary cancers (brain cancer and leukemia) among children exposed to CT-radiation.[27] Thus, the great number of scans comes with a price: economically, physically, and psychologically.

Considering the small study population, we cannot draw any conclusion on effect of the surveillance program on overall survival. Brasme et al. proved that time to diagnosis of EWS in children, is not associated with risk of metastases or survival.[28] Whether or not the same is seen in OS patients, or with relapse is unclear, but would be interesting to compare. Heinemann et al. suggest surveillance imaging may be beneficial, especially in lung recurrence.[13] Local relapse can be associated with pain,[13] and one could speculate that education in symptoms of local relapse, together with surveillance imaging of the lungs only, could constitute an equally effective surveillance program. More research is needed in this field.

This study provides a complete data set and complete FU in each patient. There are, however, some limitations. Firstly, this study included a relatively small study population as both malignancies are rare. Conducting studies that involve a larger number of participants may be challenging. Nevertheless, we believe that this study has the potential to serve as a steppingstone toward a multi-site study. Collaborating with multiple institutions and researchers across different locations could help overcome the limitations imposed by small sample sizes, this however demands almost similar follow up programs.

Furthermore, a smaller part of the population entered FUIP <5 years ago, and therefore have not completed 5 years of FU-imaging. We have not collected data regarding tumor burden (volume), which have been suggested as a predictor for relapse.[18] Lastly, it is problematic that one of the EWS patients alone contributed with 6 of the 10 abnormalities found in the contralateral bone.

5. Conclusion

The cost–benefit analysis of radiological surveillance imaging remains a subject of debate, prompting the query of what constitutes an adequate amount of follow-up imaging. Our data suggests that abnormal findings on follow-up images rarely indicate

a tumor relapse. This is also supported by the calculated sensitivity for Ewing sarcoma and osteosarcoma, respectively. However, patients with EWS demonstrated a greater occurrence of abnormalities beyond the primary site and lungs, in contrast to patients with OS. This discrepancy could be attributed to the difference in follow-up protocol.

Disclosure statement

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Institutional review board statement

The Danish Patient Safety Authority, case number 31-1521-373 approved the study and did not require Informed Consent Statement from the patients.

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ORCID

Henrik Hasle http://orcid.org/0000-0003-3976-9231
Scott Greve Brekke http://orcid.org/0000-0002-2132-806X
Thomas Baad-Hansen http://orcid.org/0000-0003-4826-8412

References

1. Stiller CA, Trama A, Serraino D, et al. Descriptive epidemiology of sarcomas in Europe: report from the RARECARE project. *Eur J Cancer*. 2013;49(3):684–695. doi:10.1016/j.ejca.2012.09.011.
2. Ottaviani G, Jaffe N. The epidemiology of osteosarcoma. *Cancer Treat Res*. 2009;152:3–13.
3. Balamuth NJ, Womer RB. Ewing's sarcoma. *Lancet Oncol*. 2010;11(2):184–192. doi:10.1016/S1470-2045(09)70286-4.
4. Ritter J, Bielack SS. Osteosarcoma. *Ann Oncol*. 2010;21 Suppl 7(Suppl 7):vii320–5. doi:10.1093/annonc/mdq276.
5. Stahl M, Ranft A, Paulussen M, et al. Risk of recurrence and survival after relapse in patients with Ewing sarcoma. *Pediatr Blood Cancer*. 2011;57(4):549–553. doi:10.1002/pbc.23040.
6. Ferrari S, Luksch R, Hall KS, et al. Post-relapse survival in patients with Ewing sarcoma. *Pediatr Blood Cancer*. 2015;62(6):994–999. doi:10.1002/pbc.25388.
7. Sankar S, Lessnick SL. Promiscuous partnerships in Ewing's sarcoma. *Cancer Genet*. 2011;204(7):351–365. doi:10.1016/j.cancergen.2011.07.008.
8. Ferguson JL, Turner SP. Bone cancer: diagnosis and treatment principles. *Am Fam Physician*. 2018;98(4):205–213.
9. Takeuchi A, Lewis VO, Satcher RL, Moon BS, Lin PP. What are the factors that affect survival and relapse after local recurrence of osteosarcoma? *Clin Orthop Relat Res*. 2014;472(10):3188–3195. doi:10.1007/s11999-014-3759-7.
10. McHugh K, Roebuck DJ. Pediatric oncology surveillance imaging: two recommendations. Abandon CT scanning, and randomize to imaging or solely clinical follow-up. *Pediatr Blood Cancer*. 2014;61(1):3–6. doi:10.1002/pbc.24757.

11. Kasalak Ö, Dammann A, Adams HJA, et al. Surveillance MRI for the detection of locally recurrent Ewing sarcoma seems futile. *Skelet Radiol*. 2018;47(11):1517–1522. doi:10.1007/s00256-018-2966-9.
12. Morgan JE, Walker R, Harden M, Phillips RS. A systematic review of evidence for and against routine surveillance imaging after completing treatment for childhood extracranial solid tumors. *Cancer Med*. 2020;9(14):4949–4961. doi:10.1002/cam4.3110.
13. Heinemann M, Ranft A, Langer T, et al. Recurrence of Ewing sarcoma: Is detection by imaging follow-up protocol associated with survival advantage? *Pediatr Blood Cancer*. 2018;65(7):e27011. doi:10.1002/pbc.27011.
14. Lakkis F, Alaiwi SA, Naffaa L, et al. Routine surveillance imaging after end of therapy for pediatric extracranial tumors: A retrospective analysis. *Pediatr Blood Cancer*. 2018;65(1):26723. doi:10.1002/pbc.26723.
15. Vaarwerk B, Limperg PF, Naafs-Wilstra MC, Merks JHM, Grootenhuis MA. Getting control during follow-up visits: the views and experiences of parents on tumor surveillance after their children have completed therapy for rhabdomyosarcoma or Ewing sarcoma. *Support Care Cancer*. 2019;27(10):3841–3848. doi:10.1007/s00520-019-04678-4.
16. Biermann JS, Chow W, Reed DR, et al. NCCN guidelines insights: bone cancer, Version 2.2017. *J Natl Compr Canc Netw*. 2017;15(2):155–167. doi:10.6004/jnccn.2017.0017.
17. Puri A, Gulia A, Hawaldar R, Ranganathan P, Badwe RA. Does intensity of surveillance affect survival after surgery for sarcomas? Results of a randomized noninferiority trial. *Clin Orthop Relat Res*. 2014;472(5):1568–1575. doi:10.1007/s11999-013-3385-9.
18. Casali PG, Bielack S, Abecassis N, et al. Bone sarcomas: ESMO-PaedCan-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2018;29(Suppl 4):iv79–iv95. doi:10.1093/annonc/mdy310.
19. Schrøder H, Rechnitzer C, Wehner PS, et al. Danish childhood cancer registry. *Clin Epidemiol*. 2016;8:461–464. doi:10.2147/CLEP.S99508.
20. Juergens C, Weston C, Lewis I, et al. Safety assessment of intensive induction with vincristine, ifosfamide, doxorubicin, and etoposide (VIDE) in the treatment of Ewing tumors in the EURO-E.W.I.N.G. 99 clinical trial. *Pediatr Blood Cancer*. 2006;47(1):22–29. doi:10.1002/pbc.20820.
21. Bielack SS, Smeland S, Whelan JS, et al. Methotrexate, doxorubicin, and cisplatin (map) plus maintenance pegylated interferon alfa-2b versus MAP alone in patients with resectable high-grade osteosarcoma and good histologic response to preoperative MAP: first results of the EURAMOS-1 good response randomized controlled trial. *j Clin Oncol*. 2015;33(20):2279–2287. doi:10.1200/JCO.2014.60.0734.
22. Giannarini G, Kessler TM, Thoeny HC, Nguyen DP, Meissner C, Studer UE. Do patients benefit from routine follow-up to detect recurrences after radical cystectomy and ileal orthotopic bladder substitution? *Eur Urol*. 2010;58(4):486–494. doi:10.1016/j.eururo.2010.05.041.
23. Park VY, Kim EK, Kim MJ, Moon HJ, Yoon JH. Breast magnetic resonance imaging for surveillance of women with a personal history of breast cancer: outcomes stratified by interval between definitive surgery and surveillance MR imaging. *BMC Cancer*. 2018;18(1):91. doi:10.1186/s12885-018-3998-1.
24. Salani R, Khanna N, Frimer M, Bristow RE, Chen LM. An update on post-treatment surveillance and diagnosis of recurrence in women with gynecologic malignancies: Society of Gynecologic Oncology (SGO) recommendations. *Gynecol Oncol*. 2017;146(1):3–10. doi:10.1016/j.ygyno.2017.03.022.
25. Young DW. What does an MRI scan cost? *Healthc Financ Manage*. 2015;69(11):46–49.
26. Kim CR, Kim B, Ning MS, et al. Cost analysis of PET/CT versus CT as surveillance for stage III non-small-cell lung cancer after definitive radiation therapy. *Clin Lung Cancer*. 2018;19(4):e517–e28. doi:10.1016/j.cllc.2018.03.012.
27. Pearce MS, Salotti JA, Little MP, et al. Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study. *Lancet*. 2012;380(9840):499–505. doi:10.1016/S0140-6736(12)60815-0.
28. Brasme JF, Chalumeau M, Oberlin O, Valteau-Couanet D, Gaspar N. Time to diagnosis of Ewing tumors in children and adolescents is not associated with metastasis or survival: a prospective multicenter study of 436 patients. *J Clin Oncol*. 2014;32(18):1935–1940. doi:10.1200/JCO.2013.53.8058.