ACTA ONCOLOGICA
2019, VOL. 58, NO. 4, 505–511
https://doi.org/10.1080/0284186X.2019.1566769

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

The radiological and clinical follow-up of osteonecrosis in cancer patients

Riitta Niinimäki[a,b], Maria Suo-Palosaari[c,d], Tytti Pokka[a,b], Arja Harila-Saari[e] and Tuukka Niinimäki[f]

[a]Department of Children and Adolescents, Oulu University Hospital, Oulu, Finland; [b]PEDEGO Research Unit, University of Oulu, Oulu, Finland; [c]Department of Diagnostic Radiology, Oulu University Hospital, Oulu, Finland; [d]Research Unit of Medical Imaging, Physics and Technology, University of Oulu, Oulu, Finland; [e]Department of Women's and Children's Health, Uppsala University, Uppsala, Sweden; [f]Department of Surgery, Oulu University Hospital, Oulu, Finland

ABSTRACT

Background: In patients with cancer, osteonecrosis (ON) lesions can affect multiple sites throughout the skeleton, including the long and short bones and the joints. The aims of this study were to explore the natural course of ON in patients treated for cancer by using radiological classification suitable for multisite ON lesions and to assess correlations between the ON grade and surgical procedures.

Material and methods: Data were retrieved from hospital databases on 233 ON lesions in 54 patients (aged 2–73 years at cancer diagnosis; mean age: 25 years). ONs were graded according to the Niinimäki classification, based on magnetic resonance images. Medical records were reviewed to identify surgical procedures.

Results: A total of 14 different ON sites were detected; the hip was the most common site ($n = 51$), followed by the femur ($n = 45$), tibia ($n = 41$) and knee ($n = 37$). Among the 233 ON lesions, 78.1% did not require surgical procedures. The remaining lesions required total joint arthroplasty (TJA; 40/233, 17.2%), core decompression (3.4%) and arthroscopy (1.3%). Most TJAs (33/40, 82.5%) were performed on the hip. ONs of the knee required TJAs only once; grade 3 knee ONs frequently healed (58%, 11/19). None of the diaphyseal or metaphyseal (grade 1–2) ONs of the long bones required surgery, and no fractures of those bones were identified.

Conclusions: In conclusion, the natural history of ONs varied by the grade and site. Based on our findings, we would not recommend routine radiological follow-ups for grades 1–2 ON lesions that do not affect the joints, because the clinical consequences of those lesions appear to be minimal, although pain relief would be warranted. In contrast, joint deformations (grade 5) require surgery; therefore, intervention studies should focus on grades 3–4 ON lesions.

ARTICLE HISTORY
Received 28 November 2018
Accepted 21 December 2018

Introduction

Osteonecrosis (ON) is a common sequel after cancer treatment, particularly in children and young adults treated for leukemia or lymphoma and after allogeneic stem cell transplantation [1,2]. The reported incidence of ON in patients treated for leukemia or lymphoma has varied from 72%, based on magnetic resonance imaging (MRI) screening, to 0.6% in symptomatic patients [3–5]. ON might lead to surgery (e.g., arthroplasty and core decompression); however, apart from the most severe cases, little is known about the natural course and mid-term consequences of ON in patients with cancer.

In patients with cancer, ON lesions can affect multiple sites throughout the skeleton, including the long and short bones and the joints; in contrast, in patients without cancer, ON lesions are typically located only in the joints (e.g., epiphysis of long bones), most commonly in the hips and knees [6,7]. Therefore, most ON studies, even in patients with cancer, have focused on the hips and knees [8,9]. The prior classification systems for grading ONs have been study-specific or joint-specific, and they were designed for patients without cancer [10–13]. To overcome the limitation of joint-specificity, a classification system was developed that included the entire skeleton; thus, all ONs could be assessed with a consistent classification system [14].

This study aimed to grade all the ONs in patients with cancer treated in tertiary level hospitals, evaluate the natural course of ON lesions, and assess the correlation between the ON grade and surgical treatments.

Patients and methods

Patients

This study was conducted in a tertiary level hospital where both children and adults were treated. The inclusion criterion was the presence of ON in any bone, identified after cancer diagnosis, between 1996 and 2017. The initial search was performed in three different databases, including outpatient, surgical, and hospital discharge databases. We identified

CONTACT Riitta Niinimäki riitta.niinimaki@oulu.fi Department of Children and Adolescents, Oulu University Hospital, Box 23, Oulu, FI-90029, Finland
Supplemental data for this article can be accessed here.

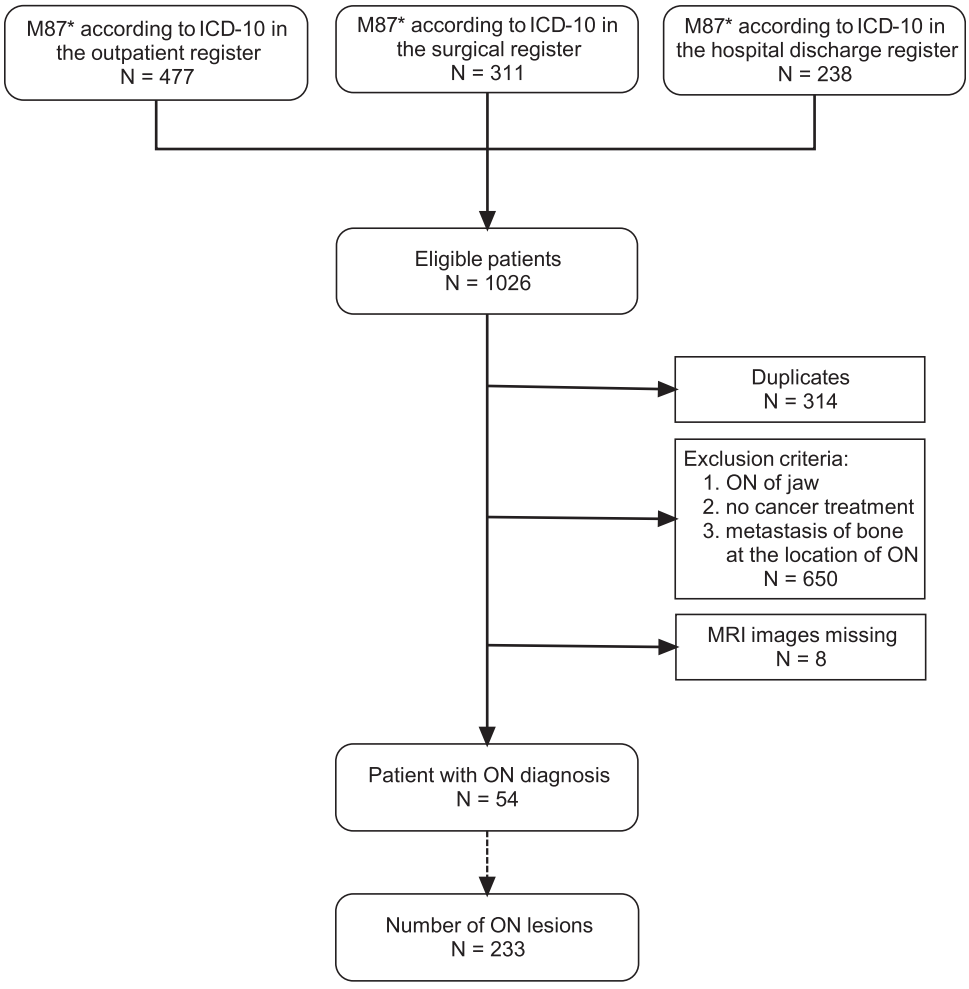

Figure 1. Flowchart shows the selection of data records of patients with cancer who developed osteonecrosis.

patients with ON based on a diagnosis recorded as code M87* of the International Classification of Disease (ICD-10). All patient reports and radiographs were reviewed to confirm the inclusion criterion and to identify ON lesions. The patient selection flowchart is shown in Figure 1.

Fifty-four patients (23 males) with a total of 233 ON lesions were included in this study (Table 1). The mean age of patients at cancer diagnosis was 24.9 years (range: 2–73 years). The most frequent (52%) type of cancer was acute lymphoblastic leukemia, followed by myeloid malignancy (22%) and lymphoma (11%). Twenty-two (41%) patients received allogeneic stem cell transplantations. The mean time from cancer diagnosis to the first diagnosis of ON was 2.1 years (range: 0.1–13.6 years). The mean follow-up time after the first diagnosis of ON was 5.2 years (range: 0.1–20.8 years).

Magnetic resonance imaging and osteonecrosis grading

MRI is regarded as the most sensitive and specific method for detection of ON [15]. Even with MRI, it may be difficult to separate ON from bone marrow edema, punctate foci of altered signal, mottled marrow changes or radiation-induced bone marrow changes, which can be early signs of progressive ON [16–18].

In this study, ON was defined as a circumscribed lesion with a distinct rim of low signal intensity in the normally high-intensity marrow on T1-weighted images (the band sign) and high signal intensity in the normally low-intensity marrow on short tau inversion recovery (STIR) images (double-line sign). Representative MRIs of ON lesions in the hip and tibial diaphysis are shown in Figure 2 [19,20].

We retrospectively analyzed MRI and clinical data for 54 patients. The MRIs were reviewed independently by a pediatric oncologist and a pediatric radiologist, and both were blinded to all patient information. After an initial review, the evaluators compared their records and reached a final consensus on the findings. The sites and grades of the ON lesions were reported according to the Niinimäki classification [13]. When the ON lesion had diminished to the extent that it could not be diagnosed as a typical ON lesion without relying on previous MRIs, it was considered healed, grade 0 (no ON), according to the classification.

Statistical analysis

We performed data manipulations (i.e., combining three databases), inclusion and exclusion criteria verifications, duplicate identifications and deletions, new variable computations/recording and data descriptions with IBM SPSS

statistical software for Windows version 25 (IBM Corp. Released 2017, Armonk, NY, USA). Figures were produced with Origin 2018 software (OriginLab, Northampton, MA, USA).

Table 1. Characteristics of patients with cancer who developed osteonecrosis.

Characteristics	No.	$n = 54$	%
Age at diagnosis, years			
Mean		24.9	
Standard deviation		18.1	
Sex			
Male	23		43
Female	31		57
Primary cancer diagnosis			
Acute lymphoblastic leukemia	28		52
Myeloid malignancies	12		22
Lymphoma	6		11
Myeloma or plasmacytoma	3		5
Breast cancer	2		4
Prostate cancer	1		2
Chronic lymphocytic leukemia	1		2
Astrocytoma	1		2
Hematopoietic stem cell transplantation			
No	29		54
Allogeneic	22		41
Autologous	3		5
Osteonecrosis			
Symptomatic	47		87
Screening at the end of the treatment	7		13
Number of follow-up MRI images			
Mean		2.1	
Standard deviation		1.4	
Time from cancer dx to the first ON dx, years			
Mean		3.9	
Standard deviation		3.5	
Follow-up time after first ON dx, years			
Mean		5.2	
Standard deviation		4.1	
Status at the end of the follow-up			
Alive	48		89
Dead	6		11

ON: osteonecrosis; dx: diagnosis

Results

The site of osteonecrosis

We identified a total of 233 ON lesions in 14 different locations. The most common site was the hip ($n = 51$), followed by the femur ($n = 45$), the tibia ($n = 41$), knee ($n = 37$), the ankle ($n = 18$), and the shoulder ($n = 13$; Figure 3).

Changes in osteonecrosis grade at follow-up MRI

Joints

There was total of 36 ON lesions in the hip joint. Ten lesions (28%) were grade 5 (deformation of joint and irreversible condition) on the first MRIs. Of 26 lesions that were grade 3 or 4 on the first MRI, 22 (85%) were the same or a higher grade on the final follow-up MRI (Figure 2(A,B)). Two lesions (7%), initially graded as 3 and 4, were completely healed at follow-up (grade 0; Figure 4).

None of the 30 ON lesions in the knee joint were classified as grade 5 on the first MRI. Only three lesions (10%) had progressed to grade 5 at the final follow-up. Fourteen lesions (47%) improved to a lower grade on the follow-up MRI, and of those, 11 (37%) had completely healed (grade 0; Supplementary Figure 1).

All 12 ON lesions in the ankle joint were graded as 3 or 4 on the first MRI. Only two lesions (12%) had worsened at follow-up, and those ended up as grade 5. Three lesions (25%) were completely healed (grade = 0; Figure 4, Supplementary Figure 2).

Only two ON lesions were identified in the shoulder joint. Both lesions were graded as 3 on the first MRI, and both progressed to grade 5 at follow-up, which caused joint collapse (Figure 4, Supplementary Figure 3).

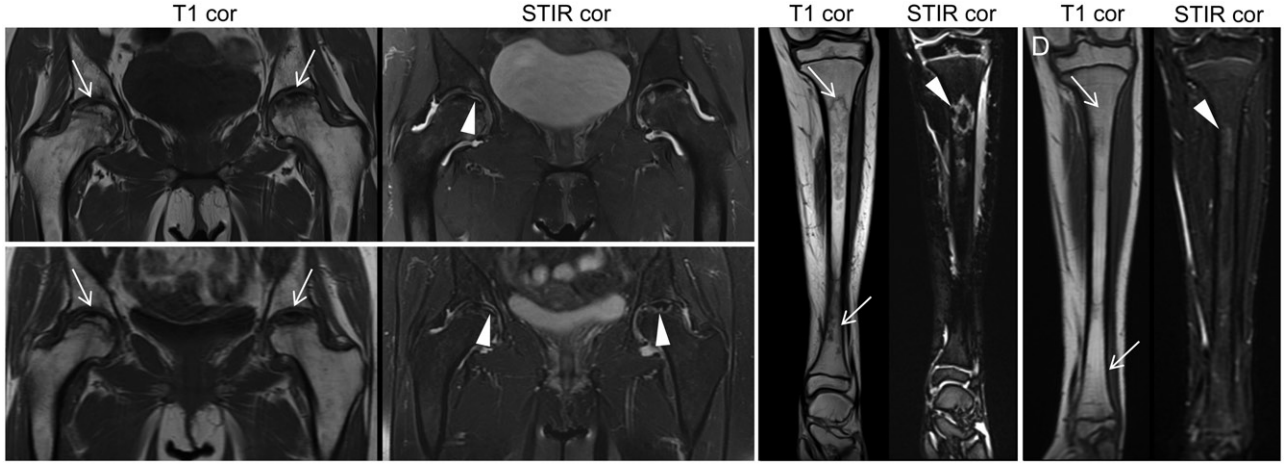

Figure 2. Representative MRIs of osteonecrosis (ON) in the hip and tibia demonstrate ON progression and healing. T1-weighted (T1W) and short tau inversion recovery (STIR) coronal (cor) sequences show osteonecrosis (ON) lesions. (A and B) ON progression in the hip; (C and D) ON healing in the lower limb. (A) Patient with acute lymphoblastic leukemia (ALL) developed bilateral ON in the hips. T1W image shows areas of low intensity (*arrows*) that indicate ≥30% articular involvement in both femoral heads, classified as 'Hip joint, Grade 4'. On the right femoral head, the STIR image shows a hyperintense inner line (*arrowhead*) between normal marrow and ischemic marrow (double line sign). (B) After three months, the T1 image shows that ON progressed, which resulted in the collapse of both femoral heads (*arrows*), which increased the classification to 'Hip joint, Grade 5'. The STIR image shows the double line sign on both femoral heads (*arrowheads*). (C) Patient with ALL developed typical metadiaphyseal ON lesions with a serpentine peripheral low-signal rim on the T1 image, classified as 'Tibia, Grade 2' (*arrows*); the STIR image shows a hyperintense double-line sign (*arrowhead*). (D) The ON lesions had completely healed at the 2-year follow-up, classified as 'Tibia, Grade 0' (*arrows* and *arrowhead*).

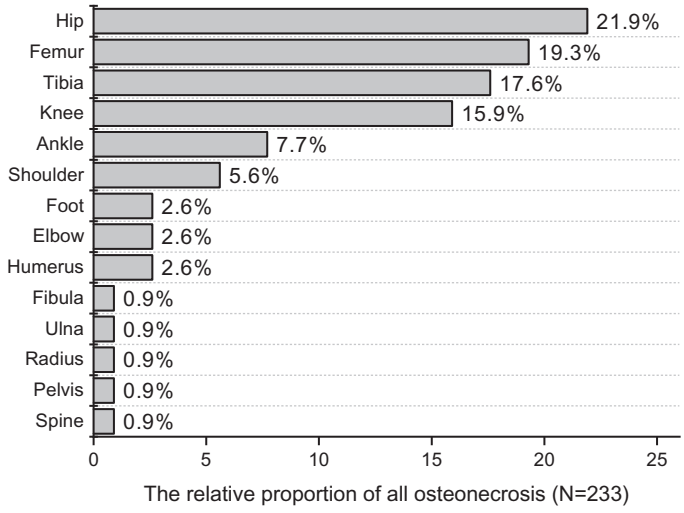

Figure 3. Frequency of osteonecrosis at different sites.

Long bones

There were 34 and 26 ON lesions on femur and tibia MRIs, respectively. All the lesions were graded as 2 on the first MRI, according to the classification system for the diaphysis or metaphysis of long bones in the lower extremity, as shown in representative images (Figure 2(C)). Twelve (35%) femoral and eight (31%) tibial lesions had completely healed at the last follow-up, as shown in representative Figure 2(D). In the upper extremities, a total of 10 grade 1 ONs were identified in the humerus, radius and ulna. None of the long bone grade 1–2 ONs were treated surgically. In addition, no bone fractures in the affected bones were evident in patient records (MRIs, plain radiographs and patient notes; Figure 4).

Surgical procedures

Surgical procedures were performed on 22% (51/233) of ON lesions in 28 different patients (Supplementary Table 1). Of these, 40 (78%) procedures were total joint arthroplasties (TJAs). Surgery was performed for most (86%, 43/50) grade 5 ON lesions, but for only 14% (4/29) of grade 4 and 9% (4/44) of grade 3 ON lesions. None of the grade 2 or 1 ON lesions ($n = 110$) that affected the diaphysis or metaphysis of long bones required surgical procedures (Table 2).

Most surgeries (33/51, 65%) were hip TJAs. Among the grade 3 ON lesions, two required TJA treatments, and of these, one was due to a pathologic fracture. Core decompression was performed in two (18%) hip grade 4 lesions. Nearly every (31/32, 97%) grade 5 hip ON was treated with a TJA. In the knee, six of 37 (16%) ON lesions were treated with surgery. Of these, three were core decompressions, two were arthroscopic debridements and one was TJA performed for a patient with a grade 5 ON lesion. In the shoulder, nearly half (6/13) of the ONs required surgery. All six procedures were arthroplasties (total or hemiarthroplasty) for grade 5 ONs; moreover, of the nine grade 5 ONs, six (67%) required operations.

Discussion

In this study, ON lesions located in the diaphysis or metaphysis of a long bone (grade 1 or 2) did not require surgery, and no fractures of those bones were found in patients with cancer. The most common surgical procedure was a TJA, and it was most often performed in the hip, but it was rarely performed in the knee. Symptomatic hip ONs were diagnosed at relatively late stages and the ON severity tended to remain unchanged or worsened gradually with time. In contrast, knee ONs seemed to be less severe at the time of diagnosis, and they showed better healing potential compared to the hip.

In this study, only a single ON lesion of the knee required a TJA. Even grades 3 and 4 ON lesions that affected the epiphyseal area of the bone had healed at follow-up. Similar healing potential was shown previously, in an MRI study by Karimova et al. [21]. Those authors also reported that ONs that affected the knees of children treated for leukemia and lymphoma were mostly asymptomatic, but they did not include follow-up MRIs [22]. Little information is available on the clinical significance or the natural course of ON lesions in the knee; however, based on the results in this study, knee ONs rarely cause severe consequences and their healing potential is relatively good.

In contrast, the natural course of the hip ON is widely recognized as a severe condition, both in cancer and non-cancer conditions [7,8,23]. In severe cases, a permanent cure is achieved only by performing a TJA, particularly when the femoral head has collapsed (grade 5). In this study, 87% (33/38) of TJAs were performed in the hip joint. Sixty-three percent (14/22) of grade 4 ON lesions in the hip progressed during follow-up to grade 5. Future studies should endeavor to identify medical or other interventions specifically for treating grade 3 and 4 ONs in the hip joint, before the collapse of the joint (grade 5).

The shoulder ON is an underappreciated adverse effect in pediatric patients treated for leukemia or lymphoma [24]. In this study, only 6% (13/233) of ONs were located in the

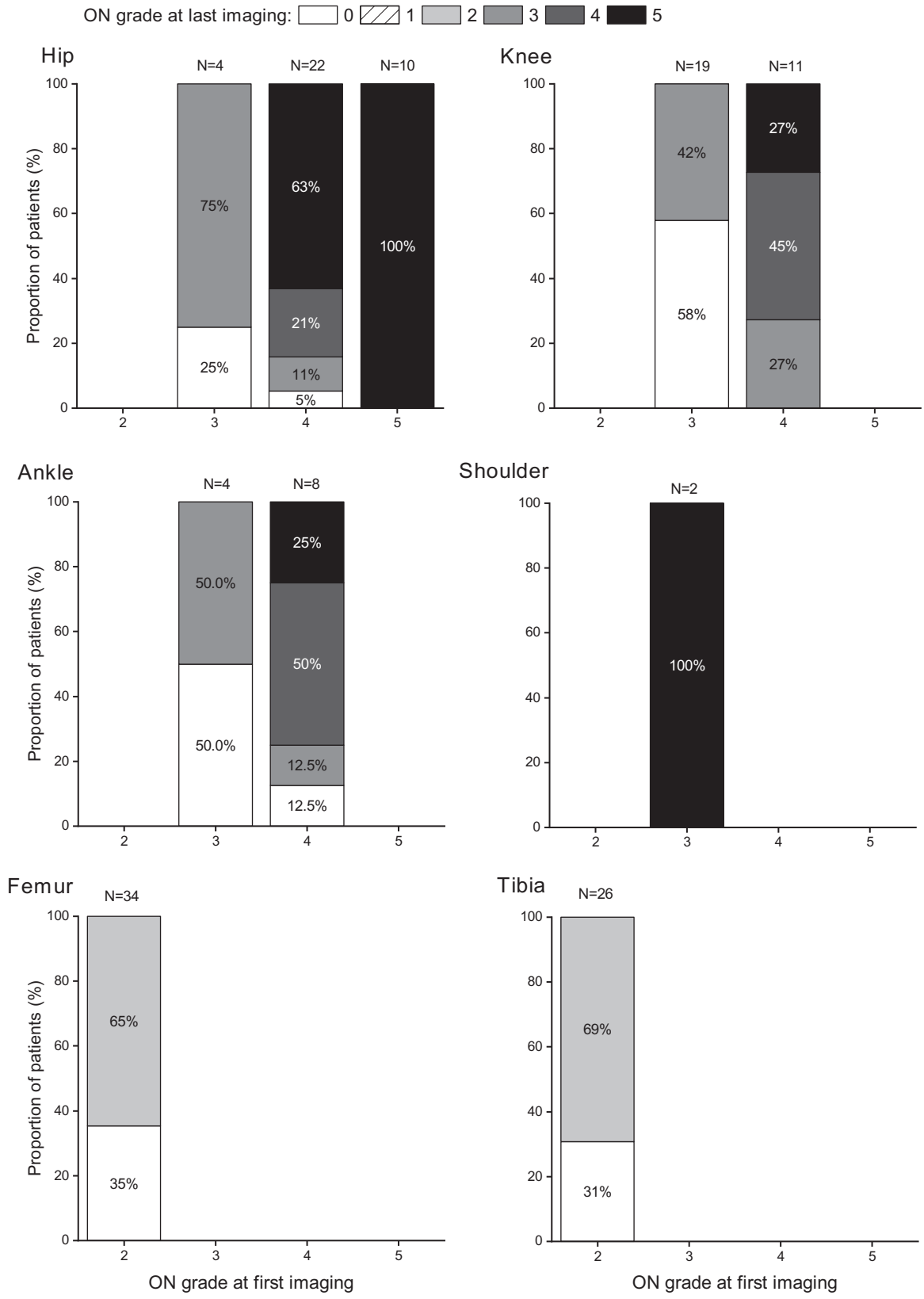

Figure 4. Changes in the ON grades of patients with osteonecrosis at follow-up.

shoulder, but nearly half of those (46%, 6/13) required arthroplasty. A similar finding was reported previously, in adults diagnosed with symptomatic glucocorticoid-induced ONs that were followed for an average of 15 years [25]. In addition, our findings were consistent with those of Miettunen et al., who suggested that shoulder involvement may occur more frequently than previously appreciated [6]. It is important to be aware of possible ONs in the upper

Table 2. Surgical procedures for different grades of osteonecrosis (ON)[a].

	Grade 1 *n* (%)	Grade 2 *n* (%)	Grade 3 *n* (%)	Grade 4 *n* (%)	Grade 5 *n* (%)	Total *n* (%)
All ON lesions	*N* = 8	*N* = 102	*N* = 44	*N* = 29	*N* = 50	*N* = 233
No surgical procedures	8 (100)	102 (100)	40 (91.0)	25 (86.2)	7 (14.0)	182 (78.1)
Total joint arthroplasty			2 (4.5)		38 (76.0)	40 (17.2)
Core decompression			2 (4.5)	3 (10.3)	3 (6.0)	8 (3.4)
Arthroscopy				1 (3.5)	2 (4.0)	3 (1.3)
Hip			*n* = 8	*n* = 11	*n* = 32	*n* = 51
No surgical procedures			6 (75.0)	9 (81.8)	1 (3.1)	16 (31.4)
Total joint arthroplasty			2 (25.0)		31 (96.9)	33 (64.7)
Core decompression				2 (18.2)		2 (3.9)
Knee			*n* = 25	*n* = 9	*n* = 3	*n* = 37
No surgical procedures			23 (92.0)	8 (88.9)		31 (83.8)
Total joint arthroplasty					1 (33.3)	1 (2.7)
Core decompression			2 (8.0)		1 (33.3)	3 (8.1)
Arthroscopy				1 (11.1)	1 (33.3)	2 (5.4)
Ankle		*n* = 1	*n* = 7	*n* = 7	*n* = 3	*n* = 18
No surgical procedures		1 (100)	7 (100)	6 (85.7)	1 (33.3)	15 (83.3)
Core decompression				1 (14.3)	2 (66.7)	3 (16.7)
Shoulder		*n* = 3	*n* = 1	*n*= 0	*n* = 9	*n* = 13
No surgical procedures		3 (100)	1 (100)		3 (33.3)	7 (53.8)
Total joint arthroplasty					6 (66.7)	6 (46.2)
Elbow		*n* = 1	*n* = 2		*n* = 3	*n* = 6
No surgical procedures		1 (100)	2 (100)		2 (66.7)	5 (83.3)
Arthroscopy					1 (33.3)	1 (16.7)

[a]ON grades represent either the grade determined before the surgical procedure or, when surgery was not performed, the most severe grade.

extremities, because lesions in the shoulders, in particular, are at risk of joint collapse, which potentially leads to the need of a TJA.

Osteonecrotic lesions of long bones have frequently been reported in screening studies, but the clinical significance of these lesions has not been established [13]. According to the Niinimäki classification, diaphyseal and metaphyseal lesions are considered grade 1 (non-weight-bearing bone) or grade 2 (weight-bearing bone), regardless of the size of the lesion. In this study, grades 1–2 lesions were common; they represented 47% (110/233) of all lesions. Follow-up images were performed for 59% of grade 2 ON lesions, and of those, 35% in the femur and 31% in the tibia healed.

The resolution of ON lesions was reported first by Ojala et al. [19]. In a screening study by Kawedia et al., 10% (14/141) of ON lesions resolved completely [3] . It has been suggested that it is essential to detect ON lesions early in patients with cancer, to ensure that interventions can be performed in the early phase [26]. However, based on the results of previous studies and this study, we suggest that grades 1–2 lesions will not require a radiological follow-up. Symptomatic patients should be treated with appropriate pain medications and encouraging, supportive physiotherapy, when needed. Re-imaging of grades 1–2 ON lesions should be considered only for clinical reasons; e.g., significant increase in pain or suspicion of etiologies other than ON for pain.

A good classification system should be simple to use, have good reliability and have prognostic clinical value. The Niinimäki classification for ONs in patients with cancer was shown to have good inter- and intra-observer reliability, but its clinical and prognostic values have not been evaluated [14]. In this study, the risk of needing surgery was positively associated with the ON grade. None of the grade 1–2 ON lesions were treated surgically. The proportions of surgeries for ONs were 11% (4/44) in grade 3, 14% (4/29) in grade 4 and 86% (43/50) in grade 5 ON lesions. Based on these results, the Niinimäki classification possesses clinical value and the degree of ON reflects the severity of ON. To evaluate the benefits of surgical and medical interventions, it is essential to use a comprehensive radiological classification.

The main limitation of this study was the heterogeneity of the patient population. In addition, follow-up imaging was not systematic, but only performed on a clinical basis. Therefore, future studies should include a systematic follow-up in more homogeneous study groups (e.g., patients treated for acute lymphoblastic leukemia [ALL]), with a non-joint-specific radiological classification system. Due to the rarity of ONs in patients with cancer, future studies should be planned as multi-center trials with international cooperation. The main strength of this study was the comprehensive electronic hospital databases, which ensured identification of all patients with ON. In addition, patient follow-ups were quite reliable, because the study center was the only hospital in the area that treated patients with cancer and ON. Therefore, we could assume that the electronic medical records were reviewed reliably, including the identification of potential fractures in study patients. Finally, this study was the first study to grade ONs regardless of the site, and to assess the correlation between the ON grade and the risk of requiring a surgical procedure.

It has become increasingly important to raise the awareness of cancer treatment-related adverse effects, such as ON [27]. Guidelines for radiological follow-ups are needed to be able to focus resources on patients that will gain the most benefit. Treating ON symptoms is important, but our findings suggested that no radiological follow-up was needed for grades 1–2 ON lesions, because apparently, the clinical consequences of those lesions were minimal. Despite many attempts to treat ON with drugs, such as bisphosphonates,

lipid-reducing agents, anticoagulants and prostacyclin, no effective medical treatment has been shown to prevent ON progression [28–31]. Because grade 5 ONs (collapse of the joint) require surgery, our findings indicated that intervention studies should particularly focus on grades 3 and 4 ONs.

Disclosure statement

Potential conflict of interest was reported by the authors.

Funding

This study was supported by the Aamu Pediatric Cancer Foundation; Special State Grants for Health Research at Oulu University Hospital; and the Alma and K.A. Snellman Foundation.

References

[1] Padhye B, Dalla-Pozza L, Little D, et al. Incidence and outcome of osteonecrosis in children and adolescents after intensive therapy for acute lymphoblastic leukemia (ALL). Cancer Med. 2016;5:960–967.

[2] Sharma S, Leung WH, Deqing P, et al. Osteonecrosis in children after allogeneic hematopoietic cell transplantation: study of prevalence, risk factors and longitudinal changes using MR imaging. Bone Marrow Transplant. 2012;47:1067–1074.

[3] Kawedia JD, Kaste SC, Pei D, et al. Pharmacokinetic, pharmacodynamic, and pharmacogenetic determinants of osteonecrosis in children with acute lymphoblastic leukemia. Blood. 2011;117:2340–2347.

[4] Arico M, Boccalatte MF, Silvestri D, et al. Osteonecrosis: an emerging complication of intensive chemotherapy for childhood acute lymphoblastic leukemia. Haematologica. 2003;88:747–753.

[5] Borchmann S, Müller H, Haverkamp H, et al. Symptomatic osteonecrosis as a treatment complication in Hodgkin lymphoma: an analysis of the German Hodgkin Study Group (GHSG). Leukemia. 2018;1–8. doi:10.1038/s41375-018-0240-8

[6] Miettunen PM, Lafay-Cousin L, Guilcher GM, et al. Widespread osteonecrosis in children with leukemia revealed by whole-body MRI. Clin Orthop Relat Res. 2012;470:3587–3595.

[7] Assouline-Dayan Y, Chang C, Greenspan A, et al. Pathogenesis and natural history of osteonecrosis. Semin Arthritis Rheum. 2002;32:94–124.

[8] Te Winkel ML, Pieters R, Hope WC, et al. Prospective study on incidence, risk factors, and long-term outcome of osteonecrosis in pediatric acute lymphoblastic leukemia. J Clin Oncol. 2011;29:4143–4150.

[9] Marchese VG, Connolly BH, Able C, et al. Relationship among severity of osteonecrosis, pain, range of motion, and functional mobility in children, adolescents, and young adults with acute lymphoblastic leukemia. Phys Ther. 2008;88:341–350.

[10] Ficat RP, Arlet J. Ischemia and necrosis of bone. Baltimore (MD): Williams & Wilkins; 1980.

[11] Steinberg ME, Brighton CT, Corces A, et al. Osteonecrosis of the femoral head. Results of core decompression and grafting with and without electrical stimulation. Clin Orthop Relat Res. 1989;249:199–208.

[12] ARCO. ARCO (Association Research Circulation Osseous) committee on terminology and classification. ARCO News. 1992;4:41–46.

[13] Niinimäki T, Harila-Saari A, Niinimäki R. The diagnosis and classification of osteonecrosis in patients with childhood leukemia. Pediatr Blood Cancer. 2015;62:198–203.

[14] Niinimäki T, Niinimäki J, Halonen J, et al. The classification of osteonecrosis in patients with cancer: validation of a new radiological classification system. Clin Radiol. 2015;70:1439–1444.

[15] Murphey MD, Foreman KL, Klassen-Fischer MK, et al. From the radiologic archives imaging of osteonecrosis: radiologic-pathologic correlation. Radiographics. 2014;34:1003–1028.

[16] Karimova EJ, Rai SN, Deng X, et al. MRI of knee osteonecrosis in children with leukemia and lymphoma: part I, observer agreement. Am J Roetgenol. 2006;186:470–476.

[17] Meixel A, Hauswald H, Delorme S, et al. From radiation osteitis to osteoradionecrosis: incidence and MR morphology of radiation-induced sacral pathologies following pelvic radiotherapy. Eur Radiol. 2018;28:3550–3559.

[18] Theruvath AJ, Sukerkar PA, Bao S, et al. Bone marrow oedema predicts bone collapse in paediatric and adolescent leukaemia patients with corticosteroid-induced osteonecrosis. Eur Radiol. 2018;28:410–417.

[19] Ojala AE, Paakko E, Lanning FP, et al. Osteonecrosis during the treatment of childhood acute lymphoblastic leukemia: a prospective MRI study. Med Pediatr Oncol. 1999;32:11–17.

[20] Zurlo JV. The double-line sign. Radiology. 1999;212:541–542.

[21] Karimova EJ, Kaste S. MR imaging of osteonecrosis of the knee in children with acute lymphocytic leukemia. Pediatr Radiol. 2007;37:1140–1146.

[22] Karimova EJ, Rai SN, Ingle D, et al. MRI of knee osteonecrosis in children with leukemia and lymphoma: part 2, clinical and imaging patterns. AJR Am J Roentgenol. 2006;186:477–482.

[23] Kaste SC, Pei D, Cheng C, et al. Utility of early screening magnetic resonance imaging for extensive hip osteonecrosis in pediatric patients treated with glucocorticoids. J Clin Oncol. 2015;33:610–615.

[24] Kaste SC, DeFeo BM, Neel MD, et al. Osteonecrosis of the shoulders in pediatric patients treated for leukemia or lymphoma: single-institutional experience. J Pediatr Orthop. 2019;33:104–110.

[25] Flouzat-Lachaniette CH, Roubineau F, Heyberger C, et al. Multifocal osteonecrosis related to corticosteroid: ten years later, risk of progression and observation of subsequent new osteonecrosis. Int Orthop. 2016;40:669–672.

[26] Kaste SC, Karimova EJ, Neel MD. Osteonecrosis in children after therapy for malignancy. AJR Am J Roentgenol. 2011;196:1011–1018.

[27] Oeffinger KC, Mertens AC, Sklar CA, et al. Chronic health conditions in adult survivors of childhood cancer. N Engl J Med. 2006;355:1572–1582.

[28] Leblicq C, Laverdiere C, Decarie JC, et al. Effectiveness of pamidronate as treatment of symptomatic osteonecrosis occurring in children treated for acute lymphoblastic leukemia. Pediatr Blood Cancer. 2013;60:741–747.

[29] Pritchett JW. Statin therapy decreases the risk of osteonecrosis in patients receiving steroids. Clin Orthop Relat Res. 2001;386:173–178.

[30] Glueck CJ, Freiberg RA, Sieve L, et al. Enoxaparin prevents progression of stages I and II osteonecrosis of the hip. Clin Orthop Relat Res. 2005;435:164–170.

[31] Disch AC, Matziolis G, Perka C. The management of necrosis-associated and idiopathic bone-marrow oedema of the proximal femur by intravenous iloprost. J Bone Joint Surg Br. 2005;87:560–564.