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ORIGINAL PAPER

Paediatrics

Radiological follow-up of osteonecrosis lesions in children and adolescents with Hodgkin lymphoma

Henri Aarnivala[1,2] | Mia Giertz[3,4] | Sascha Wilk Michelsen[5] | Caroline Björklund[6] | Annika Englund[3,4] | Marika Grönroos[7] | Lisa Lyngsie Hjalgrim[5] | Pasi Huttunen[8] | Tuukka Niinimäki[2,9] | Eva Penno[10] | Tytti Pokka[11] | Tuuli Pöyhönen[12] | Päivi Raittinen[13] | Susanna Ranta[14,15] | Johan E. Svahn[16] | Lisa Törnudd[17] | Arja Harila[4] | Riitta Niinimäki[1,2]

Correspondence
Henri Aarnivala, Department of Pediatrics, Oulu University Hospital, Oulu, Finland.
Email: henri.aarnivala@oulu.fi

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Summary
Osteonecrosis (ON) is a common complication of glucocorticoid-based Hodgkin lymphoma (HL) treatment, but the natural evolution and prognosis of ON lesions remain poorly understood. We describe the radiological evolution of ON lesions identified in a Nordic population-based cohort of paediatric HL patients. Magnetic resonance images of suspected ON lesions were centrally reviewed to confirm ON diagnosis and grade the ON lesions according to the Niinimäki classification. The study included 202 ON lesions in 46 patients, of which 77 were joint lesions. Follow-up images were available for 146/202 lesions, with a mean follow-up time of 28 months. During follow-up, 71% of the lesions remained stable, 26% improved or resolved, and 3% progressed. A higher ON grade at diagnosis was associated with a lower likelihood of spontaneous resolution. The likelihood for resolution of ON decreased by 50% for each year of added patient age, when adjusted for sex, ON location, and symptoms. Hip ON showed less spontaneous improvement compared with other joints, and the risk for surgery was 13-fold in hip ON. Grades 3–4 joint ON has the potential to either progress or resolve, warranting follow-up in patients with severe symptoms. Research on secondary prevention should be directed at grade 3–4 joint ON.

KEYWORDS
avascular necrosis, Hodgkin lymphoma, osteonecrosis, paediatric

INTRODUCTION

Osteonecrosis (ON) is regarded as one of the major late toxicities of childhood acute lymphoblastic leukaemia (ALL) therapy, attributed to treatment, especially with steroids.[1–4] Glucocorticoid-based treatment in patients with other malignancies also carries a risk for ON, especially in Hodgkin lymphoma (HL).[5,6] In adult patients with HL, incidence rates for ON range from 1%, in registry studies only considering operated hip ON, to 42% in

Abbreviations: ALL, acute lymphoblastic leukaemia; CI, confidence interval; GEE, generalised estimating equations; HL, Hodgkin lymphoma; ICD-10, International Classification of Diseases Tenth Revision; IQR, interquartile range; MRI, magnetic resonance imaging; ON, osteonecrosis; OR, odds ratio; SD, standard deviation; TJA, total joint arthroplasty.

Henri Aarnivala and Mia Giertz contributed equally.

For affiliations refer to page 8.

patients screened for ON with magnetic resonance imaging (MRI).[7,8] Yet, little is known about the natural evolution of ON lesions. ON progression to joint collapse is feared, but spontaneous resolution also occurs.[9] Identifying patient-related and radiographic risk factors for progression to joint destruction would aid in implementing preventive treatment strategies.

Niinimäki et al. introduced a non-joint-specific classification for ON suitable for addressing any ON lesion at any anatomical site, which is crucial in the often multifocal nature of ON in cancer patients.[10] In a radiological follow-up study of 54 cancer patients with various malignancies, Niinimäki et al. suggested grades 3–4 ON to have high priority regarding follow-up, due to the risk of progression to joint collapse.[5] Recently, Brivio et al. studied the evolution of ON in paediatric ALL patients and found ON lesions with a higher Niinimäki grade to have an inferior prognosis, and joint lesions especially on the convex hip and knee joint surfaces often demonstrated progression.[11] Factors impacting the prognosis of ON lesions are underexplored, and the prognosis of ON in children with HL is not known.

The aims of this study were to describe the radiographic trajectories of ON lesions over time in a cohort of patients with paediatric HL and ON and to identify clinical and radiographic risk factors associated with adverse outcomes of ON.

PATIENTS AND METHODS

Patients

The inclusion criteria for the study were HL diagnosed between 2005 and 2019 in Sweden, Denmark or Finland, age under 18 years at diagnosis of HL, and ON diagnosed during or following chemotherapy for HL. The patients were identified from a national childhood cancer registry (Sweden, Denmark) and hospital patient records (Finland) based on the *International Classification of Diseases, Tenth Revision* (ICD-10) code for HL (C81). Patient medical records and imaging studies were reviewed for entries on ON. A total of 51 HL patients with suspected ON and available MRI scans were identified. Five of these patients did not fulfil the radiographic criteria for ON used in this study, and their MRI findings were considered to represent bone marrow oedema. Thus, the final cohort consisted of 46 HL patients with ON.

Radiological diagnosis and grading of ON

Magnetic resonance imaging was used to diagnose ON in all cases, with the established definition of ON as a circumscribed lesion with a distinct rim of low signal intensity on T1-weighted images (band sign) and high-signal intensity on short tau inversion recovery images (double-line sign).[12] All MRI scans of the ON lesions were centrally reviewed by a paediatric radiologist (E.P.) and an orthopaedic surgeon (T.N.). The reviewers studied all MRI scans independently and were blinded to patient data other than the MRI scans.

The Niinimäki classification (Table S1) was applied to grade the severity of the ON lesions.[10] After the initial review, all cases with discrepant grades were re-reviewed and discussed to reach a final consensus on the grades. An ON lesion was considered healed (grade 0) when it had diminished so that it could not be diagnosed as ON according to the criteria defined above, without relying on previous MRI scans. In the present study, a joint affected by ON was considered a single site as defined in the Niinimäki classification, rather than counting opposing joint surfaces as different sites as in Brivio et al.[11] However, we compared the prognosis of ON lesions involving convex surfaces against lesions involving concave surfaces as well.

OriginPro 2021 (OriginLab, Northampton, MA, USA) was used to produce the figures, and IBM SPSS Statistics for Windows, version 27.0 (IBM Corp, Armonk, NY, USA) was used for data processing and statistical analyses. Cohen's kappa was used to evaluate inter-rater agreement, and χ^2, Fisher's exact test, and Student's *t*-test to compare groups. Considering that there were multiple ON lesions in many of the patients, the generalised estimating equation (GEE) technique was used to assess the effects of ON location, age, sex, and pain due to ON on the prognosis of ON lesions.

RESULTS

The background characteristics of the patient cohort as well as details regarding HL stage and therapy are shown in Table 1, and details on the chemotherapy protocols can be found in Table S2. Of the 46 patients, 40 (87%) had multifocal ON lesions, and 30 (65%) experienced symptoms due to ON lesions. The remaining patients were diagnosed with ON incidentally during routine MRI follow-up for HL. A total of 202 ON lesions in the 46 patients were assessed, with a median of six (range 1–16, interquartile range [IQR] 4–9) affected sites per patient. Inter-rater agreement between the two reviewers regarding ON grades was good with a kappa value of 0.79 ($p < 0.001$; standard error of kappa 0.04), which is in the range of previous reports on the Niinimäki scale.[10]

ON sites

The frequency of ON lesions at different anatomic locations is shown in Figure 1. The most common joint sites for ON were knee ($n = 36$) and hip ($n = 31$), and the most common sites in general were femur ($n = 53$) and tibia ($n = 42$). Weight-bearing joints were affected by 70 (35%) lesions and non-weight-bearing joints by seven (3%) lesions. Of the 77 joint lesions, 68 (88%) affected the same anatomic site on both the left and the right sides. Patients with joint lesions were symptomatic in 21 out of 26 (81%) cases, whereas patients with only non-joint ON were symptomatic in 9 out of 20 (45%) cases. At initial ON diagnosis, 2 (1%) of the ON lesions (both

TABLE 1 Background characteristics and details regarding the 46 Hodgkin lymphoma patients with osteonecrosis.

	Values expressed as *n* (%) unless stated otherwise	
Female	29 (63)	
Mean age at HL diagnosis, years		15.2 (SD 1.8, range 9.6–17.9)
Prepubertal at HL diagnosis	5 (11)	
Overweight at HL diagnosis[a]	11 (31)	
Overweight at ON diagnosis[a,b]	16 (44)	
Stage of HL		
I	0 (0)	
II	18 (39)	
III	12 (26)	
IV	16 (35)	
Subtype of HL		
Classical	46 (100)	
Lymphocyte predominant	0 (0)	
HL treatment protocol		
GPOH-HD95	4 (9)	
EuroNet-PHL-C1	33 (72)	
EuroNet-PHL Interim Guidelines	3 (7)	
EuroNet-PHL-C2	6 (13)	
Treatment group		
TG-1/TL-1	6 (13)	
TG-2/TL-2	15 (33)	
TG-3/TL-3	25 (54)	
Mean cumulative dose of prednisolone, mg/m^2		3500 (SD 980, range 0–6600)
Received radiotherapy	17 (37)	
Median time to ON from HL diagnosis, months		8 (IQR 5–15, range 0–124)
ON developed during chemotherapy[b,c]	16 (36)	
Symptoms due to ON	30 (65)	
Multifocal ON	40 (87)	
Median number of sites affected with ON		6 (IQR 4–9, range 0–16)
Median follow-up time after first ON, months		13 (IQR 0–35, range 0–59)
Alive at last follow-up	45 (98)	

Abbreviations: HL, Hodgkin lymphoma; IQR, interquartile range; ON, osteonecrosis; SD, standard deviation.

[a]ISO-BMI >25 kg/m^2.

[b]Numbers may not add up due to missing data.

[c]During chemotherapy, or within three months after cessation chemotherapy.

hip) were already grade 5, 29 (14%) were grade 4, 45 (22%) were grade 3, 111 (55%) were grade 2, and 15 (7%) were grade 1. The distribution of ON lesions across anatomic sites did not differ significantly between asymptomatic and symptomatic patients. In total, 39% of grade 1 lesions, 32% of grade 2 lesions, 28% of grade 3 lesions, 27% of grade 4 lesions, and 0% of grade 5 lesions were identified in completely asymptomatic patients as incidental MRI findings.

Changes in ON lesions over time

Follow-up MRI scans were available for 146 (72%) of the ON lesions, with a mean follow-up time of 28 (standard deviation [SD] 21, range 1–96) months from ON diagnosis. The outcomes of these ON lesions in relation to ON grade at initial diagnosis regardless of ON site are given in Table 2, and ON grades at initial diagnosis and last follow-up grouped by ON site are given in Table 3. All three progressive lesions in the cohort were ON of the hip. On the other hand, 31% of hip lesions improved or resolved completely. ON of the knee improved or resolved in 48% of cases, whilst ankle and shoulder lesions both showed improvement in 50% of cases, although the numbers were small. The trajectories in ON of the hip and knee lesions are depicted in Figure 2. Diaphyseal and metaphyseal lesions were more quiescent in nature than joint lesions, as only 12% of femoral, 28% of tibial, and 15% of humeral lesions resolved completely, whilst the rest

remained unchanged. No pathological fractures related to diaphyseal or metaphyseal ON were identified.

Regarding joint ON, just one of the 77 affected joints demonstrated ON involving only a concave surface (knee lesion), whilst 16 joints involved both concave and convex surfaces, and 60 joints only showed involvement of convex surfaces. Follow-up images were available for 12 lesions involving concave and 52 lesions involving convex surfaces. Univariate analyses indicated a favourable prognosis for ON involving concave joint surfaces. In all, 10 of the 12 lesions involving concave surfaces improved, compared with 23 out of the 52 lesions involving convex surfaces (83% vs. 44%, $p < 0.05$); 6 of the 12 lesions involving concave surfaces resolved completely, compared with 8 of the 52 lesions involving convex surfaces (50% vs. 15%, $p < 0.05$). All completely resolved ON lesions involving concave surfaces were knee (tibial plateau) lesions. All progressive ON lesions involved the femoral head.

The mean time to radiological progression of ON was 9 (SD 4, range 4–12) months, which in all three cases equalled hip ON progressing to grade 5 (i.e. joint collapse). Two of the three progressive lesions were diagnosed during chemotherapy, although joint collapse occurred after cessation of chemotherapy. In the 43 ON lesions that resolved, improvement could be seen until a median of 16 (IQR 9–24, range 3–80) months from initial ON diagnosis.

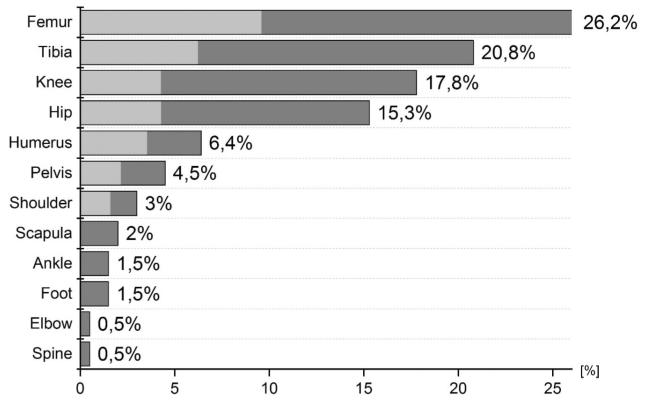

FIGURE 1 The relative proportions of all osteonecrosis (ON) lesions across different sites. The proportions of ON lesions found in completely asymptomatic patients are shown in light grey.

Factors influencing the prognosis of ON

To assess the effects of sex, age, ON location (joint or non-joint), and pain on the odds of spontaneous improvement and complete resolution of ON, GEE models were constructed (Table 4). The models indicated a roughly 50% decrease in the odds of both improvement to a lower grade and spontaneous complete resolution of ON for each added year of age at HL diagnosis. ON lesions were also less likely to improve to a lower grade if the patient was symptomatic due to ON. All three progressive ON lesions were hip lesions in female patients, but with such small numbers, it was not possible to perform any formal risk factor analysis regarding ON progression.

Interventions due to symptomatic ON

All interventions were performed due to symptomatic joint ON. A total of 10 lesions in six patients were treated surgically, including all five grade 5 lesions, as described in Table 5. Nine of the 10 interventions were due to hip ON, and 29% of hip ON lesions were treated operatively. The risk for undergoing surgery was 13-fold in hip ON lesions compared with other joint ON lesions ($p < 0.001$). Eight of the 10 surgical procedures were performed in female patients. The sole male patient undergoing surgery for bilateral hip ON also had a history of allogeneic haematopoietic stem cell transplantation prior to HL diagnosis.

Weight-bearing restrictions were ordered for eight out of 17 patients with symptomatic joint ON in weight-bearing joints, but ON lesions in these patients were less likely to improve spontaneously (11% vs. 59%, $p < 0.01$) and more often progressed to joint collapse (16% vs. 0%, $p = 0.08$) than lesions in patients without restrictions. The distribution of ON sites and grades at diagnosis were similar in both groups (Table S3). Bisphosphonates were given to five patients for pain relief, but the proportion of ON lesions improving was higher in symptomatic patients not receiving BP (24% vs. 14%, $p = 0.21$). Corticosteroid therapy was discontinued in two patients due to symptomatic hip ON during chemotherapy. Both patients eventually suffered femoral head collapse requiring total joint arthroplasty (TJA).

TABLE 2 Evolution of ON lesions with follow-up MRI scans available over a follow-up period of mean 28 months in relation to initial ON grade.

	ON grade at initial diagnosis				
Evolution	**Grade 1 ($N = 15$)**	**Grade 2 ($N = 76$)**	**Grade 3 ($N = 32$)**	**Grade 4 ($N = 22$)**	**Grade 5 ($N = 1$)**
Progressed	N/A	0%	1 (3%)	2 (9%)	N/A
Stable	13 (87%)	61 (80%)	22 (69%)	6 (27%)	1 (100%)
Improved to lower grade	N/A	N/A	0%	9 (42%)	0%
Resolved completely	2 (13%)	15 (20%)	9 (28%)	5 (21%)	0%

Abbreviations: MRI, magnetic resonance imaging; N/A, not applicable; ON, osteonecrosis.

TABLE 3 Numbers (*n*/*n*) of ON lesions with each Niinimäki grade at initial diagnosis (left *n*-value) and last follow-up (right *n*-value) grouped by anatomic site for the 146 lesions with available follow-up MRI scans.

	Location of ON lesion										
ON grade	Hip (*N* = 23)	Femur (*N* = 34)	Knee (*N* = 25)	Tibia (*N* = 29)	Ankle (*N* = 2)	Shoulder (*N* = 6)	Humerus (*N* = 13)	Foot (*N* = 2)	Pelvis (*N* = 7)	Scapula (*N* = 4)	Spine (*N* = 1)
Grade 5	1/4	-	-	-	-	-	-	-	-	-	-
Grade 4	13/5	-	6/1	-	2/1	-	-	-	-	-	1/0
Grade 3	9/9	-	19/20	-	0/1	2/0	-	-	2/1	-	-
Grade 2	-	34/30	-	29/21	-	4/5	-	2/2	5/5	2/2	-
Grade 1	-	-	-	-	-	-	13/11	-	-	2/2	-
Grade 0 (No ON)	0/5	0/4	0/4	0/8	-	0/1	0/2	-	0/1	-	0/1

Abbreviations: MRI, magnetic resonance imaging; ON, osteonecrosis.

DISCUSSION

This study describes the natural evolution of ON in a Nordic cohort of patients with paediatric HL diagnosed between 2005 and 2019. Although 71% of all ON lesions remained unchanged, almost half of the joint lesions improved, which is of particular interest, considering that joint ON lesions generally are symptomatic and hence clinically relevant lesions. However, hip ON had an inferior potential for spontaneous recovery, with less than a third improving over time.

The study may underestimate the spontaneous healing potential of ON lesions due to the limited follow-up time and imaging performed mainly on clinical grounds. However, as joint lesions are often symptomatic and thus have several follow-up scans available, the underestimation concerns mainly the non-joint lesions. Indeed, Niinimäki et al. reported higher rates of spontaneous resolution for tibial and femoral lesions in cancer patients with a longer follow-up time, although their rates for joint ON lesions improving were much in line with the present results.[5] The relatively short follow-up time may also lead to underestimation of the need for surgical intervention, which may take place years after the initial development of ON. Furthermore, young patients with ON may benefit from delaying TJA until after growth cessation to minimise issues like leg length discrepancies and technical difficulties with the procedure.[13]

Hip ON was the most severe condition with the highest potential for progression, and with grade 5 lesions being exclusively located in the hip. With the exception of one knee lesion, all surgical procedures in the cohort were due to hip ON, including all TJA, which is in accordance with the literature.[6,8,14,15] However, as TJA of the hip generally yields a better functional outcome and fewer residual symptoms than, for example, TJA of the knee, the threshold for surgical intervention differs depending on the affected joint.[16] An example of the inherent difference between hip ON and ON at other joints is a patient in the present study, with 16 ON lesions observed over a 4-year follow-up: although lesions at other locations, including other joints, showed improvement and even complete resolution, her hip ON lesions progressed to joint collapse. This underscores the unfavourable prognosis and high priority of hip ON regarding possible primary and secondary preventive measures.[17]

Brivio et al. reported a better radiological outcome for ON affecting concave joint surfaces compared with convex surfaces in children with ALL.[11] Our findings support this, although our study had a lower proportion of ON lesions affecting concave surfaces. Furthermore, the numbers of ON lesions detected by Brivio et al. are not directly comparable to our results, as an affected joint was considered a single ON site in our study, even when several surfaces within the same joint were affected. Since just one ON lesion affecting a concave joint surface in the absence of ON affecting the adjacent convex joint surface was found in the present study, we deemed it appropriate to consider the whole joint as a single site. The few identified ON lesions involving concave surfaces did show a

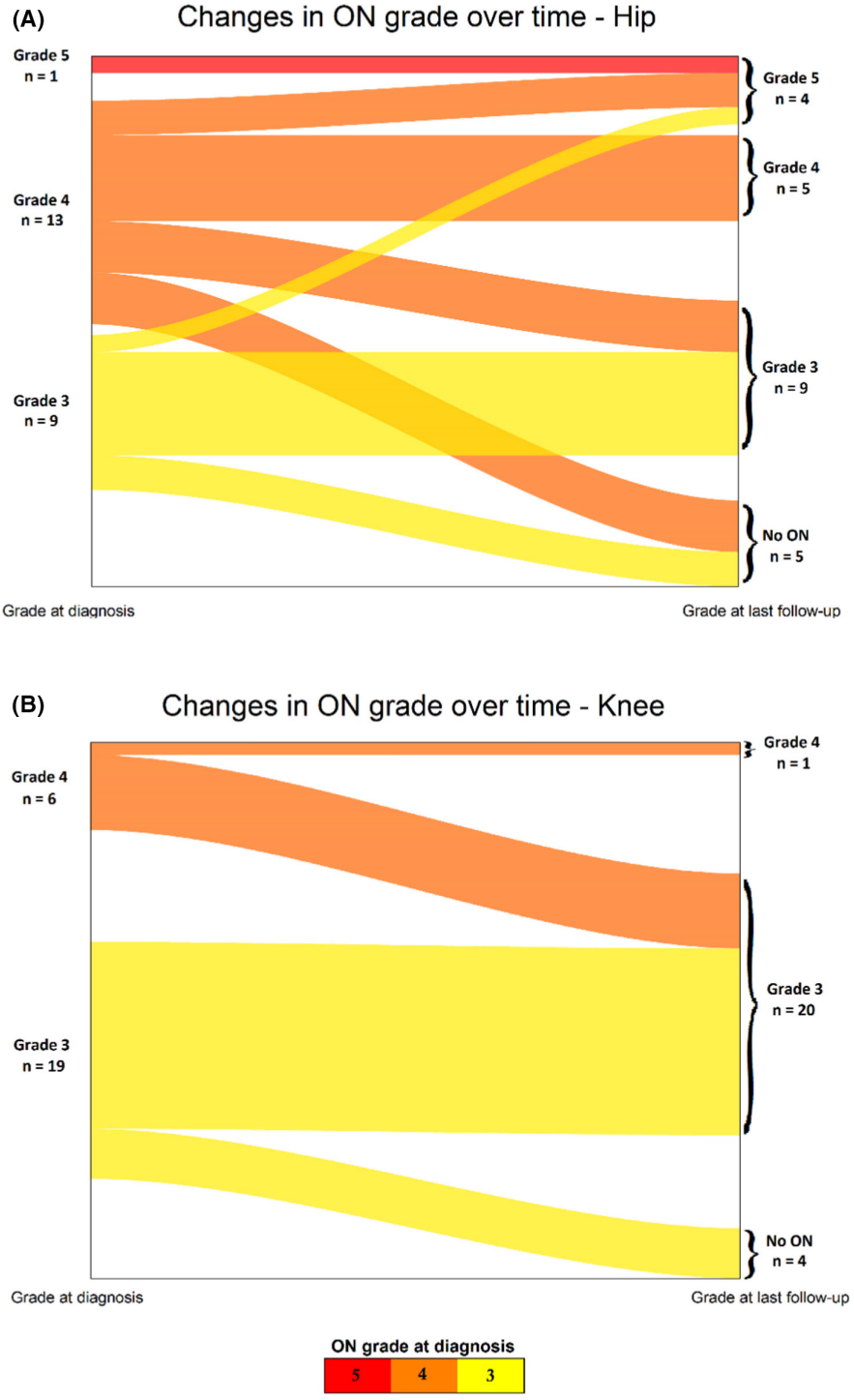

FIGURE 2 Changes in the Niinimäki grade of the hip (A) and knee (B) osteonecrosis (ON) lesions from diagnosis to last follow-up. Colours indicate ON grade at initial diagnosis: Red = grade 5; orange = grade 4; yellow = grade 3.

more favourable prognosis in the present study as well, especially in the knee.

There was a strong correlation between the Niinimäki grade and clinical outcome of ON, regarding both spontaneous resolution and surgical intervention, which is a surrogate for severe symptoms. The inter-rater reliability was excellent, supporting the usability of this classification for both clinical and research purposes. All studies on ON should use a validated radiological classification to make the results comparable and transparent. The clinical use of the Niinimäki radiological classification is also justified because, as demonstrated by this study, prognoses for ON lesions vary even within the same anatomic site. Based on the current findings, grades 1–2 lesions have no need for routine follow-up. This conclusion is based on the favourable prognosis of these lesions and the lack of pathological fractures

TABLE 4 Generalised estimating equations models of risk factors for lack of spontaneous improvement (left model) and full resolution (right model) of an osteonecrosis (ON) lesion.

	Spontaneous improvement			Spontaneous full resolution		
Factor	**OR**	**95% Confidence interval**	***p***	**OR**	**95% Confidence interval**	***p***
Patient age at HL diagnosis	1.92	1.28–3.13	<0.01	1.96	1.25–3.33	<0.01
Female sex	4.55	0.87–25.00	0.07	7.69	0.68–90.91	0.09
Pain due to ON	4.35	1.67–11.10	<0.01	4.17	0.85–20.00	0.08
Non-joint ON location	5.26	1.37–20.00	<0.05	1.67	0.44–6.25	0.46

Abbreviations: ON, osteonecrosis; OR, odds ratio.

TABLE 5 Surgical interventions due to joint ON lesions.

	Severity of joint ON lesion[a]				
	Grade 5	**Grade 4**	**Grade 3**	**Grade 2**	**Total**
All joint ON lesions	*N* = 5	*N* = 28	*N* = 39	*N* = 5	*N* = 77
No surgery	-	26 (93)	36 (92)	5 (100)	67 (87)
Total joint arthroplasty	5 (100)	2 (7)	1 (3)	-	8 (10)
Core decompression	-	-	1 (3)	-	1 (1)
Arthroscopy	-	-	1 (3)	-	1 (1)
Hip ON	*n* = 5	*n* = 16	*n* = 10	-	*n* = 31
No surgery	-	14 (87)	8 (80)	-	22 (71)
Total joint arthroplasty	5 (100)	2 (13)	1 (10)	-	8 (26)
Core decompression	-	-	1 (10)	-	1 (3)
Knee ON	-	*n* = 9	*n* = 27	-	*n* = 36
No surgery	-	9 (100)	26 (96)	-	35 (97)
Arthroscopy	-	-	1 (4)	-	1 (3)
Other joint ON	-	*n* = 3	*n* = 2	*n* = 5	*n* = 10
No surgery	-	3 (100)	2 (100)	5 (100)	10 (100)

Note: Values expressed as *n* (%).

Abbreviation: ON, osteonecrosis.

[a]ON grades represent either the grade at the time of surgery or, when surgery was not performed, the most severe grade.

associated with diaphyseal and metaphyseal ON, as reported in other studies.[5,11] Furthermore, our results speak against routine weight-bearing restrictions as an attempt to prevent ON progression or pathological fractures—a finding that could be explained by decreasing muscle strength and bone mineral density secondary to immobilisation. However, weight-bearing restrictions are sometimes recommended for pain relief in some of the participating centres, which could result in a higher proportion of patients with severe symptoms in the group with weight-bearing restrictions, possibly biasing this group towards a worse outcome.

Grades 3–4 lesions merit particular attention considering MRI follow-up, as they carry the highest risk of progression. As long as effective options for preventing ON progression are lacking, follow-up MRI scans should be reserved for patients with grades 3–4 ON and severe symptoms, or symptoms worsening over time. A reasonable interval for monitoring progression could be 6–12 months. Possible treatment studies should focus on grades 3–4 ON lesions, considering both the affected joint and possibly the joint surface shape in patient stratification. The correlation between symptoms and the shape of the involved joint surface requires further investigation, but if ON lesions on concave surfaces truly cause fewer clinical symptoms, revising the Niinimäki radiological classification to consider joint surface shape is warranted. As joints with grade 5 ON have a low potential for recovery, there is little benefit from radiological follow-up, and early referral to an orthopaedic surgeon for is encouraged for considering operative treatment.

The time to progression of ON lesions was measured in months; thus, the window of opportunity for timely secondary prevention is short. However, a third of the patients developed ON during chemotherapy for HL, which would enable modifications to chemotherapy plans if symptomatic ON develops. Evidence on modifications to HL chemotherapy due to symptomatic ON is lacking, but considering the benefit from shortening the administration of dexamethasone in paediatric ALL,[18] reducing

or shortening glucocorticoid treatment or switching to glucocorticoid-free chemotherapy could be considered, as ON in HL patients is glucocorticoid-induced. This could be feasible if symptomatic ON develops early during chemotherapy, as these patients probably are at risk of developing further ON lesions. In literature, several medical treatments to prevent ON progression have been suggested, including bisphosphonates, lipid-reducing agents, and anticoagulants. However, there are few studies on such treatments, and evidence does not currently support their effectiveness.[17,19–22]

Considering the short interval for potential secondary prevention as well as the lack of effective alternatives, primary prevention appears more feasible. Nevertheless, trials on primary prevention of ON in children with cancer are lacking. Contemporary paediatric HL and ALL protocols will investigate the incidence of ON, but to the authors' knowledge, there are no ongoing trials with ON development as a primary outcome.[23,24] As paediatric HL has an exceptionally favourable prognosis, minimising the burden of toxicity is a priority.[23] Reducing glucocorticoid dose or the duration of glucocorticoid administration would be relevant questions for a randomised trial.

The strengths of this study include the cohort size, the systematic centralised review of all MRI scans, and the systematic registration of all cases of ON rather than relying on reported ICD-10 codes (M87) for ON. The limitations include MRI imaging performed only on clinical grounds, leading to inconsistent numbers of follow-up MRI scans and varying follow-up times. Furthermore, due to the retrospective nature of the study, it was not always possible to distinguish which lesions in patients with multiple ON lesions were or were not symptomatic, which precluded some statistical analyses of interest. Additionally, as the ON lesions in the study had been diagnosed by various clinicians in several centres with different vigilance for performing MRI, the radiological follow-up on the evolution of ON lesions began at variable timepoints in relation to their actual development. Nevertheless, as all cases of ON had been identified in the clinic without systematic screening, the present results on the evolutionary trajectories for ON are generalisable to the population of paediatric patients with HL, treated with steroid-based chemotherapy.

CONCLUSIONS

Osteonecrosis lesions in paediatric HL patients display significant spontaneous healing potential, but hip ON is a cause of high morbidity. An initial watch-and-wait strategy is reasonable for Niinimäki grade 3–4 lesions, especially in the knee. For patients with painful grade 5 ON, early referral for considering operative treatment is warranted. MRI should always be used for diagnosing or excluding ON, and use of the Niinimäki grading system may aid in both clinical decision-making and follow-up.

AUTHOR CONTRIBUTIONS

Study conception and design: HA, MGi, SWM, AE, LLH, AH, RN. *Data collection*: HA, MGi, SWM, CB, MGr, LLH, PH, TPö, PR, SR, JES, LT. *Review of MRI scans*: TN and EP. *Statistical analysis*: TPo, HA, MGi. *Analysis and interpretation of results*: HA, TPo, RN, MGi, AE, AH. *Draft manuscript preparation*: HA, MGi, RN. HA and MGi contributed equally to the work. All authors reviewed the results, revised the article critically and approved the final version of the manuscript.

AFFILIATIONS

[1]Department of Pediatrics, Oulu University Hospital, Oulu, Finland
[2]Research Unit of Clinical Medicine, University of Oulu, Oulu, Finland
[3]Department of Pediatric Oncology and Hematology, Uppsala University Hospital, Uppsala, Sweden
[4]Department of Women's and Children's Health, Uppsala University, Uppsala, Sweden
[5]Department of Pediatric and Adolescence Medicine, Clinic for Pediatric Oncology and Hematology, University Hospital Rigshospitalet, Copenhagen, Denmark
[6]Department of Pediatric Hematology and Oncology, Umeå University Hospital, Umeå, Sweden
[7]Department of Pediatrics, Turku University Hospital, Turku, Finland
[8]Department of Pediatric Hematology, Oncology and Stem Cell Transplantation, New Children's Hospital, Helsinki University Hospital, Helsinki, Finland
[9]Department of Surgery, Oulu University Hospital, Oulu, Finland
[10]Department of Diagnostic Radiology, Uppsala University Hospital, Uppsala, Sweden
[11]Research Service Unit, Oulu University Hospital, Oulu, Finland
[12]Department of Pediatrics, Kuopio University Hospital, Kuopio, Finland
[13]Centre for Child Health Research, Tampere University and University Hospital, Tampere, Finland
[14]Astrid Lindgren Children's Hospital, Karolinska University Hospital, Stockholm, Sweden
[15]Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden
[16]Department of Pediatric Oncology, Skåne University Hospital, Lund University, Lund, Sweden
[17]Department of Pediatrics, Linköping University Hospital, Linköping, Sweden

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CONFLICT OF INTEREST STATEMENT

The authors declare no financial conflicts of interest.

DATA AVAILABILITY STATEMENT

Data is not available due to legal restrictions.

ETHICS APPROVAL STATEMENT

The study was approved by the National Ethical Committee in each country before the start of data collection. As this was a registry study, the need for informed consent was waived. The study adheres to the principles of the Declaration of Helsinki.

PATIENT CONSENT STATEMENT

Not applicable, as this was a retrospective study.

ORCID

Henri Aarnivala https://orcid.org/0000-0002-2025-3676
Sascha Wilk Michelsen https://orcid.org/0000-0002-6499-8581
Caroline Björklund https://orcid.org/0000-0001-8281-526X
Marika Grönroos https://orcid.org/0000-0002-5729-0059
Lisa Lyngsie Hjalgrim https://orcid.org/0000-0001-5186-3365
Pasi Huttunen https://orcid.org/0000-0002-0731-1245
Tytti Pokka https://orcid.org/0000-0001-5488-5885
Susanna Ranta https://orcid.org/0000-0001-7854-0371
Arja Harila https://orcid.org/0000-0003-2767-5828

TWITTER

Riitta Niinimäki RiittaNiinimki

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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