Riitta Niinimäki

OSTEONECROSIS IN CHILDREN, ADOLESCENTS AND YOUNG ADULTS TREATED FOR CANCER
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University of Oulu Graduate School; University of Oulu, Faculty of Medicine, Institute of Clinical Medicine, Department of Paediatrics; Oulu University Hospital
University of Oulu, P.O. Box 8000, FI-90014 University of Oulu, Finland

Abstract

Treatment-related late effects have increasingly become important, since the majority of children, adolescents and young adults with cancer become long-term survivors. Osteonecrosis (ON) is recognized as a potential debilitating sequel in patients with cancer.

The aims of this work were to define the incidence of and clinical risk factors for ON identified with end-of-therapy magnetic resonance imaging (MRI) screening among patients with childhood cancer and to investigate the incidence of and risk factors for ON requiring total joint arthroplasty (TJA) in patients treated for cancer in childhood, adolescence or young adulthood in a register-based study.

MRI of the lower extremities revealed ON in 23 (24%) of the 97 patients with acute lymphoblastic leukemia (ALL) at the end of treatment. High body mass index, female gender, older age at diagnosis, and higher cumulative dexamethasone dose were independent risk factors for ON. Six of the 32 patients (19%) treated for lymphoma or solid tumor had ON in MRI scans at the end of the treatment. All of these patients with ON had non-Hodgkin lymphoma or Hodgkin lymphoma.

In a register-based study, patients diagnosed with cancer before 31 years of age were identified from the Finnish and Danish Cancer registries. These data were combined with data from the National Hospital Discharge and the Finnish Arthroplasty registers. The cohort consisted of 6,358 patients diagnosed with hematologic malignancy and 18,542 patients diagnosed with solid tumor from 1975 to 2000 in Finland and from 1975 to 2006 in Denmark. The estimated cumulative incidence of TJA was 4.5% at 20 years for patients treated for chronic myeloid leukemia, followed by 2.1% for patients treated for acute myeloid leukemia and 0.4% for patients treated for ALL. Allogeneic stem cell transplantation increased the risk of TJA.

In conclusion, ON as determined with MRI is a common complication in children after treatment for ALL. High BMI was identified as a new significant risk factor for ON in patients with pediatric ALL. The incidence of ON requiring TJA was highest among children, adolescents and young adults treated for myeloid leukemias.

Keywords: body mass index, children, leukemia, magnetic resonance imaging, osteonecrosis, stem cell transplantation, total joint arthroplasty, young adults
Niinimäki, Riitta, Luukuoliot lapsuus- ja nuorella aikuussa syntynyttä syövän sairastaneilla.
Oulun yliopiston tutkijakoulu; Oulun yliopisto, Lääketieteellinen tiedekunta, Kliinisen lääketieteen laitos, Lastentaudit; Oulun yliopistollinen sairaala

Oulun yliopisto, PL 8000, 90014 Oulun yliopisto

Tiivistelmä

Syöpähoitojen aiheuttamien myöhäisvaikutusten merkitys on viime vuosina kasvanut, koska suuri osa lapsena tai nuorena aikuisena syöpään sairastuneista paranee. Syöpähoitojen seurauksenä voi syntyä luukuolioita, jotka heikentävät merkittävästi elämänlaatua ja liikuntakykyä.

Tämän väitöskirjatyön tarkoituksena oli selvittää magneettitutkimuksella luukuolion ilmaantuvuus ja riskitekijät syöpähoitojen lopetusvaiheessa lapsuus- ja nuorella aikuussa syntynyttä syövän sairastaneilla sekä selvittää rekisteritutkimuksella tekonivelleikkausta vaativan luukuolion ilmaantuvuus ja riskitekijät lapsena tai nuorena aikuisen hoidetuilla syövät potilailla.

Akuutin lymfaattisen leukemian (ALL) sairasta neista 23/97:lla (24 %) todettiin alaraajojen magneettitutkimuksessa luukuoloiota. Korkea painoindeksi, naispuolisuus, vanhempi ikä diagnoosihetkellä ja suurempi kumulatiivinen deksametasoniannos lisäisivät luukuolion todennäköisyyttä. Lymphooman tai kiinteän kasvaimen sairastaneista 6/32:lla (19 %) todettiin luukuolioita. Tutkimme tekonivelleikkausta vaativan luukuolion ilmaantuvuutta Suomen ja Tanskan väestöpohjaisen rekisterekurssin avulla. Tutkimusohjelma muodostui 6 358 leukemiaan ja lymphoomaan sekä 18 542 kiinteän kasvaimen sairastaneesta potilaasta. Tekonivelleikkausta vaativan luukuolion kumulatiivinen ilmaantuvuus 20 vuoden seurannan aikana oli kronisen myeloinen leukemian sairastaneilla 4,5 %, akuutin myeloinen leukemian sairastaneilla 2,1 % ja ALL:n sairastaneilla 0,4 %. Allogeeninen kantasolujen siirto lisäsi luukuolionen todennäköisyyttä.


Asiasanat: kantasolujen siirto, lapset, leukemia, luukuolio, magneettitutkimus, nuoret aikuiset, painoindeksi, tekonivelet
To my family
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Oulu, November 2013

Riitta Niinimäki
### Abbreviations

<table>
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<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>ALL</td>
<td>acute lymphoblastic leukemia</td>
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<tr>
<td>Allo-SCT</td>
<td>allogeneic stem cell transplantation</td>
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<td>AML</td>
<td>acute myeloid leukemia</td>
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<tr>
<td>AYA</td>
<td>adolescent and young adult</td>
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<tr>
<td>BFM</td>
<td>Berlin-Frankfurt-Munster</td>
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<tr>
<td>BMI</td>
<td>body mass index</td>
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<tr>
<td>CI</td>
<td>confidence interval</td>
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<tr>
<td>CML</td>
<td>chronic myeloid leukemia</td>
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<tr>
<td>CNS</td>
<td>central nervous system</td>
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<tr>
<td>CT</td>
<td>computer tomography</td>
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<tr>
<td>DNHDR</td>
<td>Danish National Hospital Discharge Register</td>
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<tr>
<td>EFS</td>
<td>event-free survival</td>
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<tr>
<td>FNHDR</td>
<td>Finnish National Hospital Discharge Register</td>
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<tr>
<td>GC</td>
<td>glucocorticoid</td>
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<tr>
<td>GVHD</td>
<td>graft versus host disease</td>
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<td>HL</td>
<td>Hodgkin lymphoma</td>
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<tr>
<td>HR</td>
<td>high-risk</td>
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<tr>
<td>IR</td>
<td>intermediate-risk</td>
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<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
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<tr>
<td>NCI</td>
<td>National Cancer Institute</td>
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<tr>
<td>NHL</td>
<td>non-Hodgkin lymphoma</td>
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<tr>
<td>NOPHO</td>
<td>Nordic Society of Pediatric Hematology and Oncology</td>
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<tr>
<td>ON</td>
<td>osteonecrosis</td>
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<tr>
<td>OR</td>
<td>odds ratio</td>
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<tr>
<td>OS</td>
<td>overall survival</td>
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<tr>
<td>PAI-1</td>
<td>plasminogen activator inhibitor-1</td>
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<tr>
<td>SCT</td>
<td>stem cell transplantation</td>
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<tr>
<td>SR</td>
<td>standard-risk</td>
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<tr>
<td>TBI</td>
<td>total body irradiation</td>
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<tr>
<td>TJA</td>
<td>total joint arthroplasty</td>
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List of original publications

This thesis is based on the following publications, which are referred to in the text by their Roman numerals.


III Niinimäki R, Mølgaard Hansen L, Niinimäki T, Olsen JH, Pokka T, Sankila R, Vetternranta K, Hasle H & Harila-Saari A. Incidence of Severe Osteonecrosis Requiring Total Joint Arthroplasty in Children and Young Adults Treated for Leukemia or Lymphoma: A Nationwide, Register-Based Study in Finland and Denmark. J Adolesc Young Adult Oncol. In press.

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1 Introduction

Therapeutic advances in managing childhood malignancies have resulted in the long-term survival of more than 80% of children, adolescents, and young adults (AYAs) with cancer (Aben et al. 2012, Gatta et al. 2009), and almost 90% with pediatric acute lymphoblastic leukemia (ALL) (Pui et al. 2012). The successful treatment of childhood cancer using combinations of chemotherapy, surgery, and/or radiotherapy may be associated with significant morbidity in later life (Pritchard-Jones et al. 2006). Glucocorticoids (GCs), dexamethasone and prednisone, are essential in treating various cancers. GCs have contributed to improved cure rates in ALL but can cause osteonecrosis (ON), potentially debilitating toxicity after cancer treatment (Bostrom et al. 2003, Gaynon & Carrel 1999, Sala et al. 2007).

The overall incidence of symptomatic ON varies from 0.4% to 1.4% in pediatric and adolescent cancer survivors (Kadan-Lottick et al. 2008, Lackner et al. 2005) and from 1.1% to 9.3% in pediatric and adolescent ALL survivors (Arico et al. 2003, Mattano et al. 2000, te Winkel et al. 2011). Patients with a hematological malignancy seem to have higher incidence of ON. In patients with ALL, magnetic resonance imaging (MRI) screening has revealed that the incidence may range from 16% to 72% (Kawedia et al. 2011, Ojala et al. 1999, Ribeiro et al. 2001).

The pathogenesis of ON is multifactorial, and GC-induced apoptosis of the endothelium, osteoblasts and osteoclasts, increased intraosseous pressure secondary to adipocyte hypertrophy, an increased prothrombotic state and impaired repair of bone and vascular damage have been suggested (Kerachian et al. 2009, Motomura et al. 2008, Zalavras et al. 2003). Clinical risk factors for ON include age above 10 years at diagnosis, female gender, white race, higher dose, and longer exposure to dexamethasone (Vora 2011).

ON may cause severe pain, loss of function and even joint damage and articular collapse (Mankin 1992). However, the majority of pediatric cancer patients with ON identified with systematic MRI screening remain asymptomatic, do not require treatment, and improve with time (Kawedia et al. 2011, Ojala et al. 1998, Ojala et al. 1999). The incidence of the long-term consequences of symptomatic and asymptomatic ON are unknown. Total joint arthroplasty (TJA) is performed in patients with symptomatic joint destruction. The proportion of cancer survivors who need TJA has not been reported. In the TJA procedure, the
affected femoral head and damaged acetabular cartilage are removed and replaced with an implant.

The aims of this work were to define the incidence of and clinical risk factors for ON identified with end-of-therapy MRI screening among patients with childhood cancer and to investigate the incidence of and risk factors for severe ON requiring TJA in patients treated for cancer in childhood, adolescence, or young adulthood in a register-based study.
2 Review of the literature

2.1 Cancer in childhood

The annual incidence of cancer in children between 0 and 14 years is about 150 new cases per 1 million in the US (Siegel et al. 2013). Approximately 150 children are diagnosed with cancer each year in Finland (Fig. 1). Whereas adult cancers are overwhelmingly carcinomas, in children, hematological malignancies and tumors of the central nervous system (CNS) account for the majority of all cancers. Leukemias (approximately 30%) and CNS tumors (approximately 30%) make up most childhood cancers, followed by a miscellaneous group of tumors, consisting of nephroblastomas, neuroblastomas, soft tissue sarcomas, Hodgkin lymphomas (HLs), and non-Hodgkin lymphomas (NHLs) (Howlader et al. 2013). Among newly diagnosed childhood cancers, the incidence rates for all cancers yield a male-to-female ratio of 1.2 (Bleyer et al. 2006).

The prognosis of childhood cancer has improved dramatically over the past 40 years. Mortality rates for all malignant childhood cancers combined declined by more than 50% between 1975 and 2006 (Smith et al. 2010). The five-year survival for all cancers combined has exceeded 80% in children (Gatta et al. 2009, Siegel et al. 2013).

![Fig. 1. Incidence of the 10 most common cancers among children diagnosed at 0–14 years of age in Finland. ASR = age-standardized rate (per 100,000).](image)
2.2 Cancer in adolescence and young adulthood

In AYAs between 15 and 29 years old, the distribution of cancer types is very different compared with children and older adults (Bleyer et al. 2008, Wu et al. 2005). In children, embryonal tumors represent the most prevalent neoplasms, whereas the most common cancers in older adults are epithelial malignancies of the lung, prostate, breast, and colorectum (Bleyer et al. 2008). In AYAs, nearly all invasive cancers are lymphomas, leukemias, germ cell tumors, melanomas, or carcinomas (Jemal et al. 2011). Lymphomas are the most common malignancy in AYAs (Engholm et al. 2013).

In male AYAs aged 15 to 29 years, testicular cancer is the most frequently observed cancer, followed by HL and melanoma. In female AYAs aged 15 to 19 years, HL is the most common cancer, followed by melanoma and NHL. In female 20- to 29-year-old women, melanoma is most frequently diagnosed, followed by HL and thyroid cancer in women aged 20 to 24 years and breast and cervical cancer in women aged 25 to 29 years (Aben et al. 2012).

Compared to the total incidence rate for cancer, AYAs represent only slightly more than 1%. However, compared to cancer incidence in children, which is 12 per 100,000 person years, the incidence among AYAs is more than three times higher (Aben et al. 2012). The age-adjusted incidence rate of cancer in AYAs with an age at diagnosis between 15 and 29 years is 41 per 100,000 person years. Five-year survival for all cancers combined has been more than 80% in AYAs (Aben et al. 2012, Gatta et al. 2009). Survival in AYAs is even slightly higher compared with children, which is explained by tumors with very good prognosis, such as testicular cancer and lymphomas.

2.3 Leukemia

2.3.1 Acute lymphoblastic leukemia

ALL is a systemic malignant disease originating in bone marrow. The peak incidence is between the ages of 2 and 5 years (Pui et al. 2008), with a decrease during later childhood, adolescence and young adulthood before a second, smaller peak at age of more than 50 years (Faderl et al. 2003). ALL accounts for about 85% of all childhood leukemias and 25% of all malignancies (Engholm et al. 2013, Linabery & Ross 2008). The annual incidence of ALL in the Nordic
The incidence rate for ALL is higher in boys than in girls (Bleyer et al. 2008).

Remission was first reported in 1948 in children with ALL treated with a folic acid antagonist, aminopterin (Farber & Diamond 1948). GCs were among the first drugs used in treatment, and since 1949, GCs have been essential in treating ALL (Pearson & Eliel 1950, Pui & Evans 2006). Despite temporary remissions, ALL was invariably fatal until the 1960s, when consecutive studies of combination chemotherapy resulted in longer survival (Seibel 2008). In the late 1960s, the CNS was recognized as a sanctuary of leukemic cells, and use of cranial irradiation and intrathecal therapy was initiated (Seibel 2008). In the 1980s, delayed intensification, which includes GCs, was added to the treatment protocols (Henze et al. 1981). Probability of 10-year event-free survival (EFS) improved from 65% in study ALL-Berlin-Frankfurt-Munster (BFM) 81 to 78% in ALL-BFM 95 (Moricke et al. 2010). Since then, an increase in the intensity of treatment and improved supportive care have improved the overall survival (OS) in ALL close to 90% in developed countries (Pui et al. 2010).

The prognosis for ALL worsens dramatically with the onset of adolescence and continues to be dismal in adulthood, which may partially be explained by higher frequency of high-risk leukemias in adults compared with children (Toft et al. 2013). In a recent review of outcomes in ALL for Children’s Oncology Group protocols 2000–2005, the outcomes decreased significantly as age increased. The 5-year OS was 94% for patients 1–9 years, 85% for patients 10–14 years, and 76% for patients 15–21 years (Hunger et al. 2012). In adults, 5-year EFS is even poorer, 40% (Rowe et al. 2005), although Finnish data revealed higher EFS of 60% in young adults (Usvasalo et al. 2008).

Current treatment protocols consist of induction, consolidation, intensification and maintenance phases. In the past, the most commonly used GC was prednisone during the induction and intensification phases. However, over the past few years, dexamethasone has increasingly been studied in treatment of ALL. Dexamethasone is preferred GC because of its long half-life, excellent CNS penetration and anti-inflammatory properties (Eadie et al. 1984).

Currently, all pediatric patients in Nordic countries and young adults up to 45 years old in Denmark, Norway, and Sweden are treated according to the Nordic Society of Pediatric Hematology and Oncology (NOPHO) ALL-2008 protocol. In Finland, patients aged more than 15 years are mainly treated according to adult protocols introduced by the Finnish Leukemia Group (Usvasalo et al. 2008).
2.3.2 Acute myeloid leukemia

Acute myeloid leukemia (AML) accounts for about 15% of leukemias in childhood (Engholm et al. 2013, Linabery & Ross 2008). The incidence rate of AML in Nordic countries is approximately 0.7 per 100,000 children under 15 years (Hjalgrim et al. 2003). The incidence of AML is highest during the first 2 years of life, decreasing to the lowest at around 10 years of age, before increasing again throughout the teenage years to reach stable incidence by early adult life (Hjalgrim et al. 2003). Currently, up to 60% of children and adolescents with AML will become long-term survivors (Howlader et al. 2013, Kaspers & Creutzig 2005, Pui et al. 2011).

Treatment for AML consists of an induction period with diverse intensive chemotherapy regimens based on cytarabine and an anthracycline followed by consolidation. Traditionally, treatment does not include GCs. Possibilities for consolidations are allogeneic stem cell transplantation (allo-SCT) and chemotherapy (Niewerth et al. 2010). Most studies have shown that the relapse rate is lower and disease-free survival is higher following SCT, but there is no difference on OS (Niewerth et al. 2010) because the lower relapse rate after SCT is balanced by increased treatment-related mortality (Gibson et al. 2005). NOPHO protocols are used in treating patients with pediatric AML in the Nordic countries (Lie et al. 2005). In Finland, patients older than 15 years of age are treated according to the Finnish Leukemia Group protocols (Koistinen et al. 2007).

2.3.3 Chronic myeloid leukemia

Chronic myeloid leukemia (CML) occurs uncommonly in children, accounting for 2% to 3% of leukemias in this age group (Ries et al. 1999). CML is a clonal myeloproliferative disorder of hematopoietic stem cells that carry the Philadelphia chromosome (Nowell & Hungerford 1960). In contrast to acute leukemias, CML is indolent, with a natural history usually spanning several years. The median age of diagnosis is in the fifth and sixth decade of life with a wide range from childhood to senescence (Hoglund et al. 2013).

Most patients are diagnosed in the chronic phase. The leukocyte count at diagnosis ranges from approximately $8 \times 10^9/L$ to $800 \times 10^9/L$. An important finding of CML, especially at the time of primary diagnosis, is hyperleukocytosis with leukostasis. Severe hyperleukocytosis is more frequent in the cases of
childhood CML compared with the cases of adulthood CML (Rowe & Lichtman 1984).

Tyrosine kinase inhibitors have revolutionized the treatment of adult CML by eliminating allo-SCT for almost all patients in the chronic phase. In pediatric CML in the chronic phase, the first-line therapy is increasingly tyrosine kinase inhibitor therapy without SCT, but allo-SCT with well-matched donor, remains the treatment of choice. Patients in accelerated or blast crisis or who have intolerance or resistance to tyrosine kinase inhibitors should pursue SCT (Andolina et al. 2012). The 6-year OS in adults who receive imatinib with CML has been 95% (Hochhaus et al. 2009) and the estimated 3-year OS in children 98% (Hochhaus et al. 2009, Millot et al. 2011).

2.4 Lymphomas

Lymphomas, including HL and NHL, comprise the third most common group of malignancies in children after leukemias and CNS tumors (Ries et al. 1999). GCs are an essential component of chemotherapy for lymphomas.

HL is rare before 10 years of age, but is one of the most common cancers in adolescents (Engholm et al. 2013). Clinical trials for children with HL aim to further separate patients into risk groups so that those who are highly curable can receive less toxic therapy, whereas high-risk patients can receive augmented therapy (Hodgson et al. 2007). Currently, the standard treatment for childhood HL is risk-adapted, and radiotherapy is being omitted, if response to treatment after two cycles of chemotherapy is good (Kluge & Korholz 2011).

The annual incidence of NHL in Nordic countries is 0.9 per 100,000 children, with a median age of 8 years (Marky et al. 2004). The four major subtypes of NHL include Burkitt’s lymphoma (40%), diffuse large cell lymphoma (20%), lymphoblastic lymphoma (30%), and anaplastic large cell lymphoma (10%) (Sandlund et al. 1996). With modern intensive chemotherapy, more than 85% of patients with NHL and more than 90% of patients with HL will remain in first complete remission (Clavel et al. 2006, Marky et al. 2004).

2.5 Solid tumors

The most common extracranial tumors in children are neuroblastoma (8–10%), Wilms’ tumor (6%) and soft tissue sarcomas (4–8%) (Gurney et al. 1996, Stein-Wexler 2011, Varan 2008). The five-year survival rates for children with nonhigh-
risk and high-risk neuroblastoma are 90% and 50%, respectively (Park et al. 2013), above 90% for Wilms’ tumor (Smith et al. 2010), and approximately 70% for soft tissue sarcomas (Stiller et al. 2001).

Testicular cancer is the most common solid malignancy in AYAs, and the cure rate for this cancer currently exceeds 95% (Dearnaley et al. 2001, Vaughn et al. 2002). The median age at diagnosis for cancer of the testis is 33 years (Howlader et al. 2013).

Breast cancer is a common malignancy in women with the median age at diagnosis 61 years of age of whom 1.8% is diagnosed before 35 years of age (Howlader et al. 2013). In addition to surgery, nonsurgical treatments such as hormone therapy, chemotherapy, radiation, and use of bisphosphonates improve the prognosis (Hirbe et al. 2006). The 5-year relative OS is 89% (Howlader et al. 2013).

Usually, the protocols for solid tumors do not include GCs. However, dexamethasone is commonly used in supportive care, for example, for controlling chemotherapy-induced nausea (Navari 2009).

### 2.6 Osteonecrosis

Osteonecrosis (ON), also known as avascular or aseptic necrosis, is characterized by the death of one or more segments of bone following a compromise of blood flow to the bone. ON is either primary (idiopathic ON) or secondary to trauma or nontraumatic factor, such as coagulation defects, storage disorders, alcoholism, autoimmune diseases, marrow infiltrating diseases, radiation and GC exposure (Assouline-Dayan et al. 2002, Mankin 1992). In general, nontraumatic ON is a very rare condition in children and young adults, with the exception of its occurrence in children with Legg-Calve-Perthes disease (Mankin 1992, Nixon 1983). Occurrence as a sequel after treatment for pediatric ALL was first reported in 1977 (Kaufmann & Lampert 1977).

Patients with ON may present with slow-onset, insidious unilateral, or bilateral pain. ON may be asymptomatic in early stages of the disease (Ojala et al. 1999) or cause severe pain, bone destruction, loss of function and, ultimately, joint damage and articular collapse (Mankin 1992). Symptoms are generally amplified with weight-bearing and relieved with rest if the ON lesions are located in weight-bearing joints. ON lesions are typically bilateral in distribution (Hungerford & Jones 2004, Karimova et al. 2006, Lackner et al. 2005, Mont et
al. 2010) unless there has been local radiation therapy, surgery or other focal insult that would unilaterally predispose a joint to this toxicity.

The joints most often reported to be involved with ON vary among reports of symptomatic and asymptomatic cases. Typically, the hips and knees are most often reported for symptomatic patients (Kadan-Lottick et al. 2008). In addition, the ankle, shoulder, elbow, wrist, and vertebrae can be affected with ON (Elmantaser et al. 2010, Mattano et al. 2012). The extension of epiphyseal lesions to the articular surface and estimated percentage involvement of the articular surface are important for evaluating the eventual outcome of joint function and risk of arthroplasty (Ha et al. 2006, Hungerford & Jones 2004, Karimova et al. 2007, Kokubo et al. 1992, Takatori et al. 1993).

2.6.1 Pathogenesis of glucocorticoid-related osteonecrosis

GCs are the most common nontraumatic cause of ON (Assouline-Dayan et al. 2002). GC-related ON has been a recognized sequel for more than 50 years (Bloch-Michel et al. 1959, Epstein et al. 1965). GCs cause hyperlipidemia, hypercoagulation and hypofibrinolysis in the circulatory system (Smith et al. 1950, Yamamoto et al. 1995). GC side effects depend on the dose and the duration of treatment.

The pathogenesis of GC-related ON is not fully understood despite intense research in animal models (Boss et al. 2004, Kerachian et al. 2009) and appears to be multifactorial (Assouline-Dayan et al. 2002). According to animal models, mechanism of GC-related ON include apoptosis of the endothelium, osteoblasts, and osteoclasts, increased intraosseous pressure secondary to adipocyte hypertrophy, an increased prothrombotic state, and impaired repair of bone and vascular damage (Kerachian et al. 2009, Miyaniishi et al. 2001, Motomura et al. 2008, Yamamoto et al. 1997, Zalavras et al. 2003).

Apoptosis of osteoblasts, osteocytes and bone marrow stromal cells is a key feature of ON (Calder et al. 2004, Eberhardt et al. 2001). GC-induced osteocyte apoptosis, disruption of bone vascularity and diminution of bone hydraulic support could be the mechanism behind ON and greater decrease in bone strength rather than in loss of bone mass due to excess of GC (Weinstein 2012).

GCs have many effects on the endothelial cells that line the sinusoids and the inner layer of blood vessels in the femoral head. Experimental evidence of GC-induced hypertension indicates that raised arterial blood pressure is related to elevated peripheral resistance (Whitworth et al. 1995). GCs can directly injure
endothelial cells, and the cell damage may result in abnormal blood coagulation and thrombi formation with ON occurring distal to the site of the arterial occlusion (Kerachian et al. 2009).

Thrombophilia and hypofibrinolysis have been implicated as causative factors of ON in adults (Glueck et al. 2001, Van Veldhuizen et al. 1993). It is suspected that, at higher doses of GCs, the fibrinolytic pathway may be inhibited via increased plasma plasminogen activator inhibitor and decreased tissue plasminogen activator activity (Gray et al. 1996, van Giezen & Jansen 1992).

Angiogenesis is part of the normal bone turnover process. Inhibition of angiogenesis could partly induce ON (Smith 1997). Following necrosis of the femoral head, a repair process begins with the entry of blood vessels into the necrotic region, followed by bone resorption and subsequent bone formation (Vadasz et al. 2004). Several essential factors, such as vascular endothelial growth factor, act directly on endothelial cells and induce angiogenesis (Yang et al. 2003). Dysregulation of these essential factors will have an effect on angiogenesis, and consequently the repair process.

The increased size of the marrow adipocytes, high intraosseus pressure, accumulation of the lipids in the osteocytes, and a fat embolus has been suggested to induce ON (Jones 1993, Miyanishi et al. 2002, Mont & Hungerford 1995, Wang et al. 2000). GCs increase the blood levels of free fatty acid and prostaglandin E₂ in blood and bone (Jones 1992). The free fatty acids formed by hydrolysis of fat emboli trigger intravascular coagulation (Jones & Sakovich 1966). GCs can induce bone marrow stromal cells to become adipocytes (Li et al. 2005), which, in turn, causes fat accumulation in the medullary cavity. Consequently, the intraosseous pressure rises, leading to sinusoidal compression, venous stasis and, eventually, arterial obstruction, accounting for the ischemic ON (Miyanishi et al. 2002, Motomura et al. 2005).

### 2.6.2 Pathogenesis of nonglucocorticoid-related osteonecrosis in cancer patients

ON is rare without GC exposure and is probably related to underlying medical conditions, coagulopathies, and genetic susceptibility. ON has been reported before GC treatment at diagnosis of ALL (Gurkan et al. 2006) and without GC exposure in a child with AML in remission (Ghosh et al. 2008). Several cases of ON of the femoral head have been reported as the initial manifestation of CML (Gibson et al. 1984, Gupta et al. 2003, Kozuch et al. 2000, Kraemer et al. 2003, 2005).
Leone et al. 1996, Salimi et al. 1988). The mechanism of ON in untreated CML is poorly understood. Leukostasis, vascular compression by leukemic foci, or vascular obstruction by microthrombi in the presence of disseminated intravascular coagulation has been proposed (Leone et al. 1996). In Gupta et al.’s (2003) case presentation, the core biopsy from the femur head revealed hypercellular leukemic foci, which, by causing vascular compression, could have led to ON. There are some case reports about the development of ON in patients with solid tumor receiving chemotherapy without GCs (Bernbeck et al. 2002, Geetha et al. 1998, Harper et al. 1984, Ishii et al. 1984).

2.6.3 Radiological diagnosis and classification of osteonecrosis

At the presentation of limping, joint-specific pain or decreased range of motion, plain radiographs are useful for identifying potential sources of joint pain such as fracture, or metastasis, but they are insensitive to detecting the early stages of ON (Mont et al. 2006b). MRI is the most sensitive and specific method for detecting and monitoring ON (Mitchell et al. 1987, Robinson et al. 1989, Saini & Saifuddin 2004).

In MRI, the double-line sign (Fig. 2) is a diagnostic change of ON on T2-weighted spin echo sequences, occurring at the interface between viable and nonviable tissue (Saini & Saifuddin 2004). The high-signal-intensity inner zone represents hyperemic granulation tissue, and the low-signal-intensity outer zone represents adjacent sclerotic bone (Mitchell et al. 1987).

Several ON classification systems have been described for grading the severity of ON of the femoral head (Ficat 1985, Lee & Steinberg 2012, Mont & Hungerford 1995, Steinberg et al. 1995) and the knee (Karimova et al. 2006, Mont et al. 2000a). The Ficat and Arlet classification system is based on plain radiographs (Ficat 1985, Lee & Steinberg 2012). The Steinberg classification system for ON of the femoral head differentiates subchondral collapse from femoral head articular collapse based on MRI images (Steinberg et al. 1995). The Association Research Circulation Osseous (ARCO) staging system utilizes MRI and plain radiograph images (Mont & Hungerford 1995).

In addition to radiological grading, the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events grading system has been used in ON studies (Vora 2011). The establishment of a uniform definition and classification of ON in patients after treatment of cancer is important, because comparing studies is challenging if the endpoint is unclear.
In addition to plain radiographs and MRI, other ON imaging methods have been used to diagnose ON. Computer tomography (CT) has the distinct advantage of being able to better detect subchondral collapse and even subtle depression of the articular surface (Yeh et al. 2009). However, patient exposure to ionizing radiation limits the use of CT in pediatric patients to assess joint integrity. Skeletal scintigraphy has long been advocated as a sensitive diagnostic tool for detecting ON because it is widely available and can provide whole-body assessment (Mont et al. 2008, Sakai et al. 2001). However, MRI has largely superseded skeletal scintigraphy because of superior anatomic detail, lack of exposure to ionizing radiation and improved specificity (Mont et al. 2008). Whole-body MRI is useful for screening the entire skeleton with a single diagnostic test, but clinical use is currently limited (Darge et al. 2008, Miettunen et al. 2012).

Fig. 2. Osteonecrosis of the ankle joint in a child with acute lymphoblastic leukemia. Coronal T1-weighed image demonstrating the double-line sign (arrow).
2.6.4 Incidence of osteonecrosis

The reported incidences of ON in children and young adults vary widely from 0.4% to 71.8% (Kadan-Lottick et al. 2008, Kawedia et al. 2011) depending on the definition of ON, primary diagnosis, treatment protocol, study design, and selection of patients (Table 1). The incidence was highest in prospective MRI screening studies, including asymptomatic and symptomatic patients. However, most patients who had signs of ON in MRI examination did not develop progressive joint destruction, even with continued prednisone therapy, and the majority had minimal or no symptoms (Ojala et al. 1999, Ribeiro et al. 2001). Kawedia et al. (2011) reported the highest incidence of ON (72%), which was graded using the NCI Common Terminology Criteria for Adverse Events. In the NCI classification, symptomatic and asymptomatic ON lesions are included regardless of the size of ON. In addition, NCI classification is based on clinical findings and does not include a definition of ON in the radiographs, which may explain the much higher incidence of ON compared with all other studies.

Symptomatic ON has had a low incidence in retrospective and cross-sectional studies that include all childhood cancers. In a U.S. childhood cancer survivor study, the self-reported 20-year cumulative incidence of ON was 0.4% (52/9,261) in survivors treated from 1970 to 1986 (Kadan-Lottick et al. 2008). The incidence was slightly higher in patients treated for ALL compared with all cancer survivors. In pediatric patients with ALL, retrospective studies by Arico et al. (2003) and Burger et al. (2005) reported the incidence of symptomatic ON to be 1–2%. However, in contrast, in Strauss et al.’s (2001) study, the incidence was higher at 7%. In these studies, the majority of the patients were treated according to low-risk protocols. This difference could be due to different definitions and sites of ON, but also due to the three times higher total GC dose used by Strauss et al. compared to Burger et al. (Table 1). The incidence was significantly higher (9%) in the study by Mattano et al.’s (2000) study, which included only high-risk patients with ALL, depicting the impact of older age and higher intensity of treatment on the risk of ON.

The reported incidence of ON is markedly elevated in patients among recipients of allo-SCT ranging from 3.9% to 44.2% (Balduzzi et al. 1995, Faraci et al. 2006, Kaste et al. 2004, Socie et al. 1994) (Table 1).
Table 1. Incidence of osteonecrosis in pediatric cancer patients and in pediatric patients after SCT.

<table>
<thead>
<tr>
<th>References</th>
<th>Incidences</th>
<th>No. of patients</th>
<th>Diagnosis</th>
<th>Study setting</th>
<th>Identification of ON patients</th>
<th>Identification of ON</th>
<th>Involved sites</th>
<th>Classification of ON</th>
</tr>
</thead>
<tbody>
<tr>
<td>Girard et al. 2013</td>
<td>2.8% (10-year cumulative incidence)</td>
<td>24 of 943 (all)</td>
<td>ALL, AML</td>
<td>Retrospective</td>
<td>Medical records, symptoms at follow-up visits</td>
<td>MRI Not defined</td>
<td>Not used</td>
<td>Not used</td>
</tr>
<tr>
<td></td>
<td>6.8% after SCT (10-year cumulative incidence)</td>
<td>15 of 256 (SCT)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Lebléeq et al. 2013</td>
<td>7.7%</td>
<td>17 of 220</td>
<td>ALL</td>
<td>Prospective</td>
<td>Symptomatic</td>
<td>MRI</td>
<td>Hip, knee</td>
<td>Steinberg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>knee, ankle</td>
<td></td>
</tr>
<tr>
<td>Riccio et al. 2013</td>
<td>1.2%</td>
<td>4 of 328</td>
<td>ALL, AML</td>
<td>Retrospective</td>
<td>Medical records</td>
<td>Radiograph</td>
<td>Hip, knee</td>
<td>Karimova</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ankle</td>
<td></td>
</tr>
<tr>
<td>Vrooman et al. 2013</td>
<td>6% (5-year cumulative incidence)</td>
<td>23 of 408</td>
<td>ALL</td>
<td>Prospective</td>
<td>Symptomatic</td>
<td>Not defined</td>
<td>Not defined</td>
<td>Not used</td>
</tr>
<tr>
<td>Mattano et al. 2012</td>
<td>7.7% (5-year cumulative incidence)</td>
<td>143 of 2,056</td>
<td>ALL</td>
<td>Prospective</td>
<td>Symptomatic</td>
<td>Radiograph, MRI</td>
<td>Various</td>
<td>Not used</td>
</tr>
<tr>
<td>Mattunen et al. 2012</td>
<td>28%</td>
<td>9 of 32</td>
<td>ALL</td>
<td>Retrospective</td>
<td>Symptomatic, medical records</td>
<td>Whole body MRI</td>
<td>Various</td>
<td>Karimova</td>
</tr>
<tr>
<td>Sansgiri et al. 2012</td>
<td>4.3%</td>
<td>21 of 481</td>
<td>ALL</td>
<td>Prospective</td>
<td>Symptomatic</td>
<td>MRI</td>
<td>Hip, knee</td>
<td>Sugano</td>
</tr>
<tr>
<td>Kawedia et al. 2011</td>
<td>71.8%</td>
<td>262 of 365</td>
<td>ALL</td>
<td>Prospective</td>
<td>MRI screening</td>
<td>MRI</td>
<td>Hip, knee</td>
<td>NCI 3.0</td>
</tr>
<tr>
<td>Madadi et al. 2011</td>
<td>0.8%</td>
<td>7 of 865</td>
<td>ALL</td>
<td>Prospective</td>
<td>Symptomatic</td>
<td>Radiograph</td>
<td>Hip</td>
<td>Steinberg</td>
</tr>
<tr>
<td>Te Winkel et al. 2011</td>
<td>6.1% (3-year cumulative incidence)</td>
<td>38 of 694</td>
<td>ALL</td>
<td>Prospective</td>
<td>Symptomatic</td>
<td>MRI</td>
<td>Hip, knee, ankle</td>
<td>NCI 3.0</td>
</tr>
<tr>
<td>Elmantaser et al. 2010</td>
<td>9.7%</td>
<td>18 of 186</td>
<td>ALL</td>
<td>Retrospective</td>
<td>Medical records</td>
<td>Radiograph, MRI</td>
<td>Various</td>
<td>Not used</td>
</tr>
<tr>
<td>Kadan-Lotick et al. 2008</td>
<td>0.4% (20-year cumulative incidence)</td>
<td>52 of 9,261</td>
<td>Cancer survivors</td>
<td>Retrospective</td>
<td>Questionnaire, medical records</td>
<td>Not defined</td>
<td>Various</td>
<td>Not used</td>
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<tr>
<td>Te Winkel et al. 2008</td>
<td>14.9%</td>
<td>24 of 161</td>
<td>ALL</td>
<td>Retrospective</td>
<td>Medical records</td>
<td>MRI</td>
<td>Not defined</td>
<td>Not used</td>
</tr>
<tr>
<td>Hogler et al. 2006</td>
<td>12.1% (5-year incidence)</td>
<td>10 of 109</td>
<td>ALL</td>
<td>Retrospective</td>
<td>Medical records</td>
<td>Not defined</td>
<td>Various</td>
<td>Not used</td>
</tr>
<tr>
<td>References</td>
<td>Incidences</td>
<td>No. of patients</td>
<td>Diagnosis</td>
<td>Study setting</td>
<td>Identification of ON patients</td>
<td>Identification of ON</td>
<td>Involved sites</td>
<td>Classification of ON</td>
</tr>
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<td>-------------------</td>
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</tr>
<tr>
<td>Burger et al. 2005</td>
<td>1.8% (5-year cumulative incidence)</td>
<td>31 of 1,951</td>
<td>ALL</td>
<td>Retrospective</td>
<td>Questionnaire, medical records</td>
<td>Not defined</td>
<td>Various</td>
<td>Not used</td>
</tr>
<tr>
<td>Lackner et al. 2005</td>
<td>1.4%</td>
<td>9 of 630</td>
<td>ALL, AML, HL, NHL</td>
<td>Retrospective</td>
<td>Symptomatic</td>
<td>MRI</td>
<td>Various</td>
<td>Own definition</td>
</tr>
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<td>Arico et al. 2003</td>
<td>1.1%</td>
<td>15 of 1,421</td>
<td>ALL</td>
<td>Retrospective</td>
<td>Symptomatic</td>
<td>Radiograph, MRI, CT</td>
<td>Various</td>
<td>Not used</td>
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<tr>
<td>Ribeiro et al. 2001</td>
<td>15.5%</td>
<td>17 of 116</td>
<td>ALL, NHL</td>
<td>Prospective</td>
<td>MRI screening</td>
<td>MRI, radiograph</td>
<td>Hip, knee</td>
<td>Ficat, Arlet</td>
</tr>
<tr>
<td>Strauss et al. 2001</td>
<td>7.0% (5-year cumulative incidence)</td>
<td>13 of 176</td>
<td>ALL</td>
<td>Retrospective</td>
<td>Medical records</td>
<td>Radiographic</td>
<td>Various</td>
<td>Not used</td>
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<tr>
<td>Mattano et al. 2000</td>
<td>9.3% (3-year life-table)</td>
<td>111 of 1,409</td>
<td>ALL</td>
<td>Retrospective</td>
<td>Medical records</td>
<td>Not defined</td>
<td>Various</td>
<td>Not used</td>
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<tr>
<td>Wei et al. 2000</td>
<td>4.0%</td>
<td>8 of 202</td>
<td>ALL</td>
<td>Retrospective</td>
<td>Medical records</td>
<td>MRI, radiograph</td>
<td>Various</td>
<td>Not used</td>
</tr>
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<td>Ojala et al. 1999</td>
<td>38%</td>
<td>9 of 24</td>
<td>ALL</td>
<td>Prospective</td>
<td>MRI screening</td>
<td>MRI</td>
<td>Humerus, femur, tibia</td>
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<td>Korholz et al. 1998</td>
<td>8.3%</td>
<td>10 of 121</td>
<td>ALL</td>
<td>Prospective</td>
<td>Symptomatic</td>
<td>MRI</td>
<td>Various</td>
<td>Not used</td>
</tr>
<tr>
<td>Sharma et al. 2012</td>
<td>29.5%</td>
<td>44 of 149</td>
<td>SCT</td>
<td>Retrospective</td>
<td>Medical records</td>
<td>MRI</td>
<td>Hip, knee</td>
<td>Karimova</td>
</tr>
<tr>
<td>Faraci et al. 2006</td>
<td>3.9%</td>
<td>43 of 1,091</td>
<td>SCT</td>
<td>Retrospective</td>
<td>Medical records</td>
<td>Not defined</td>
<td>Not defined</td>
<td>Not used</td>
</tr>
<tr>
<td>Kaste et al. 2004</td>
<td>44%</td>
<td>19 of 43</td>
<td>SCT</td>
<td>Retrospective</td>
<td>Medical records</td>
<td>MRI</td>
<td>Hip, knee</td>
<td>Not used</td>
</tr>
<tr>
<td>Balduzzi et al. 1995</td>
<td>5.7%</td>
<td>5 of 88</td>
<td>SCT</td>
<td>Retrospective</td>
<td>Medical records</td>
<td>Not defined</td>
<td>Hip, knee</td>
<td>Not used</td>
</tr>
<tr>
<td>Socie et al. 1994</td>
<td>8.1% (5-year estimated incidence)</td>
<td>27 of 727</td>
<td>SCT</td>
<td>Retrospective</td>
<td>Medical records</td>
<td>Various</td>
<td>Various</td>
<td>Not used</td>
</tr>
</tbody>
</table>

Classification methods are described in articles by Ficat (1985), Karimova et al. (2006b), Steinberg et al. (1995) and Sugano et al. (1992).
2.6.5 Risk factors for osteonecrosis in cancer patients

Age

Older age at diagnosis of ALL, especially age more than 10 years, is consistently identified as a risk factor for ON (Table 2). The risk of symptomatic ON is very low below 10 years of age and increases above that age. Those more than 15 years of age represent the population at highest risk (Burger et al. 2005, Mattano et al. 2000). The maturing bone of adolescents may be more susceptible to developing of ON. In contrast, immature bone may buffer increased pressure at the epiphyseal plate (Mattano et al. 2000). In one study, the highest risk was in adolescents between 16 and 20 years of age, and the risk was lower above age 20 years (Patel et al. 2008).

Gender and race

Females have a higher incidence for ON (Table 2). In the study by Mattano et al. (2000) including 1,409 patients treated for high-risk ALL, females had a higher 3-year incidence (19.2% vs. 9.8%) of ON than males. In addition, in Arico et al.’s (2003) and te Winkel et al.’s (2011) studies, the incidences in adolescent females were significantly higher than in males. The underlying mechanism for a possible female predominance for ON is unclear, but according to te Winkel et al. (2011), it could be earlier progression through puberty, with subsequent changes in hormone levels, earlier closure of the growth plate and different changes in lipid metabolism. The known polymorphisms that affect the pharmacokinetics of antileukemic medication or intravascular coagulation have not been shown to occur at different frequencies among the genders (Glueck et al. 2001, Relling et al. 2004, Zalavras et al. 2002). However, some trials did not demonstrate a female predominance (Burger et al. 2005, Ribeiro et al. 2001, Strauss et al. 2001).

White race has been observed as a risk factor for ON (Table 2). The 3-year incidence rate of ON was 16.7% in whites, 3.3% in blacks and 6.7% in other ethnic groups (Mattano et al. 2000).

Dose and timing of dexamethasone in patients with ALL

Higher dose and longer exposure to dexamethasone are known clinical risk factors for ON (Table 2). The reason to use dexamethasone instead of prednisone
is that it is more potent and penetrates the blood-brain barrier more easily than prednisone (Bostrom et al. 2003, Ito et al. 1996). The exact bioequivalence of these drugs is unclear, but prednisone equivalents by multiplying the dexamethasone dose by 6.67 based on the anti-inflammatory properties of the two drugs have been used (Haynes & Murad 1985, Strauss et al. 2001). A high risk of ON was identified in the CCG-1882 trial (Mattano et al. 2000) in which two 21-day courses of dexamethasone were compared with one course for patients with a slow early response to initial therapy, but augmented treatment was associated with better EFS and OS. To reduce the risk of ON, in the CCG-1961 trial, which followed CCG-1882, the trial patients received either two phases of interim maintenance and delayed intensification including alternate-week dexamethasone (days 0–6 and 14–20) or one phase of interim maintenance and delayed intensification including continuous dexamethasone (days 0–20) (Mattano et al. 2012). For patients aged 10 years and older, the use of alternate-week dexamethasone during the delayed intensification phases significantly decreased ON incidence compared with continuous dexamethasone (8.7% vs. 17.0%). The phenomenon of lower rates of ON in patients receiving discontinuous steroid administration was also described in a mouse model in which a similar schedule of discontinuous steroid administration led to lower ON rates (Yang et al. 2009).

Other possible risk factors

Local radiation therapy has been proposed to induce ON within the radiation field. In adults treated for head and neck tumors, ON of the mandible is a recognized serious side effect of local radiation therapy (Lee et al. 2009). Hanif et al. (1993) described ON of the femoral head in 15 children or young adults treated for malignancies, of whom four had received local irradiation involving the femoral head and one underwent TBI. The researchers postulated patients who receive high doses of GCs or local irradiation involving femoral heads are at risk for ON. In addition, in Libshitz et al.’s (1981) study, ON of the femoral head as a sequel of radiation in childhood was described in 25% (8/32) three years after treatment for malignancy.

Gonadal irradiation was independent risk factor of ON in Kadan-Lottick et al.’s (2008) study. They speculated that it could be due to radiation-induced damage to bone within the radiation field or an indirect effect of radiation-induced gonadal damage and insufficient production of sex hormones. This theory is supported by studies showing that estrogen and testosterone deficiencies are
associated with reduced bone density (Rochira et al. 2006, Seeman 2004). Kadan-Lottick et al. (2008) hypothesized that reduced gonadal sex steroids could also affect the risk of ON by a similar or separate mechanisms.

Chemotherapeutics have been suggested as potential risk factors for ON. Hanada et al. (1989) reported a child with ALL who developed simultaneous ON of the vertebrae and cerebral thrombosis with coagulation abnormalities after asparaginase was administered. Asparaginase may play an important role in the development of symptomatic ON in patients with ALL, as illustrated by coagulation defects in all patients after this drug is introduced (te Winkel et al. 2008). In the study by Kawedia et al. (2011), associations with treatment arm, lower albumin, and higher dexamethasone exposure were consistent with the hypothesis that agents such as asparaginase might potentiate the osteonecrotic effect of dexamethasone. However, the association of asparaginase-induced coagulopathy and ON has not been confirmed. The association between methotrexate and ON has also been studied because several authors have proposed that high-dose methotrexate is a risk factor for osteoporosis (Pfeilschifter & Diel 2000). However, a clear association between ON and methotrexate has not been found.

### Table 2. Clinical risk factors for ON in children and AYAs treated for hematologic malignancy.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>No. of studies</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender</td>
<td>3</td>
<td>Arico et al. 2003, Mattano et al. 2000, te Winkel et al. 2011</td>
</tr>
<tr>
<td>White race</td>
<td>2</td>
<td>Mattano et al. 2000, Relling et al. 2004</td>
</tr>
</tbody>
</table>

### Risk factors in patients after stem cell transplantation

In patients after SCT graft versus host disease (GVHD), older age at SCT, total body irradiation (TBI) and female gender have been identified as risk factors for ON (Table 3). Faraci et al. (2006) hypothesized that ON is mainly due to vascular damage secondary to the synergistic effect of GVHD and TBI. Vascular damage
may be the consequence of early and late toxicity of radiotherapy, which is known to induce a decrease in the number of osteoblasts and microvascular changes due to sub-intimal fibrosis and thickening of the median layer of small vessels (Hopewell 2003). However, in Socie et al.’s (2001) study, ON was associated with GVHD but not radiation, which suggests that GC therapy is a more important determinant of ON than radiation exposure among transplantation patients.

Table 3. Clinical risk factors for ON in children and AYAs treated with SCT.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>No. of studies</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>(posttransplant use of glucocorticoids)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total body irradiation</td>
<td>2</td>
<td>Faraci et al. 2006, Fink et al. 1998</td>
</tr>
<tr>
<td>Female gender</td>
<td>2</td>
<td>Leung et al. 2007, Sculte &amp; Beelen 2004</td>
</tr>
</tbody>
</table>

Genetic risk factors

Plasminogen activator inhibitor-1 (PAI-1) regulates coagulation and fibrinolytic systems. Increased serum levels have been associated with increased incidence of thrombophilia (Juhan-Vague et al. 1987) and ON (Ferrari et al. 2002, Glueck et al. 1999) although reports are not consistent. High levels of PAI-1, induced by GC treatment (Halleux et al. 1999) or through polymorphisms in PAI-1 gene lead to suppression of fibrinolysis through inhibition of the tissue plasminogen activator and promotion of thrombosis (Sprengers & Kluft 1987). Polymorphism in the PAI-1 gene was described as a contributing factor for ON in children with ALL (French et al. 2008).

Increased susceptibility to ON may be associated with polymorphisms of the thymidylate synthase and the vitamin D receptor (Relling et al. 2004), the methylenetetrahydrofolate reductase (Zalavras et al. 2002), GC receptor (Russcher et al. 2005), apolipoprotein A1 and B (Hirata et al. 2007, Wang et al. 2008), 11ß-hydroxysteroid dehydrogenase type 2 (Cooper et al. 2002), P-glycoprotein (Han et al. 2010) and mutation of chromosome 12q13 in the type II collagen gene (COL2A1) (Liu et al. 2005) or low inducing vascular endothelial growth factor haplotypes (Lee et al. 2012). In Kawedia et al.’s (2011) study, the
polymorphisms of acid phosphatase-1, which regulates lipid levels and osteoblast differentiation, were associated with the risk of ON, but interestingly, none of the previously reported genetic associations, including PAI-1 (French et al. 2008), methylenetetrahydrofolate reductase (Zalavras et al. 2002), the vitamin D receptor (Relling et al. 2004), and COL2A1 (Liu et al. 2005) genes were significant. At the moment, no genetic risk factors have been identified to be valid in clinical setting.

2.6.6 Treatment for osteonecrosis

Data concerning the optimal treatment for ON in cancer patients are scarce. It has been proposed that conservative treatment, including weight loss, appropriate use of analgesia, avoidance of weight-bearing and appropriate physical therapy are probably the most useful interventions in early stage ON (Lackner et al. 2005). Hip prognosis can be significantly improved with early diagnosis, before articular collapse (Mont & Hungerford 1995).

Medical treatment options for osteonecrosis

Many pharmacologic agents have been tested to prevent or treat progression of ON of the hip or knee, including bisphosphonates (Leblicq et al. 2013), lipid-reducing agents (Pritchett 2001), anticoagulants (Glueck et al. 2005) and prostacyclin (Disch et al. 2005), but their efficacy has remained uncertain in the treatment for GC-induced ON.

Bisphosphonates are antiresorptive agents that reduce edema at the site of ON, possibly through their anti-inflammatory action and in the rate of remodeling and preventing the progression of bone collapse (Davis et al. 2003, Russell 2011). Bisphosphonates have been reported to prevent progression of ON in animal models (Little et al. 2003, Little et al. 2005). However, in studies that include adult and pediatric patients with ON due to various underlying diseases, bisphosphonates diminished pain, improved mobility and may have slowed the process of joint destruction, but did not prevent joint destruction and collapse of the hip joint (Agarwala et al. 2005, Chen et al. 2012, Kotecha et al. 2010, Leblicq et al. 2013, Nguyen & Zacharin 2006, Padhye et al. 2013).

Statins decrease the serum lipid levels and counteract the effect of GCs on the differentiation of the precursor cells in bone marrow adipocytes (Cui et al. 1997, Wang et al. 2000). Treatment with statins can significantly decrease the incidence
of ON in steroid-treated rabbits (Iwakiri et al. 2008, Pengde et al. 2008). Pritchett reported that, at a mean of 7.5 years, ON of the femoral head had developed in only three of 284 patients who were taking high-dose GCs as well as various statin drugs (Pritchett 2001).

Prostacyclin may promote bone regeneration on a cellular or systemic level (Jager et al. 2008). The effects of the prostacyclin derivate iloprost have been studied in patients with ON of the femoral head, and clinical and radiograph improvements in patients with early stage ON of the femoral head have been observed (Disch et al. 2005, Meizer et al. 2005).

Anticoagulants may inhibit the aggregation of platelets and enhance blood flow to ischemic areas of bone (Glueck et al. 2005). Enoxaparin was used to treat patients who had thrombophilic or hypofibrinolytic disorders and early stages of ON of the femoral head. Enoxaparin prevented clinical and radiograph progression of ON of the femoral head in 31/35 (89%) hips at two years (Glueck et al. 2005).

Non-medical and nonsurgical treatment options of osteonecrosis

Various external, biophysical, and nonoperative modalities have been utilized to treat ON of the femoral head. These modalities include electromagnetic stimulation, extracorporeal shockwave therapy (Ludwig et al. 2001, Tingart et al. 2004, Wang et al. 2005) and hyperbaric oxygen (Kim 2004, Reis et al. 2003, Scherer et al. 2000).

Surgical treatment options of osteonecrosis

Various surgical procedures have been used to prevent progression from early ischemic to destructive ON. The utility of these treatments varies depending on the staging of the ON (Mankin 1992, Mont et al. 2010). The first approach before surgical treatment is usually to reduce weight-bearing using canes, crutches or a walker.

Core decompression involves drilling a hole through the distal end of the greater trochanter, which reduces the elevated intramedullary pressure within the femoral head (Ficat 1985, Plancher & Razi 1997). This procedure should be performed only during treatment for early stage lesions, because core decompression efficiency in preventing progressive deformation of the femoral head is questionable at best. However, this procedure almost always provides pain
relief (Lieberman 2004, Mont et al. 1996, Mont et al. 2006a). Multiple drilling of the femoral head osteonecrotic lesion is an alternative (Song et al. 2007). Core decompression can also be performed using autologous bone marrow grafting, which may prevent the progression of early stage ON (Hernigou & Beaujean 2002, Zhao et al. 2012).

Free vascularized fibula graft transfer in the early precollapse stages of ON is a salvage procedure of the necrotic femoral head, and in patients with postcollapse ON, this procedure delays hip arthroplasty (Korompilias et al. 2011). Scully et al. (1998) compared core decompression with vascularized fibular grafting, and core decompression was preferable because there was no difference in the results. Core decompression is technically easy and associated with low morbidity.

Osteotomy shifts the necrotic bone segment away from the weight-bearing acetabular cartilage supported by healthy bone promises success, but solely in patients with pre-collapse stage disease (Mont et al. 2000b). Osteotomies should be performed only for selected patients because these procedures can be difficult to perform. Total hip replacements performed after an osteotomy are often technically more difficult than those performed in patients with ON of the femoral head who have never had an osteotomy (Mont et al. 2006a).

Arthroplasty is the only procedure for which there is conclusive evidence of benefit in terms of pain relief and function (Beaule & Amstutz 2004, Lieberman et al. 2003, Mont et al. 2001). Indications of TJA of hip are not well defined, but TJA should be considered for advanced disease with obliteration of the acetabular articular space and osteophyte formation (Fig. 3). If ON affects greater than 30% of the femoral head volume, 80% of such hips will collapse within 2 years of diagnosis, and 50% will require hip arthroplasty (Karimova et al. 2007). TJA of the hip offers a good functional and symptomatic outcome; however, long life expectancy and increased physical activity in young patients put them at increased risk for multiple revisions resulting from implant failure (Letson et al. 1996, Ortiguera et al. 1999).
Fig. 3. ALL survivor with bilateral ON of the hip joint at age 21, right side treated with total joint arthroplasty.
3  Aims of the study

The specific aims of the research were:

1. To determine the incidence of and clinical risk factors for radiographic ON in children treated for ALL using the Nordic ALL protocols (I).
2. To find out the incidence of and clinical risk factors for radiographic ON in children treated for lymphoma or solid tumors (II).
3. To assess the incidence of ON requiring TJA in children, adolescents and young adults treated for cancer in Finland and Denmark (III, IV).
4 Materials and methods

A summary of the studies is shown in Table 4.

Table 4. Summary of the subjects and methods of studies I–IV.

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Data source</th>
<th>Study period</th>
<th>No. of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>I Prospective MRI</td>
<td>Patients with ALL in Oulu and Kuopio University hospitals</td>
<td>Oulu: from Sep. 1992 to Dec. 2005</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td>MRI screening</td>
<td>Kuopio: from Sep. 1994 to Dec. 1999</td>
<td></td>
</tr>
<tr>
<td>II Prospective MRI</td>
<td>Patients with lymphoma or solid tumor in Oulu and Kuopio University hospitals</td>
<td>Oulu: from Sep. 1998 to May 2007</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>MRI screening</td>
<td>Kuopio: from May 1994 to July 1999</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Discharge registers and with Finnish Arthroplasty Registry</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

4.1 MRI screening of ON (I, II)

Patients who had received chemotherapy for primary ALL, lymphoma, or solid tumors were eligible for the prospective MRI study in two centers during the study period (Table 4). MR scanning covering the lower extremities from the femoral head to the ankle was performed at the cessation of therapy. Patient files were carefully reviewed manually by two of the authors (R.N. and A.H-S). Age at diagnosis, gender, height and weight at diagnosis and at the end of the treatment, any symptoms or procedures for ON as well as disease and treatment details were recorded. Eligible patients had to be in continuous complete remission at the end of the treatment and give informed consent.

The actual received doses of prednisone and dexamethasone were carefully calculated from the patient files. The cumulative dose of GCs per square meter was calculated as prednisone equivalents. Dexamethasone doses were converted to prednisone equivalents by multiplying the dexamethasone dose by 6.67 based on the anti-inflammatory properties of the two drugs (Haynes & Murad 1985,
The cumulative doses of high-dose methotrexate were also calculated from the patient files.

4.1.1 A study of ON after treatment for ALL

A total of 122 patients with ALL were diagnosed and treated according to the Nordic ALL protocols during the study period. Reasons for exclusion from the study were death during treatment or referral to SCT (n = 9), Down syndrome (n = 4), and relapse before the end of the treatment (n = 3). Of the remaining 106 eligible patients, nine patients refused to give consent, which resulted in a participation rate of 91.5%. Ninety-seven patients were included in the analysis. There were 51 boys and 46 girls, and their mean age at diagnosis was 6.4 years (range 1.2–15.3).

Childhood body mass index (BMI) values were computed and converted into percentiles for age and gender by using graphs based on the growth data of 2,514 Finnish children born between 1954 and 1972 (Sorva et al. 1990, Wei et al. 2006). Overweight was defined as BMI > 85th to < 95th percentile, obesity as BMI > 95th percentile, underweight as BMI < 5th percentile and normal weight as BMI > 5th to 85th percentile, all by gender (Whitaker et al. 1997).

All the patients were treated using the Nordic ALL protocols: ALL-NOPHO 86, 92, and 2000. The patients were divided into standard-risk (SR), intermediate-risk (IR), and high-risk (HR) groups according to the criteria used in the Nordic countries (Gustafsson et al. 2000). The HR protocol was updated once and the IR and SR protocols twice during the study period. They have been presented in detail elsewhere (Gustafsson et al. 1998, Gustafsson et al. 2000).

The total cumulative dose of prednisone and dexamethasone in each therapeutic protocol is shown in Table 5. The IR 86 protocol included a delayed intensification phase with dexamethasone 10 mg/m²/day for 4 weeks followed by a 10-day taper, and the HR and IR 92 protocols included dexamethasone for 3 weeks followed by a 7- to 10-day taper. The latest protocols, IR and HR 2000, comprise an intensification phase with dexamethasone 6–10 mg/m²/day only for 2 weeks followed by a 2-week taper. In the other phases of treatment, dexamethasone is given in short 5-day pulses in all protocols, and the minimum interval between the start points of these pulses is 4 weeks. Some patients had also received remarkable cumulative doses of dexamethasone (up to 375 mg/m²) to treat nausea or as prophylaxis during cranial radiation therapy.
Table 5. Age, gender, cumulative¹ doses of prednisone and dexamethasone, and number of ON patients for each therapeutic protocol.

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Age (N = 97)</th>
<th>Gender (N = 97)</th>
<th>Glucocorticoid doses</th>
<th>No. of patients with ON (N = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 10 years</td>
<td>≥ 10 years</td>
<td>Prednisone dose (mg/m²)</td>
<td>Dexamethasone dose (mg/m²)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>Male</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard-risk 86</td>
<td>7</td>
<td>0</td>
<td>2</td>
<td>4,800</td>
</tr>
<tr>
<td>Standard-risk 92</td>
<td>21</td>
<td>0</td>
<td>13</td>
<td>4,740</td>
</tr>
<tr>
<td>Standard-risk 2000</td>
<td>5</td>
<td>0</td>
<td>1</td>
<td>2,400</td>
</tr>
<tr>
<td>Intermediate-risk 86</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1,980</td>
</tr>
<tr>
<td>Intermediate-risk 92</td>
<td>12</td>
<td>10</td>
<td>7</td>
<td>4,260</td>
</tr>
<tr>
<td>Intermediate-risk 2000</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td>2,400</td>
</tr>
<tr>
<td>High-risk 92</td>
<td>25</td>
<td>6</td>
<td>20</td>
<td>2,800/3,200³</td>
</tr>
<tr>
<td>High-risk 2000</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2,400</td>
</tr>
</tbody>
</table>

¹Cumulative doses represent total prednisone or dexamethasone (mg/m²) in the protocol.
²Patients were randomly assigned to receive or not to receive eight 5-day reinductions of dexamethasone during maintenance.
³Values are for ≥ 5 / < 5 years old.

4.1.2 A study of ON after treatment for lymphoma or solid tumor

A total of 32 consecutive patients, 20 males and 12 females, were included in the study (mean age 7.1 years, range 1.3 to 15.3). Patients with brain tumor were excluded. MRI of the lower extremities was performed in connection with imaging of the primary tumor, MRI was not performed if the patient required long MRI imaging time because of the extent of the primary disease or needed imaging of two sites for other clinical reasons, for example, imaging of the brain because of neurological symptoms. Approximately 40% of all the eligible patients were imaged. The underlying malignancies were Wilms’ tumor in 8 patients, NHL in 8 patients, HL in 7 patients, rhabdomyosarcoma in 6 patients and other solid tumors in 3 patients (pleuropulmonary blastoma, neuroblastoma, and germinoma testis). Treatment was carried out according to the respective national and international cooperative therapy studies. The medical records were reviewed manually with special attention to the patients’ treatment, clinical course, and possible symptoms of ON. All patients had been treated with combination chemotherapy including GCs in lymphoma patients. Very high cumulative doses of dexamethasone (up to 1,080 mg/m²) were administered to some patients to treat nausea.
4.2 Register-based study of ON requiring TJA (III, IV)

The cohort consisted of 6,358 patients diagnosed with hematologic malignancy and of 18,542 patients diagnosed with solid tumor before 31 years of age. Patients were identified from the Finnish and Danish Cancer registries. These data were combined with data from the Finnish and Danish National Hospital Discharge registers and the Finnish Arthroplasty Registry. Data on the orthopedic procedures performed and the appropriate diagnosis codes given before the age of 40 were also retrieved.

4.2.1 Finnish and Danish Cancer registries

The population-based and nationwide Finnish Cancer Registry has collected data on all cancers diagnosed in Finland since 1953. The registry is more than 99% complete and very accurate (Teppo et al. 1994). The Danish Cancer Registry is a population-based registry containing data on the incidence of cancer throughout Denmark since 1943. Details of individual cases of cancer are available according to the 7th revision of the International Classification of Diseases (ICD) for all years and according to the ICD-O since 1978 (Storm et al. 1997). The patient population was identified from the two cancer registries: cancer diagnosed at age 0–30 years from 1975 to 2000 in Finland and from 1975 to 2006 in Denmark. Only patients who survived for at least two years after diagnosis were included. The study population included all patients diagnosed with cancer, excluding nonmelanoma skin cancers and bone and connective tissue cancers. Patients with bone and connective tissue cancers were excluded because TJA was frequently performed in these patients due to primary cancer, not due to ON.

4.2.2 Finnish and Danish National Hospital Discharge registers

The Finnish National Hospital Discharge Register (FNHDR) is maintained by the National Institute for Health and Welfare and contains comprehensive healthcare records on inpatients, provided by all hospitals and municipal health centers in Finland. In the FNHDR, information about the discharge diagnoses, surgical procedures, dates of admission and discharge, and hospital code has been recorded since 1967. The coverage and accuracy of the diagnosis registration are approximately 90% (Mattila et al. 2008). During the study period, Finnish
Procedure Coding 1983 and 1996, Classification of diseases 1969 and 1987, and ICD-10 were used in Finland.

The Danish National Hospital Discharge Register (DNHDR) has information on all discharges from Danish hospitals since 1977 and records 99.4% of all discharges from public somatic hospitals in Denmark (Andersen et al. 1999). The register includes information about the discharged patients’ hospital, surgical procedures, discharge diagnoses and date of discharge. Discharge diagnoses in the DN HDR are classified according to the ICD-8 from 1977 to 1993 and the ICD-10 from 1994 to the present.

The personal identification codes of the cancer registries were combined with the FNHDR and DNHDR data. The data from the NHDRs were used to determine the number of discharges according to the ICDs and procedures coding. Patients’ orthopedic diagnoses and procedures performed before the age of 40 during 1980–2008 were extracted. This age limit was chosen because the incidence of TJA increases significantly after the age of 40 (Finnish National Institute for Health and Welfare 2011). From the extracted data, this study reports the cases in which patients underwent primary hip or knee TJA. We also obtained data concerning the diagnoses of ON and rheumatoid diseases, fractures, and allo-SCT. Data on allo-SCT were retrieved for analysis as a potential risk factor. Patients with rheumatoid diseases or fractures as an indication for TJA were excluded from the analysis.

4.2.3 Finnish Arthroplasty Registry

The Finnish Arthroplasty Registry has been collecting information on total hip and knee replacements since 1980 (Puolakka et al. 2001). All hospitals that perform TJA procedures are required to provide the National Agency for Medicines information essential for maintaining the registry. The Finnish Cancer Registry personal identification codes were combined with the Finnish Arthroplasty Registry data to ensure that all patients with TJA were included. For Finland, we used the Arthroplasty Registry and the Hospital Discharge Register to identify all the arthroplasties performed. For Denmark, we used only the Hospital Discharge Register, because the Danish Arthroplasty Registry was not initiated until 1995.
4.3 Definition of ON (I, II)

The MRI examinations were performed using a 1.5-T (Magnetom; Siemens, Erlangen, Germany; or Signa EchoSpeed; GE Medical Systems, Milwaukee, WI) or a 1.0-T superconducting system (Magnetom; Siemens). T1-weighted (time of repletion 500 to 800, echo time 9–15) and T2-weighted (4,700/90) and stir (3,000/48/150) coronal images were obtained covering the lower extremities from the femoral head to the ankle. The field of view was 30 to 50 cm, section thickness was 4 to 5 mm with a 0.5- to 1.5-mm gap, one to two acquisitions, and 192 to 224 × 256 to 512 matrix. Sagittal T1-weighted images were also occasionally obtained from the thighs. A body coil or a torso phased array coil was used. In all patients, at least T1-weighted coronal images were obtained from the thighs, but otherwise, the protocols in the different hospitals varied in such a way that T2-weighted images were obtained in Kuopio, whereas stir images were recorded in Oulu. The images were reviewed and analyzed in consensus by two radiologists (A.J. and E.P.) blinded to the treatment protocols and the patients’ symptoms.

Circumscribed lesions with a rim of low signal (T1-weighted images) or a double-line sign (T2-weighted images) were considered typical of ON. Patchy low-intensity lesions without a typical rim were also classified as ON. The involved sites of ON were first determined exactly and then classified according to the closest joints.

4.4 Statistical methods (I–IV)

The statistical analyses were conducted using the Pearson χ² test or Fisher’s exact test for the categorical variables and Student’s two-tailed t test for the continuous variables. Univariate and multivariate logistic regression analyses were performed to determine whether prospectively defined factors were useful in predicting patient’s ON risk.

Incidences rates of ON requiring TJA and 95% confidence intervals (CIs) were calculated for the various cancer diagnoses. The differences in incidence rates per 1,000 person-years between patients with and without allo-SCT were tested using Fisher’s exact test. Hazard ratios and 95% CI between patient characteristics and TJA were analyzed with univariate and multivariate Cox regression analyses. The timing of TJA from the date of cancer diagnosis to event was estimated according to Kaplan-Meier analysis. To assess differences in
cumulative survival between the different types of cancers, we used the log-rank test to plot Kaplan-Meier survival curves and evaluate their statistical significance.

The data were analyzed with SPSS for Windows (versions 11.0, 14.0, and 20.0.0, IBM Company, Chicago, IL, USA) and with StatsDirect (version 2.7.2, StatsDirect Ltd, Cheshire, UK). Two-tailed p values of less than 0.05 were considered statistically significant.

4.5 Ethical considerations (I–IV)

The research protocols for studies I and II were approved by the ethical committees of the Oulu and Kuopio University Hospitals. Informed consent was obtained from all the participating patients or their guardians for patients aged 15 years or less.

Studies III and IV were approved by the Ethics Committee of Oulu University Hospital in Finland and the Danish Data Protection Agency. The Ministry of Social Affairs and Health and Statistics in Finland gave permission for the use of data from the registers.
5 Results

5.1 MRI screening for ON after treatment for ALL (I)

Incidence and influence of gender, age, and GC and methotrexate doses

ON was detected with MRI in 23 (24%) of the 97 patients. ON was less frequent in patients treated with the SR protocol (6%) compared to those treated with the IR (30%) or HR protocols (35%). The patients with ON were older at diagnosis than the patients without ON, and had received significantly more dexamethasone compared to the patients without ON. However, there was no difference in the prednisone equivalents. The incidence of ON was not associated with higher cumulative doses of methotrexate (Table 6).

Influence of the duration of dexamethasone treatment

The incidence of ON was significantly higher in the patient group that had received dexamethasone for more than 3 weeks with a taper during the delayed intensification phase compared to those who had received dexamethasone for 2 weeks with a taper or less (Table 6).

Role of obesity

BMI was significantly greater in the patients with ON at diagnosis and at the end of the treatment than in patients without ON (Table 6). At diagnosis, 30.4% of the patients with ON were obese, while only 5.4% of the patients without ON were obese according to the national criteria. All patients gained weight during the treatment, but the patients with ON gained more weight than those without ON. At the end of the treatment, 47.8% of the patients with ON and 18.9% of the patients without ON were obese. Weight for height showed the same differences as BMI (Table 6). The mean weight for height for the patients with ON was higher at diagnosis and at the end of the treatment. Both differences were statistically significant. However, gaining weight during the treatment was not a statistically significant risk factor.
Table 6. Characteristics of patients with and without ON.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients with ON (N = 23)</th>
<th>Patients without ON (N = 74)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Age at diagnosis, years</td>
<td>9.4 ± 3.5</td>
<td>5.4 ± 3.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>10</td>
<td>43</td>
<td>41</td>
</tr>
<tr>
<td>Female</td>
<td>13</td>
<td>57</td>
<td>33</td>
</tr>
<tr>
<td>Risk group and protocol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard-risk</td>
<td>2</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Intermediate-risk</td>
<td>9</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>High-risk</td>
<td>12</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Dexamethasone, mg/m²</td>
<td>283 ± 133</td>
<td>195 ± 157</td>
<td>0.02</td>
</tr>
<tr>
<td>Prednisone equivalent, mg/m²</td>
<td>5,260 ± 740</td>
<td>5,034 ± 634</td>
<td>0.2</td>
</tr>
<tr>
<td>Methotrexate, g/m²</td>
<td>26.0 ± 16.1</td>
<td>33.1 ± 13.2</td>
<td>0.04</td>
</tr>
<tr>
<td>Weight for height at diagnosis (%)</td>
<td>11.3 ± 22.2</td>
<td>-0.8 ± 10.9</td>
<td>0.001</td>
</tr>
<tr>
<td>Weight for height at the end of the treatment (%)</td>
<td>25.3 ± 25.2</td>
<td>8.8 ± 15.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Weight for height change (%)</td>
<td>14.0 ± 15.1</td>
<td>9.6 ± 9.2</td>
<td>0.1</td>
</tr>
<tr>
<td>BMI percentile at diagnosis¹</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 5th</td>
<td>1</td>
<td>4.3</td>
<td>8</td>
</tr>
<tr>
<td>5th–85th</td>
<td>13</td>
<td>56.5</td>
<td>56</td>
</tr>
<tr>
<td>85th–95th</td>
<td>2</td>
<td>8.7</td>
<td>6</td>
</tr>
<tr>
<td>&gt; 95th</td>
<td>7</td>
<td>30.4</td>
<td>4</td>
</tr>
<tr>
<td>BMI percentile at the end of the treatment¹</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 5th</td>
<td>1</td>
<td>4.3</td>
<td>1</td>
</tr>
<tr>
<td>5th–85th</td>
<td>8</td>
<td>34.8</td>
<td>46</td>
</tr>
<tr>
<td>85th–95th</td>
<td>3</td>
<td>13.0</td>
<td>13</td>
</tr>
<tr>
<td>&gt; 95th</td>
<td>11</td>
<td>47.8</td>
<td>14</td>
</tr>
<tr>
<td>Treatment with dexamethasone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>For 3–4 weeks (HR 92, IR 86, and 92)</td>
<td>20</td>
<td>35.7</td>
<td>36</td>
</tr>
<tr>
<td>For 0–2 weeks (SR 86, 92, and 2000, IR 2000, HR 2000)</td>
<td>3</td>
<td>7.3</td>
<td>38</td>
</tr>
</tbody>
</table>

¹ < 5th underweight; 5th to 85th normal weight; 85th to 95th overweight; > 0.95th obese

Data are expressed as mean ± standard deviation or number (%) of patients.

**Details of patients with ON**

The ON sites were classified according to the closest joints. Seven (30%) of the patients with ON were symptomatic, and three of them required surgical interventions. The femoral head was the affected site in all patients requiring...
surgery. All patients suffered from severe pain. The surgical operations consisted of drilling, osteotomy, and excision of the femoral head, each used once.

**Risk factors in logistic regression analysis**

In the logistic regression analysis in the univariate context, when ON was used as the dependent variable, older age at diagnosis, higher dose of dexamethasone, and higher BMI at diagnosis and at the end of the treatment emerged as significant risk factors for radiographic ON. In addition, weight for height both at diagnosis and at the end of the treatment was identified as a risk factor for radiographic ON. Gender did not show a significant association with ON in the univariate analysis. The multiple logistic regression analysis demonstrated that older age at diagnosis, higher dose of dexamethasone, higher BMI at the end of the treatment, and female gender were independent risk factors for ON (Table 7).
Table 7. Logistic regression analysis of risk factors using osteonecrosis as a dependent variable.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Univariate analysis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>1.349</td>
<td>1.169–1.556</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Female gender</td>
<td>1.615</td>
<td>0.629–4.148</td>
<td>0.3</td>
</tr>
<tr>
<td>BMI percentile at diagnosis¹</td>
<td></td>
<td></td>
<td>0.03</td>
</tr>
<tr>
<td>5th–85th</td>
<td>1.000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 5th</td>
<td>0.538</td>
<td>0.062–4.691</td>
<td>0.6</td>
</tr>
<tr>
<td>85th–95th</td>
<td>1.436</td>
<td>0.260–7.941</td>
<td>0.7</td>
</tr>
<tr>
<td>&gt; 95th</td>
<td>7.538</td>
<td>1.918–29.627</td>
<td>0.004</td>
</tr>
<tr>
<td>BMI percentile at the end of the treatment¹</td>
<td></td>
<td></td>
<td>0.04</td>
</tr>
<tr>
<td>5th–85th</td>
<td>1.000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 5th</td>
<td>5.750</td>
<td>0.325–101.584</td>
<td>0.2</td>
</tr>
<tr>
<td>85th–95th</td>
<td>1.327</td>
<td>0.307–5.729</td>
<td>0.7</td>
</tr>
<tr>
<td>&gt; 95th</td>
<td>4.518</td>
<td>1.520–13.432</td>
<td>0.007</td>
</tr>
<tr>
<td>Weight for height at diagnosis</td>
<td></td>
<td></td>
<td>0.04</td>
</tr>
<tr>
<td>5th–85th</td>
<td>1.000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 5th</td>
<td>1.051</td>
<td>1.017–1.087</td>
<td>0.003</td>
</tr>
<tr>
<td>85th–95th</td>
<td>1.327</td>
<td>1.017–1.071</td>
<td>0.001</td>
</tr>
<tr>
<td>&gt; 95th</td>
<td>4.986</td>
<td>1.956–12.470</td>
<td>0.005</td>
</tr>
<tr>
<td>Weight for height at the end of the treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexamethasone, mg/m²</td>
<td>1.000</td>
<td>1.001–1.007</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Multivariate analysis</strong></td>
<td></td>
<td></td>
<td>0.03</td>
</tr>
<tr>
<td>Risk group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard-risk</td>
<td>1.000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate-risk</td>
<td>6.643</td>
<td>1.303–33.878</td>
<td>0.02</td>
</tr>
<tr>
<td>High-risk</td>
<td>8.455</td>
<td>1.718–41.606</td>
<td>0.009</td>
</tr>
<tr>
<td>Age, years</td>
<td>1.405</td>
<td>1.172–1.683</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Female gender</td>
<td>7.587</td>
<td>1.573–36.601</td>
<td>0.01</td>
</tr>
<tr>
<td>Dexamethasone, mg/m²</td>
<td>1.005</td>
<td>1.000–1.010</td>
<td>0.03</td>
</tr>
<tr>
<td>BMI percentile at the end of the treatment¹</td>
<td></td>
<td></td>
<td>0.04</td>
</tr>
<tr>
<td>5th–85th</td>
<td>1.000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 5th</td>
<td>3.542</td>
<td>0.140–89.829</td>
<td>0.4</td>
</tr>
<tr>
<td>85th–95th</td>
<td>4.986</td>
<td>0.746–33.310</td>
<td>0.1</td>
</tr>
<tr>
<td>&gt; 95th</td>
<td>9.141</td>
<td>1.956–42.720</td>
<td>0.005</td>
</tr>
</tbody>
</table>

¹ < 5th underweight; 5th to 85th normal weight; 85th to 95th overweight; > 0.95 obese

5.2 MRI screening for ON after treatment for lymphoma or solid tumor (II)

A total of 32 patients, 20 males and 12 females, were included in the study (mean age 7.1 years, range 1.3–15.3). A total of six (19%) out of the 32 patients (5 boys, 1 girl) included in the series developed ON. All had been diagnosed with
lymphoma, either HL (n = 4) or NHL (n = 2) (Table 8). The incidence of ON in patients with HL was as high as four out of seven (57%), while in patients with NHL it was two out of eight (25%). None of the patients with other malignancies had ON. The patients with ON were older at diagnosis than the patients without ON, and had received more prednisone compared to the patients without ON. Patients with lymphoma who developed ON were older than the patients without ON. At diagnosis mean age for HL and NHL patients with ON was 12.6, whereas mean age without ON was 8.9 (p = 0.04). There was no statistically significant difference in the dose of dexamethasone or in the prednisone equivalents between the patients with and without ON.

Table 8. Characteristics of pediatric cancer patients who developed osteonecrosis.

<table>
<thead>
<tr>
<th>Case</th>
<th>Gender / age&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Diagnosis</th>
<th>Treatment protocol</th>
<th>PDN mg/m²</th>
<th>DXM&lt;sup&gt;2&lt;/sup&gt; mg/m²</th>
<th>Involved sites</th>
<th>Bone pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Female/14 HL</td>
<td>MOPP-ABVD</td>
<td>1,360</td>
<td>0+24</td>
<td>Hip B, knee B</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Male/15 NHL</td>
<td>NOPHO-ALL 92</td>
<td>2,800</td>
<td>240+185</td>
<td>Femur R</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Male/12 HL</td>
<td>MOPP-ABVD</td>
<td>3,360</td>
<td>0</td>
<td>Knee R</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Male/15 HL</td>
<td>MOPP-ABVD</td>
<td>3,360</td>
<td>0</td>
<td>Femur B, Knee B</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Male/15 HL</td>
<td>MOPP-ABVD</td>
<td>3,360</td>
<td>0</td>
<td>Femur B, Knee L</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Male/6 NHL</td>
<td>LMB 2001</td>
<td>1,740</td>
<td>15</td>
<td>Femur L</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

<sup>1</sup>Age at diagnosis of cancer.

<sup>2</sup>Dose included in the protocol + dose given for nausea.

Abbreviations: ABVD = adriamycin, bleomycin, vinblastine and dacarbazine, B = bilateral, DXM = dexamethasone, L =left, LMB = lymphoma malignancy B, MOPP = mechlorethamine, vincristine, procarbazine and prednisone, PDN = prednisone, R= right

Analysis of risk factors

Older age at diagnosis (odds ratio [OR] = 1.810, p = 0.016) and higher cumulative doses of prednisone (OR = 1.001, p = 0.05) were risk factors for radiographic ON in univariate logistic regression analysis, when ON was used as a dependent variable. We did not find statistically significant differences in BMI between patients with and without ON.
Outcome of ON

The femur and the knee were affected in four patients. In two of those patients both femurs and knees were affected. One of those with the femur and knee affected suffered from pain during the treatment and had progressive pain after the treatment for her primary tumor. A follow-up MRI examination 4 years later showed notable progression of her caput and knee necroses, but no procedures were undertaken because of a subsequent relapse and death. In another patient whose femur and knee were affected, the follow-up MRI scan 1 year later was unchanged. There is no information about follow-up MRIs in the remaining patients with ON.

5.3 Register-based study of ON requiring TJA after treatment for leukemia or lymphoma (III)

Patients requiring total joint arthroplasty

The total number of patients in this cohort was 6,358 (Table 9). TJA was performed on 48 (0.8%) patients, of whom 33 were male. The mean age at primary cancer diagnosis was 21.7 years (range 7.5–30.8) for patients requiring TJA. The mean time from cancer diagnosis to the first TJA was 6.4 years (range 0.1–23.7; Fig. 4). The estimated cumulative incidence of TJA was 4.5% at 20 years from diagnosis for patients treated for CML, followed by 2.1% for patients treated for AML (Fig. 4). In comparison, the rate was considerably lower for patients with ALL at only 0.4%. The hip was the most commonly involved joint (n = 45); knee TJA was performed in only three patients. Allo-SCT was performed in 574 of the 6,358 (9.0%) patients; TJA was primarily detected in this group (Table 10). Included in this cohort was one patient with HL who had TJA only 1 month after his primary cancer was diagnosed, which is unusual. He was included as he did not have any excluding diagnoses of fracture or rheumatoid arthritis.
Table 9. Patients with total joint arthroplasty by leukemia or lymphoma type (N = 6,358).

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Patients with TJA N (hip/knee)</th>
<th>No. of patients</th>
<th>Proportion of patients with TJA (95% CI)</th>
<th>Mean age in years (range) at cancer diagnosis among patients with TJA</th>
<th>Mean age in years (range) at time of TJA</th>
<th>Mean time in years (range) from cancer diagnosis to TJA</th>
</tr>
</thead>
<tbody>
<tr>
<td>CML</td>
<td>8 (8/0)</td>
<td>201</td>
<td>4.0 (1.7–7.7)</td>
<td>20.5 (11.0–27.4)</td>
<td>26.9 (20.1–36.0)</td>
<td>6.4 (2.8–10.1)</td>
</tr>
<tr>
<td>AML</td>
<td>8 (7/1)</td>
<td>449</td>
<td>1.8 (0.8–3.4)</td>
<td>24.3 (19.1–28.2)</td>
<td>29.1 (23.6–34.3)</td>
<td>4.8 (0.7–9.6)</td>
</tr>
<tr>
<td>HL</td>
<td>17 (16/1)</td>
<td>2,319</td>
<td>0.7 (0.4–1.2)</td>
<td>22.3 (14.0–29.0)</td>
<td>29.9 (17.3–40.0)</td>
<td>7.6 (0.1–17.1)</td>
</tr>
<tr>
<td>NHL</td>
<td>6 (6/0)</td>
<td>1,191</td>
<td>0.5 (0.2–1.1)</td>
<td>21.0 (16.5–30.8)</td>
<td>25.5 (18.5–39.1)</td>
<td>4.5 (0.8–8.4)</td>
</tr>
<tr>
<td>ALL</td>
<td>9 (8/1)</td>
<td>2,198</td>
<td>0.4 (0.2–0.8)</td>
<td>19.9 (7.5–30.2)</td>
<td>26.7 (17.3–37.1)</td>
<td>6.7 (1.7–23.7)</td>
</tr>
<tr>
<td>All cancers</td>
<td>48 (45/3)</td>
<td>6,358</td>
<td>0.8 (0.6–1.0)</td>
<td>21.7 (7.5–30.8)</td>
<td>28.1 (17.3–40.0)</td>
<td>6.4 (0.1–23.7)</td>
</tr>
</tbody>
</table>
Fig. 4. Cumulative incidence of total joint arthroplasty due to osteonecrosis following cancer diagnosis.

Table 10. Comparison of incidence rate of total joint arthroplasty per 1,000 person-years between patients with and without allo-SCT.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Patients with allo-SCT</th>
<th>TJA / person-years</th>
<th>IR</th>
<th>N= 574</th>
<th>Patients without allo-SCT</th>
<th>TJA / person-years</th>
<th>IR</th>
<th>Rate ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CML</td>
<td>7/935</td>
<td>1/2,791</td>
<td>0.3</td>
<td>20.9</td>
<td>2.7–942</td>
<td>&lt; 0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AML</td>
<td>8/1,485</td>
<td>0/5,214</td>
<td>0</td>
<td>∞</td>
<td>6.0–∞</td>
<td>&lt; 0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HL</td>
<td>0/633</td>
<td>17/39,921</td>
<td>0.4</td>
<td>0</td>
<td>0–15</td>
<td>0.999</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NHL</td>
<td>2/510</td>
<td>4/19,148</td>
<td>0.2</td>
<td>18.8</td>
<td>1.7–131</td>
<td>0.009</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALL</td>
<td>3/3,526</td>
<td>6/33,477</td>
<td>0.2</td>
<td>4.7</td>
<td>1.0–19</td>
<td>0.053</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All cancers</td>
<td>20/7,089</td>
<td>28/100,551</td>
<td>0.3</td>
<td>10.1</td>
<td>5.4–19</td>
<td>&lt; 0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IR = incidence rate

*Age at cancer diagnosis in patients with total joint arthroplasty*

The probability of ON requiring TJA was very low in children diagnosed before the age of 10. The single case was a patient diagnosed with ALL before the age of 10.
who underwent TJA 23 years after the cancer diagnosis. The incidence increased among those diagnosed at age 10 years or older and continued to steadily increase thereafter (Fig. 5).

Fig. 5. Age at cancer diagnosis for patients with total joint arthroplasty.

Risk factors in Cox regression analysis

Univariate analyses for allo-SCT, age at diagnosis and gender revealed allo-SCT was an important risk factor for ON requiring TJA in patients with CML, AML, and NHL. Older age at diagnosis of ALL significantly increased the risk of undergoing TJA (Table 11). None of the tested variables was statistically significant in patients with HL.

The results of the multivariate analysis with allo-SCT, age and gender entered into the model revealed that allo-SCT and age at diagnosis were significant risk factors for undergoing TJA. SCT increased the risk of TJA (HR = 9.4, 95% CI 5.3–16.9, p < 0.001). Older age at diagnosis increased the risk of undergoing TJA for patients aged 10–19 years old (HR = 26, 95% CI 3.2–192, p = 0.002) and for those 20 years or older at diagnosis (HR = 27, 95% CI 3.6–196, p = 0.001)
compared to those younger than 10 years of age at diagnosis. Gender was not significantly associated with TJA (HR = 1.6, 95% CI 0.84–2.9, p = 0.160).

Table 11. Univariate analysis of risk factors in patients with leukemia and lymphoma using total joint arthroplasty as a dependent variable (N = 6,538).

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Characteristic</th>
<th>TJA- (N)</th>
<th>TJA+ (N)</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CML</td>
<td>allo-SCT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>126</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>67</td>
<td>7</td>
<td>13.2</td>
<td>1.6–109.3</td>
<td>0.017</td>
</tr>
<tr>
<td>AML</td>
<td>allo-SCT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>315</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>126</td>
<td>8</td>
<td>42.4</td>
<td>2.4–740.1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>236</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>205</td>
<td>7</td>
<td>8.1</td>
<td>0.96–66.7</td>
<td>0.052</td>
</tr>
<tr>
<td>NHL</td>
<td>allo-SCT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>1,143</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>42</td>
<td>2</td>
<td>13.6</td>
<td>2.4–76.4</td>
<td>0.003</td>
</tr>
<tr>
<td>ALL</td>
<td>Age at diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt; 10 years</td>
<td>1,588</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10–19 years</td>
<td>447</td>
<td>4</td>
<td>14.2</td>
<td>1.6–127.5</td>
<td>0.018</td>
</tr>
<tr>
<td></td>
<td>20–30 years</td>
<td>154</td>
<td>4</td>
<td>41.2</td>
<td>4.6–71.3</td>
<td>0.001</td>
</tr>
<tr>
<td>All cancers</td>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>female</td>
<td>2,768</td>
<td>15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>male</td>
<td>3,542</td>
<td>33</td>
<td>1.7</td>
<td>0.9–3.2</td>
<td>0.083</td>
</tr>
<tr>
<td></td>
<td>Age at diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt; 10 years</td>
<td>2,058</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10–19 years</td>
<td>1,628</td>
<td>18</td>
<td>22.8</td>
<td>3.0–170.6</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>20–30 years</td>
<td>2,624</td>
<td>29</td>
<td>22.8</td>
<td>3.1–67.1</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>allo-SCT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>5,766</td>
<td>28</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>554</td>
<td>20</td>
<td>7.4</td>
<td>4.2–13.3</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

5.4 Register-based study of ON requiring TJA after treatment for solid tumor (IV)

The total number of patients in this cohort was 18,542. TJA was performed on 25 (0.13%) patients (Table 12). Of the 25 patients, 15 were female. The hip was the most commonly involved joint (n = 18). TJA of the knee was performed in seven patients. The mean time to the first TJA after a cancer diagnosis was 8.1 years.
(range 0.3–18.8). The overall 20-year cumulative incidence of ON requiring TJA was 1% in patients treated for kidney cancer, followed by 0.5% in those treated for breast cancer, and 0.2% in those treated for testicular cancer. The mean age at cancer diagnosis was 22.9 years (range 1.2–30.6). Four patients were younger than 10 years, and 21 were older than 20 years of age at diagnosis of primary cancer. None of the patients were diagnosed with primary cancer between age 10 and 20 years. The absolute number of TJAs was highest in patients with testicular cancer (six cases).
<table>
<thead>
<tr>
<th>Primary diagnosis</th>
<th>Patients with TJA N (hip/knee)</th>
<th>Patients N</th>
<th>Person-years</th>
<th>Incidence rate per 1000 person-years (95% CI)</th>
<th>Mean age in years (range) at cancer diagnosis among patients with TJA</th>
<th>Mean age in years (range) at time of TJA</th>
<th>Mean time in years (range) from cancer diagnosis to TJA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney tumor</td>
<td>3 (2/1)</td>
<td>536</td>
<td>9,572</td>
<td>0.3 (0.07–0.9)</td>
<td>10.2 (1.2–22.8)</td>
<td>24.0 (20.1–29.7)</td>
<td>13.8 (6.8–18.8)</td>
</tr>
<tr>
<td>Breast tumor</td>
<td>4 (3/1)</td>
<td>848</td>
<td>15,520</td>
<td>0.3 (0.07–0.7)</td>
<td>28.1 (25.2–30.4)</td>
<td>32.6 (30.1–34.2)</td>
<td>4.5 (2.0–5.9)</td>
</tr>
<tr>
<td>Testicular tumor</td>
<td>6 (3/3)</td>
<td>3,347</td>
<td>59,369</td>
<td>0.1 (0.04–0.2)</td>
<td>25.3 (22.0–28.6)</td>
<td>33.0 (24.6–37.5)</td>
<td>7.7 (2.7–14.7)</td>
</tr>
<tr>
<td>Other tumor</td>
<td>7 (7/0)</td>
<td>6,578</td>
<td>116,187</td>
<td>0.06 (0.02–0.1)</td>
<td>23.1 (2.1–29.3)</td>
<td>30.0 (15.4–38.3)</td>
<td>7.0 (0.3–13.3)</td>
</tr>
<tr>
<td>CNS tumor</td>
<td>3 (2/1)</td>
<td>4,637</td>
<td>78,211</td>
<td>0.04 (0.01–0.1)</td>
<td>19.4 (7.5–27)</td>
<td>30.0 (21.3–29.4)</td>
<td>10.6 (2.4–15.5)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>2 (1/1)</td>
<td>2,596</td>
<td>42,115</td>
<td>0.05 (0.01–0.2)</td>
<td>29.5 (28.4–30.6)</td>
<td>37.3 (34.7–39.9)</td>
<td>7.8 (6.3–9.4)</td>
</tr>
<tr>
<td>All cancers</td>
<td>25 (18/7)</td>
<td>18,542</td>
<td>320,974</td>
<td>0.08 (0.05–0.12)</td>
<td>22.9 (1.2–30.6)</td>
<td>31.0 (20.1–39.9)</td>
<td>8.1 (0.3–18.8)</td>
</tr>
</tbody>
</table>
6 Discussion

6.1 Main findings

The purpose of the current study was to define the incidence of and clinical risk factors for ON identified with end-of-therapy MRI screening among patients with childhood cancer and to investigate the incidence of and risk factors for severe ON requiring TJA in patients treated for cancer in childhood or young adulthood.

First, in the prospective MRI study, which included consecutive patients with childhood ALL, ON was detected frequently, i.e. in 24% of the MRI scans obtained at the end of the treatment. Most patients with ON were asymptomatic, but orthopedic procedures were required frequently in patients with symptomatic ON (in three out of seven cases). A new observation in this study was high BMI and high weight for height emerged as new risk factors for radiographic ON. Long continuous exposure to dexamethasone increased the risk for ON significantly.

Second, in the MRI screening study that included pediatric patients diagnosed with solid tumor or lymphoma, ON was found in six out of 32 (19%). All the patients with ON had NHL (2 cases) or HL (4 cases). Accordingly, the incidence of ON was as high as 40% in this patient group. None of the patients with solid tumor developed ON during the treatment. Only two of the six patients with ON were symptomatic, and none underwent surgery. Older age at diagnosis and a cumulative prednisone dose were identified as risk factors for ON.

Third, the first population-based study of the incidence of ON requiring TJA in children, adolescents and young adults treated for leukemia or lymphoma was performed. The highest estimated cumulative incidence at 20 years from diagnosis was in patients treated for CML (4.5%); the lowest was in patients treated for ALL (0.4%). Allo-SCT was the most important risk factor. Older age at diagnosis increased the risk of undergoing TJA: Patients who were 10–19 and 20–30 years old at diagnosis were at a higher risk of TJA than those < 10 years old at diagnosis.

Finally, in the population-based study, osteonecrosis requiring total joint arthroplasty was detected in 0.13% of the patients treated for solid tumor in childhood, adolescence or young adulthood. The overall 20-year cumulative incidence of osteonecrosis requiring total joint arthroplasty was highest in patients
treated for kidney cancer (1%) followed by breast (0.5%) and testicular cancer (0.2%).

6.2 Discussion of results

6.2.1 MRI screening for ON after treatment for ALL

The incidence of ON in this prospective study was 24%. In a previous large prospective MRI study including asymptomatic ALL and lymphoma patients, ON was found in 17 (15%) of 116 patients (Ribeiro et al. 2001), which is less than in the present study and could be due to the variation in the time point of MRI from on therapy to off therapy for some years and different GCs used. In the study by Ribeiro et al., the protocol included only prednisone, contrary to our study, which included dexamethasone.

High BMI and high weight for height percentage at diagnosis and at the end of the treatment were significant risk factors for radiographic ON, indicating that obesity may notably contribute to the development of ON. Only one study investigated the role of BMI in the development of ON in patients with leukemia before our results were published, and that study failed to find an association (Ribeiro et al. 2001). Since our study was performed, some studies have tried to find an association between ON and BMI (Kawedia et al. 2011, te Winkel et al. 2011), but the methods were different compared with our study and an association has not been found. However, in a different patient population, Metselaar et al. (1985) found the relative increase in body weight at 180 days after renal transplantation was predictive regarding risk of ON.

According to earlier studies, BMI is a good measure of adiposity (Lindsay et al. 2001, Pietrobelli et al. 1998). High BMI could cause ON due to the increased fat content of the bone marrow or through the development of fat embolism in the marrow. Some studies suggest that abnormal lipid metabolism may be associated with the development of ON. In an autopsy study on steroid-induced ON, the size of the bone marrow fat cells increased significantly at the early stages of ON development (Motomura et al. 2005). A significant increase in bone marrow fat cell size has been reported in cortisone-treated rabbits (Wang et al. 1977), and the diameter of marrow fat cells was significantly larger in the rabbits with ON than in the rabbits without ON (Miyanishi et al. 2002).
The dose of dexamethasone and the duration of dexamethasone treatment, but not the total cumulative dose of GCs, were found to be risk factors for ON in this study. Most reports of children with leukemia and ON suggest GCs are the main pathogenic factor (Arico et al. 2003, Mattano et al. 2000, Mattano et al. 2012, Ojala et al. 1999). Our study patients treated with older protocols had more ON than the patients treated with the latest protocols, which include a larger total dose of dexamethasone but for a shorter time. This indicates that the duration of dexamethasone treatment might be as important as the total dose as shown in Mattano et al.’s (2012) study published after our results.

Methotrexate is a known risk factor for osteoporosis (Pfeilschifter & Diel 2000). Methotrexate has also been suggested to be involved in the development of ON. We did not find an association between the development of ON and the higher cumulative dose of methotrexate. In fact, a higher cumulative dose of methotrexate was associated with a decreased risk for ON, probably because patients with higher doses of methotrexate received lower doses of GCs.

6.2.2 MRI screening for ON after treatment for lymphoma or solid tumor

In our study, all patients who developed ON were treated with combination chemotherapy including GCs. Three of our patients with HL did not receive GCs or develop ON; instead, the other four patients with HL treated with chemotherapy including GCs developed ON. It is postulated, also based on the earlier adult studies, that the GCs present in the Nitrogen Mustard, Oncovin, Procarbazine, and Prednisone (MOPP) combination of treatment play an important role (Cruess 1977, Mould & Adam 1983, Tombolini et al. 1992). The MOPP courses include prednisone 40 mg/m² administered continuously over 2 weeks.

ON associated with HL and NHL was first reported in adults in 1975 (Ihde & DeVita 1975). The prevalence of ON in adults has varied from 0.12% to 14% in patients with NHL and from 1.6% to 15% in patients with HL (Engel et al. 1981, Prosnitz et al. 1981, Ratcliffe et al. 1995). Two retrospective studies of patients with symptomatic ON included children treated for various malignancies. In the study of 630 patients, the incidence of symptomatic ON was highest in patients with NHL (7.1%, 2/28) followed by patients with HL (4.4%, 2/45), ALL (3.4%, 4/116) and AML (2%, 1/50) (Lackner et al. 2005). None of the patients with other solid tumor than lymphomas developed symptomatic ON. In the study of 5,278
patients treated for various malignancies the incidence of symptomatic ON in the femoral head was as low as 0.3% (15/5,278) (Hanif et al. 1993). The incidence of ON was 0.5% (2/391) in patients with HL and 0.2% (1/376) in ones with NHL.

In our series, patients with solid tumors other than lymphomas did not develop ON, which is consistent with the study by Lackner et al. (2005). Explanations for this are probably their younger age compared to patients with ON (mean 5.8 years compared to 12.7 years) and protocols not including GCs. We did not find the cumulative dose of dexamethasone was a risk factor for ON, even in patients who received notably high doses of dexamethasone to treat nausea (up to 1,080 mg/m²). The patients who received high doses of dexamethasone for nausea had solid tumors other than lymphoma. When dexamethasone is used to treat nausea, the drug is administered in short periods, usually for only a few days. According to this study, it is quite safe regarding ON to give dexamethasone for nausea to young patients with non-CNS solid tumors.

6.2.3 Register-based study of ON requiring TJA after treatment for leukemia or lymphoma

In this study of patients treated for leukemia or lymphoma, total hip arthroplasty (n = 45) was far more common than total knee arthroplasty (n = 3). The rate of total hip arthroplasties performed was 0.7% (45/6,358). A Finnish population-based study of the same study period found that the respective rate of hip arthroplasties was estimated at 0.08% (80/100,000) among patients between 30 and 39 years of age (Finnish National Institute for Health and Welfare 2011), indicating that TJA is an extremely rare procedure in young patients, even among those slightly older than our study population.

The high risk of severe ON in patients treated for myeloid leukemia could be due to the higher frequency of allo-SCT in this group: 37% of patients with CML and 30% of patients with AML had undergone allo-SCT. For CML in particular, the disease itself and the high leukocyte count could explain the high risk of severe ON and TJA. Some case reports have described patients who developed ON at cancer diagnosis when laboratory investigations revealed hyperleukocytosis and leukostasis (Hughes et al. 2007, Kraemer et al. 2003, Moon et al. 2005), which may be associated with microcirculatory obstruction of the femoral head.

Allo-SCT was a significant independent risk factor for ON requiring TJA among patients with AML, NHL, and CML, but not in patients with HL or ALL.
Patients treated for HL were the largest group with ON requiring TJA but who had not had allo-SCT, which may be explained by the intensive use of GCs in HL protocols. Previous studies among patients treated with allo-SCT have revealed that acute and chronic GVHD and its treatment with GCs are risk factors for ON (Faraci et al. 2006, Schulte & Beelen 2004, Socie et al. 1997). Patients with ALL were at the lowest risk for severe ON requiring TJA. Only 0.4% of the patients with ALL required TJA, which is consistent with the results of a recent Dutch study (te Winkel et al. 2011) in which only 2 of 694 (0.3%) patients with pediatric ALL received total hip arthroplasties. Despite the high reported incidence of ON in patients with ALL the incidence of the most severe form of ON necessitating TJA appears to be rare (te Winkel et al. 2011). However, the incidence of severe ON requiring TJA may be even higher because the follow-up ended at 40 years of age.

Although it is well-established that patients diagnosed between 10 and 20 years of age are at increased risk of ON (Vora 2011), there is a paucity of studies about ON in young adults. Patel et al. (2008) found that adolescents younger than 20 years of age at the time of diagnosis with ALL were at higher risk of ON than patients with ALL over 20 years of age at the time of diagnosis. In our study, the risk of ON requiring TJA increased with age at diagnosis even for patients diagnosed between 20 and 30 years of age.

6.2.4 Register-based study of ON requiring TJA after treatment for solid tumor

In our study, the 20-year cumulative incidence of ON requiring TJA was highest in patients with kidney cancer. Two had a nephroblastoma, and one had renal cell carcinoma. Only one previous publication has reported the development of ON in a child with a nephroblastoma (Bernbeck et al. 2002). Bone complications, including ON (Sikgenc et al. 2010), have been reported after renal transplantation. Pelvic irradiation for nephroblastoma could cause radiation necrosis in the hip, but not in the knee, which was the site of ON in one case in our study.

In our cohort, four patients with breast cancer required TJA. In the review by Shim et al. (2008), ON was found in six patients with breast cancer. Cases of ON have been reported after receiving GCs for radiation pneumonitis in patients with breast cancer (Kosaka et al. 2006). GCs are commonly used in treatment for breast cancer, usually in supportive care. The skeleton is a common site of breast
cancer metastasis (Domchek et al. 2000), and radiation therapy may be used to manage of associated bone pain. Bone irradiation can cause radiation-related ON (Hatano et al. 2004), although most breast tumor patients with bone metastases usually have shorter survival than 4.5 years, which was the mean time for the development of ON after a cancer diagnosis in our series.

In a previous study of patients with solid tumors, patients with testicular cancer were most commonly affected by ON (Winquist et al. 2001). In a study using screening with MRI, the incidence of ON in the hip was as high as 9%, and the incidence of symptomatic ON was 3.8% (Cook et al. 2001). In a systematic review of all ON cases with solid tumors in all age groups, the authors found 54 cases, of whom 39 (70%) had testicular cancer, and ON was diagnosed when the patients were younger than 42 years (Shim et al. 2008).

6.3 Strengths and limitations of the study

6.3.1 Strengths of the study

MRI screening of ON

Advantages of this study were ON was defined clearly and MRI images were reviewed and analyzed in consensus by two radiologists. MRI is the most sensitive imaging method in the early diagnosis of ON (Mitchell et al. 1987, Robinson et al. 1989, Saini & Saifuddin 2004). MRI was designed for all cancer patients prospectively, and it was performed on all of them at the same time point, at the end of the treatment. In children treated for ALL, including asymptomatic and symptomatic patients, only two prospective MRI screening studies of ON had been performed (Kawedia et al. 2011, Ojala et al. 1999). MRI screening studies of ON in patients with solid tumor have not been performed.

Register-based study of ON requiring TJA

Strengths of the current study are the nationwide coverage of cancer patients in cancer registries and systematic follow-up using the national hospital discharge registers of two countries. Arthroplasty and hospital discharge registers are used worldwide as a source for orthopedic research. The registers used in this study have been shown to be very reliable (Mattila et al. 2008, Storm et al. 1997). The
cohort size of 6,358 survivors with hematological malignancies and 18,542 survivors of solid tumors enabled us to investigate less prevalent late effects, such as ON requiring TJA. Even large osteonecrosis on an MRI scan can be asymptomatic and not cause problems to the patient in the future. By using TJA as an endpoint, the most severe symptomatic cases of ON can be identified.

### 6.3.2 Limitations of the study

**MRI screening of ON**

In Study II, the patient group was heterogeneous and small, and represented only approximately 40% of all eligible patients. However, it still counts as the largest prospective study in this patient category.

**Register-based study of ON requiring TJA**

The weakness of this study is that register-based data do not include detailed information on medical treatment, such as doses of GCs, radiological staging of ON or precise indication for TJA. In the orthopedic literature, there are no standardized clinical or radiological indications for TJA. The generally accepted indications for TJA are symptomatic destruction of the joint caused by arthritis, ON or trauma that is not treatable with conservative protocols, such as pain medication, physiotherapy or other surgical means. Therefore, even the availability of all medical records would not have changed the study in terms of determining indication for TJA. Indications for TJA are always relative, but symptoms and radiological findings have to be severe enough to justify a major operation. This is always a patient-dependent consideration. We identified only patients who needed TJA, which is a clear end-point for the progression of severe ON. The incidence of ON requiring TJA was lower than the overall incidence of this complication, but it reflects the true incidence of symptomatic severe ON.

Although the studied cohort was large, the final number of patients with ON that required TJA was small. This resulted in low statistical power, and it was not possible to test independent risk factors in patients treated for solid tumors. Due to low statistical power, it is possible that highest incidence of ON requiring TJA in patients with kidney cancer is coincidental.
6.4 Theoretical discussion

ON after childhood ALL is a well-known late effect, and the risk factors and incidence have been increasingly studied over the last decade. Usually, in ON studies the patient population, anti-leukemic treatment, and doses of GCs are well described. However, in many of these studies, it is unclear how the primary endpoint, ON, was defined. Due to this essential lack of data, comparing different studies and drawing conclusions for clinical practice is challenging.

The site of ON is crucial when determining the clinical relevance of the lesion. ON in lower weight-bearing limbs is more likely to cause symptoms than ON in upper limbs. Even large lesions, apart from the joint line in the non-weight-bearing limb, are most likely not to cause any consequences after the acute phase. In contrast, even small sized ON in the superior part of the femoral head may lead to the collapse of the hip joint and a subsequent arthroplasty operation. In the future, ON classification that is easy to use, independent of the site of ON, reliable and considers the severity of ON including the needed interventions must be developed. In the meantime, ON should be clearly defined so different studies can be compared.

In our first MRI screening study, we found in children treated for ALL had a high incidence of ON lesions at the end of the treatment. However, only three out of 23 patients needed orthopedic procedures. To learn more about the scale of this problem, we used register-based data to investigate how many patients will have TJA, most likely due to ON in later life. In our third study, we found that the incidence of ON requiring TJA in patients treated for ALL was low, only 0.4% and the incidence of ON requiring TJA was much higher in patients treated for myeloid leukemias. Even the incidence of ON is much higher in patients treated for myeloid leukemia, the problem is more important in ALL due to the higher total number of ALL cases.

Based on our results, prospective MRI screening of patients with leukemia and lymphoma after SCT should be considered, but patients with other cancer should not be screened for ON with MRI outside the context of a well-designed clinical trial. The main problem is lack of any effective intervention in patients with asymptomatic ON. However, there is a need to raise awareness of ON in symptomatic patients, especially patients after SCT or diagnosed for leukemia or lymphoma at 10 years of age and older. In symptomatic patients MRI should be performed without delay after symptoms emerge. Late consequences, for
example, potential articular collapse in a weight-bearing joint, may be prevented with early diagnosis and appropriate interventions.

It is important to design a treatment for ALL that is as harmless to bones as possible without reducing the survival rates. GCs are an essential part of ALL treatment. Thus, because avoiding the use of them is impossible according to current knowledge, finding the best way to use them is necessary. Mattano et al. (2012) concluded that alternate-week rather than continuous dexamethasone during delayed intensification is associated with a two-time reduction in the relative risk of symptomatic ON in children age 10 and older, even though children given alternate-week dexamethasone were exposed to a higher total dose of dexamethasone. In the current NOPHO ALL-2008 protocol the two-weeks of dexamethasone in delayed intensification is split, since this approach significantly reduced the risk of ON in the CCG-1961 trial (Mattano et al. 2012). It might be that the dosing dexamethasone schedule supersedes cumulative exposure as the main factor in the development of treatment-related ON (Mattano et al. 2012).

The role of genetic predisposition is under active research in patients treated for ALL. Even though older children and adolescents are at a highest risk for ON, younger children still have a risk of developing ON, which suggests that some genetic factors might play a significant role in determining predisposition to ON. The risk factors that could help identify the patients more vulnerable to developing ON have not been found. An interesting way to find the associations between clinical features and genetic polymorphisms is to use the classification and regression tree analysis, which allows sequential division of the cohort by risk factors in order of importance (Kawedia et al. 2011).

Obesity is a potential late effect of therapy in survivors of childhood ALL (Oeffinger et al. 2003). BMI was significantly higher in patients with ON at diagnosis and at the end of the treatment than in patients without ON. However, the role of obesity in the development of ON is unclear and requires further studies. During treatment for ALL the changes in diet, physical activity, and body composition are remarkable, and interventions such as health-promoting programs would be useful for minimizing the risk of obesity (Fuemmeler et al. 2013), which potentially could also reduce obesity-related side effects.

6.5 Further studies

The definition and classification of ON in cancer patients vary widely; therefore, comparing studies is challenging. In the future, there is an evident need for a
generally accepted classification system for ON, which is reliable, considers the severity of ON and is independent of the site of ON. A widely accepted classification system is one of the most important factors that could improve the quality of ON research in cancer patients in the future.

Further studies are needed to identify patients at highest risk for ON. That can be achieved by better understanding of clinical and genetic risk factors, and by developing better models that combine these risk factors. Patients at the highest risk could then be recruited for ON prevention studies. Randomized trials of bisphosphonates, lipid-lowering agents and anticoagulants in primary or secondary prevention are required to test their efficacy in this setting.

Characterization of the natural history of ON in various cancer patient groups is also needed so the appropriate patients could be targeted for early therapy modification, or surgical or medical intervention studies. A wide variety of joint-preserving surgical procedures have been used to treat ON. The benefit of these surgical procedures, optimal timing and the impact on a patient’s quality of life are not well defined. TJA is the last treatment choice in advanced ON when the joint has collapsed. Further studies in cancer patients with ON requiring TJA are needed to assess the outcome of the procedure, quality of life and implant survival.
7 Conclusion

1. We found that the incidence of radiographic ON was 24% (23/97) in children treated for ALL at the end of the treatment. High body mass index was identified as a new risk factor for ON. In addition, female gender, older age at diagnosis, and higher cumulative dexamethasone dose were independent risk factors for ON. Long continuous exposure to dexamethasone significantly increases the risk for ON. Revision of the ALL protocols by shortening the single exposure to dexamethasone diminished the risk for ON remarkably.

2. Six of the 32 patients (19%) treated for lymphoma or solid tumor had ON in MRI scans. Older age at diagnosis and a cumulative prednisone dose were identified as risk factors for ON.

3. ON requiring TJA was rare among survivors of leukemia and lymphoma in childhood and young adulthood. ON requiring TJA was most prevalent among those treated for myeloid leukemia between 10 and 30 years of age, particularly following allo-SCT. The frequency of TJA was lowest in patients with ALL among leukemia and lymphoma. Among survivors of solid tumors in childhood and young adulthood, the incidence of ON requiring TJA was rare.
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Original publications


III  Niinimäki R, Molgaard Hansen L, Niinimäki T, Olsen JH, Pokka T, Sankila R, Vettenranta K, Hasle H & Harila-Saari A. Incidence of Severe Osteonecrosis Requiring Total Joint Arthroplasty in Children and Young Adults Treated for Leukemia or Lymphoma: A Nationwide, Register-Based Study in Finland and Denmark. J Adolesc Young Adult Oncol. In press.

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