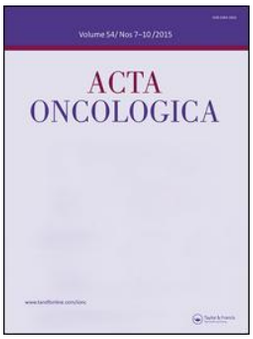

Acta Oncologica

ISSN: 0284-186X (Print) 1651-226X (Online) Journal homepage: informahealthcare.com/journals/ionc20

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To cite this article: Riitta Niinimäki, Tuukka Niinimäki, Lene Mølgaard Hansen, Jørgen H. Olsen, Tytti Pokka, Henrik Hasle & Arja Harila-Saari (2014) Osteonecrosis requiring total joint arthroplasty is a rare sequel in children and young adults treated for solid tumors, Acta Oncologica, 53:4, 481-485, DOI: 10.3109/0284186X.2013.864049

To link to this article: https://doi.org/10.3109/0284186X.2013.864049

Acta Oncologica, 2014; 53: 481–485

informa
healthcare

ORIGINAL ARTICLE

Osteonecrosis requiring total joint arthroplasty is a rare sequel in children and young adults treated for solid tumors

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ABSTRACT

Background. Osteonecrosis (ON) is a potential sequel in patients treated for malignancies. The goal of this population-based register study was to determine the incidence of ON requiring total joint arthroplasty (TJA) in patients treated for solid tumors in childhood, adolescence, or early adulthood.

Material and methods. Patients diagnosed with a solid tumor before the age of 31 years were identified from the Finnish and Danish Cancer Registries. Patients with non-melanoma skin cancers and bone and connective tissue cancers were excluded. The data were combined with data from the National Hospital Discharge Registers and the Finnish Arthroplasty Registry. Data on the orthopedic procedures performed and the diagnosis codes given before the age of 40 years were retrieved.

Results. Twenty-five of 18 542 (0.13%) patients had undergone TJA. The overall 20-year cumulative incidence of ON requiring TJA was 1% in patients treated for kidney cancer, followed by 0.5% in patients with breast cancer and 0.2% in patients with testicular cancer.

Conclusion. Severe ON requiring TJA is a rare sequel in children and young adults treated for solid tumors. It was observed most commonly in patients treated for renal, breast, or testicular cancer.

Over 75% of children, adolescents and young adults with cancer are expected to be cured and become long-term survivors [1,2]. These long-term survivors are vulnerable to treatment-related effects in later life. Osteonecrosis (ON) is recognized as a potential sequel in cancer patients treated with cytotoxic chemotherapy, but it is an extremely rare disorder in the general population [3].

The overall incidence of symptomatic ON in pediatric and adolescent cancer survivors has been reported to be low, ranging from 0.4% to 1.4% [4,5]. The incidence of ON has been found to be higher in patients with leukemia and lymphoma than in patients with solid tumors [4]. In patients with pediatric or adolescent acute lymphoblastic leukemia, the incidence of symptomatic ON was reported to vary from 1.1% to 9.3% [6,7]. Studies have found that ON occurs most commonly as a late effect of corticosteroid therapy, especially following prolonged treatment with dexamethasone [4,5], and adolescent age between 10 and 20 years at diagnosis [7]. Allogeneic stem cell transplantation [8] and treatment with radiation have also been reported to increase the risk of ON [5].

Chemotherapy-associated ON was reported in adult cases with solid tumors, mainly in patients with testicular cancer, breast cancer, ovarian cancer, and osteosarcoma [9], but only sparse data are available in survivors of solid tumors in childhood. Two case reports of ON in pediatric patients with neuroblastomas [10,11] and one case of ON in a pediatric patient with a nephroblastoma have been published [12]. ON after cancer may be asymptomatic and heal without any surgical procedures, but in most severe

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(Received 31 August 2013; accepted 2 November 2013)

ISSN 0284-186X print/ISSN 1651-226X online © 2014 Informa Healthcare
DOI: 10.3109/0284186X.2013.864049

cases it may require total joint arthroplasty (TJA). The incidence of severe symptomatic ON requiring TJA in children and young adults treated for solid tumors is unknown.

The purpose of this study was to assess the incidence of severe ON requiring TJA in patients treated for solid tumors in childhood or early adulthood in a nationwide, population-based register study in Finland and Denmark.

Material and methods

Patients diagnosed with a solid tumor before 31 years 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 diagnosis codes given before the age of 40 years were also retrieved.

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 [13]. The Danish Cancer Registry is a population-based registry containing data on the incidence of cancer throughout Denmark since 1943. Details on individual cancer cases 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 [14]. The patient population was identified from the two cancer registries: a solid tumor diagnosed at age 0–30 years in the period from 1975 to 2000 in Finland and from 1975 to 2006 in Denmark. The study population included all patients diagnosed with a solid tumor, excluding non-melanoma 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. Only patients who survived for at least two years after the diagnosis were included.

The 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. The records are provided by all hospitals and municipal health centers in Finland. Since 1967, the FNHDR has recorded information on the discharge diagnoses, surgical procedures, dates of admission and discharge, and the hospital code. The coverage and accuracy of the diagnosis registration are approximately 90% [15]. During the study period, the Finnish Procedure Coding 1983 and 1996, the Classification of Diseases 1969 and 1987, and ICD-10 were used in Finland, and ICD-8 and ICD-10 were used in Denmark.

The Danish National Hospital Discharge Register (DNHDR) contains information on all discharges from Danish hospitals since 1977 covering 99.4% of all discharges from somatic hospitals [16]. The register includes information about discharge diagnoses, surgical procedures, the hospital, and the date of discharge. Discharge diagnoses in the DNHDR are classified according to the ICD-8 for 1977 to 1993 and the ICD-10 for 1994 to the present.

The personal identification codes of the cancer registers were combined with the data from the FNHDR and DNHDR. The data from the NHDRs were used to determine the number of discharges according to the ICDs and procedure coding. Orthopedic diagnoses and procedures performed before the age of 40 years during years 1980–2008 were extracted. This age limit was chosen because the incidence of TJA increases significantly after the age of 40 [17]. From the extracted data, patients who underwent primary hip or knee TJA were identified. Data concerning the diagnoses of ON, rheumatoid diseases and fractures were also obtained. Patients with rheumatoid diseases or fractures as an indication for TJA were excluded from the analysis.

The Finnish Arthroplasty Registry

The Finnish Arthroplasty Registry has been collecting information on total hip and knee joint replacements since 1980 [18]. Healthcare authorities, institutions, and orthopedic units are obliged to provide the National Agency for Medicines with information on all arthroplasty procedures. The personal identification codes used by the Finnish Cancer Registry were combined with those of the Finnish Arthroplasty Registry to ensure that all patients with TJA were included. The Arthroplasty Registry and the Hospital Discharge Register were used in Finland. Only the DNHDR was used in Denmark because the Danish Arthroplasty Register was not initiated until 1995.

Statistical analysis

The cumulative 20-year incidence of TJA was estimated using the Kaplan-Meier method. The incidence rates of ON requiring TJA per 1000 person years and their 95% confidence interval (CI) were

calculated for the different cancer diagnoses. All the analyses were performed with IBM SPSS Statistics version 20.0.0 (IBM, Chicago, IL, USA) and StatsDirect 2.7.2 (StatsDirect Ltd., UK).

This study was 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 the data from the registers.

Results

Patients requiring TJA

The total number of patients in this cohort was 18 542. TJA was performed on 25 (0.13%) patients (Table I). 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 years). 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 years). 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 10 and 20 years. The characteristics of the patients who developed ON requiring TJA are shown in Table II. The absolute number of TJAs was highest in patients with testicular cancer (six cases).

Discussion

In this population-based study, ON requiring TJA was detected in 0.13% of the patients with a solid tumor in childhood, adolescence, or young adulthood. The overall 20-year cumulative incidence of ON requiring TJA was highest in patients treated for kidney cancer (1%) followed by breast (0.5%) and testicular cancer (0.2%).

In our study, the 20-year cumulative incidence of ON requiring TJA was highest in patients with kidney cancer. Two of them 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 [12]. Bone complications, including ON [19], 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 literature review by Shim et al., ON was found in six patients with breast cancer [9]. Cases of ON have been reported after receiving glucocorticoids for radiation pneumonitis in patients with breast cancer [20]. Glucocorticoids are commonly used in the treatment of breast cancer, as part of chemotherapy protocols or in supportive care. The skeleton is a common site of breast cancer metastasis [21], and radiation therapy may be used in the management of associated bone pain. Bone irradiation can cause radiation-related ON [22], 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, testicular cancer patients were most commonly affected by ON [23]. In a study using screening with magnetic resonance imaging (MRI), the incidence of ON in the hip was as high as 9%, and the incidence of symptomatic ON was 3.8% [24]. In a systematic review of all ON cases with solid tumors in all age groups, the authors found 54 cases, of which 39 (70%) had testicular cancer, and the ON was diagnosed when the patients were younger than 42 years [9].

Table I. Patients with total joint arthroplasty in different cancer groups.

Primary diagnosis	Patients with TJA n (hip/knee)	Total no. of patients	Person-years	IR per 1000 person-years (95% CI)	Mean age in years (range) at cancer diagnosis among patients with TJA	Mean age in years (range) at time of TJA	Mean time in years (range) from cancer diagnosis to TJA
Kidney tumor	3 (2/1)	536	9572	0.3 (0.07–0.9)	10.2 (1.2–22.8)	24.0 (20.1–29.7)	13.8 (6.8–18.8)
Breast tumor	4 (3/1)	848	15520	0.3 (0.07–0.7)	28.1 (25.2–30.4)	32.6 (30.1–34.2)	4.5 (2.0–5.9)
Testicular tumor	6 (3/3)	3347	59369	0.1 (0.04–0.2)	25.3 (22.0–28.6)	33.0 (24.6–37.5)	7.7 (2.7–14.7)
Other tumor	7 (7/0)	6578	116187	0.06 (0.02–0.1)	23.1 (2.1–29.3)	30.0 (15.4–38.3)	7.0 (0.3–13.3)
CNS tumor	3 (2/1)	4637	78211	0.04 (0.01–0.1)	19.4 (7.5–27)	30.0 (21.3–29.4)	10.6 (2.4–15.5)
Melanoma	2 (1/1)	2596	42115	0.05 (0.01–0.2)	29.5 (28.4–30.6)	37.3 (34.7–39.9)	7.8 (6.3–9.4)
All cancers	25 (18/7)	18 542	320974	0.08 (0.05–0.12)	22.9 (1.2–30.6)	31.0 (20.1–39.9)	8.1 (0.3–18.8)

CI, cumulative incidence; CNS, central nervous system; IR, incidence rate; TJA, total joint arthroplasty.

Table II. Characteristics of patients with solid tumors who developed osteonecrosis requiring total joint arthroplasty.

Case	Gender/age at diagnosis in years	Solid tumor according to ICD-7/ICD-10	Histology	Age at diagnosis of TJA in years	Time in years to TJA after cancer diagnosis	Involved site
1	M/24	Mediastinum	Yolk sac tumor	33	9.2	Hip
2	F/26	Ascending colon	Carcinoid tumor	34	8.3	Hip
3	F/31	Malignant melanoma of lower limb, including hip	Malignant melanoma	40	9.4	Hip
4	F/2	Primary liver tumor	Embryonal tumor	15	13.3	Hip
5	F/29	Thyroid gland	Follicular adenocarcinoma	34	4.4	Hip
6	F/28	Malignant melanoma of overlapping sites of skin	Nodular melanoma	35	6.3	Knee
7	F/28	Vulva	Peripheral neuroectodermal tumor	31	3.0	Hip
8	F/24	Border of tongue	Squamous cell carcinoma	25	0.3	Hip
9	F/23	Malignant neoplasm of kidney	Renal cell carcinoma	30	6.8	Hip
10	F/1	Malignant neoplasm of kidney	Nephroblastoma	20	18.8	Hip
11	M/7	Malignant neoplasm of kidney	Nephroblastoma	22	15.7	Knee
12	M/8	Craniopharyngeal duct	Craniopharyngeoma	21	13.9	Hip
13	F/24	Brain, supratentorial	Unknown	39	15.5	Knee
14	M/27	Brain stem	Hemangioblastoma	29	2.4	Hip
15	M/26	Testis	Seminoma	37	11.6	Knee
16	M/23	Testis	Embryonal carcinoma	37	14.7	Knee
17	M/29	Testis	Malignant teratoma	37	8.3	Knee
18	M/22	Testis	Teratocarcinoma	25	2.7	Hip
19	M/29	Testis	Embryonal carcinoma	35	6.0	Hip
20	M/24	Testis	Embryonal carcinoma	27	3.1	Hip
21	F/29	Breast	Lobular carcinoma	34	5.1	Hip
22	F/30	Breast	Adenocarcinoma	32	2.0	Hip
23	F/28	Breast	Medullary carcinoma	34	5.9	Knee
24	F/25	Breast	Lobular carcinoma	30	4.9	Hip
25	F/28	Ovary	Papillary serous cystadenoma	38	10.4	Hip

Some limitations of the current study must be considered. Although the studied cohort was large, the final number of ON requiring TJA was small. This resulted in low statistical power, and it was not possible to test independent risk factors. Moreover, register-based data do not include detailed information on the treatment. 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.

The strengths of our study include its nationwide coverage of patients with cancer and systematic follow-up utilizing the national hospital discharge registers. The size of the cohort of 18 542 survivors of solid tumors allowed a study of the less prevalent late effects, such as ON. The registries employed have been shown to be very reliable [14]. In this study, we limited the age of the patients with TJA to 40 years. A Finnish population-based analysis of the same study period found that the estimated rate of hip arthroplasties was 0.08% (80/100 000) among patients between 30 and 39 years of age [17], indicating that TJA is an extremely rare procedure in young patients, even among those slightly older than our study population.

We conclude that among survivors of solid tumors in childhood, adolescence, and young adulthood, the incidence of severe ON requiring arthroplasty is rare. However, there is a need awareness of the potential risk of this complication, especially in patients with renal, breast, or testicular cancer. Based on our results, routine MRI screening for ON in patients with solid tumors cannot be recommended.

Acknowledgments

The authors would like to acknowledge Prof. Risto Sankila for his contribution to the data extraction from the Finnish Cancer Registry.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

This work was supported by grants from the Nona and Kullervo Väre Foundation, the Foundation for Paediatric Research, the Cancer Society of Northern Finland, the Alma and K.A. Snellman Foundation and the Finnish Medical Foundation.

These foundations had no role in the study design, data collection, analysis and writing or in the decision to submit the manuscript.

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