ARTICLE

Multiple primary malignancies in osteosarcoma patients. Incidence and predictive value of osteosarcoma subtype for cancer syndromes related with osteosarcoma

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The overall incidence of osteosarcoma is low. However, the occurrence of osteosarcoma in a setting of multiple primary tumours is not infrequent, although population-based incidence numbers are unknown. The occurrence of osteosarcoma and other malignancies is frequently related to treatment, and can also be the result of genetic predisposition as in patients with retinoblastoma, Li-Fraumeni syndrome, Werner syndrome and Rothmund–Thomson syndrome. The aim of our study is to establish the incidence of osteosarcoma associated with other malignancies in a populationwide study and to find out if these osteosarcomas have a specific subtype, that could draw attention to a genetic predisposition to malignancy. A list of all patients registered in the Dutch National Pathology Register, named PALGA, with a diagnosis of osteosarcoma between 1975 and May 2000 was retrieved. All patients with another malignancy besides osteosarcoma were selected. All patients registered in the same period with a tonsillectomy served as a control for the occurrence of malignancy in a normal population. In a second step, only osteosarcoma patients with a history of retinoblastoma or a malignancy before the age of 46 years, since these are most probable to have a hereditary cancer syndrome, were retained for further analysis. The osteosarcomas were subtyped as common, chondroblastic, fibroblastic, teleangiectatic, anaplastic, osteoclast-rich or small cell. As a control for osteosarcoma subtypes the data of 570 patients entered in two studies from the European Osteosarcoma Intergroup (EORTC/MRC) were used. Of all 938 patients registered with the diagnosis of osteosarcoma, 66 had a history of multiple primary tumours. Four patients had a surface osteosarcoma, three an extraskeletal osteosarcoma and 59 had intramedullar high-grade osteosarcoma. Of this last group, one patient was known with Rothmund–Thomson syndrome, one had retinoblastoma and 30 had their malignancies before the age of 46. Of these 32 patients, 17 had osteosarcoma of the long bones. Especially women seem to be more susceptible for the development of multiple primaries. In nine patients, the histological subtype could be assessed by revision of available histological slides. All of these patients had an osteosarcoma subtype other than common as opposed to 29% in the control group of the European Osteosarcoma Intergroup. It is concluded that although the

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incidence of osteosarcoma is low, the occurrence of another malignancy in osteosarcoma patients is higher than in the normal population. Specifically, osteosarcoma patients have a relative risk of 2.4 (95% confidence interval 1.88–3.07) to develop another malignancy. A noncommon subtype of osteosarcoma should draw attention to a possible genetic predisposition of the patient involved.

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Introduction

Osteosarcoma is the most frequent nonhaematogenic malignant bone tumour.^{1–3} Central high-grade osteosarcoma accounts for approximately 20–22% of all primary malignant bone tumours. Although the overall incidence of osteosarcoma is low, osteosarcoma is one of the most frequent tumours associated with other malignancies. Aetiology is multifactorial. Case reports on second malignancies including osteosarcoma after radiation or chemotherapy treatment in cohorts of patients with cancer in childhood and adolescence are many. These studies have been substantially reviewed by Cullen and Meadows.^{4,5} The occurrence of multiple primary tumours including osteosarcoma can also be the result of genetic predisposition as is the case in retinoblastoma^{6–13} and the Li-Fraumeni syndrome.^{14,15} There is also an elevated risk for osteosarcoma in Werner syndrome^{16–18} and Rothmund-Thomson syndrome.¹⁹ Data on syndrome-related osteosarcoma patients are mostly calculated from clusters and families of patients already diagnosed with a specific genetic syndrome and thus give no indication of the incidence of hereditary cancer syndromes including osteosarcoma in a population. Based on histological criteria, osteosarcomas can be subtyped as common, chondroblastic, teleangiectatic, fibroblastic, small cell, giant cell rich and sclerotic/osteoblastic. The histological subtype of osteosarcoma is a predictive factor for response to chemotherapy,^{20,21} is related with disease-free survival²² and tends to be related with overall survival.²¹

In order to have an estimate of the number of osteosarcoma patients with a possible hereditary cancer syndrome in a population, we studied all patients with high-grade intramedullary osteosarcoma, who either had a retinoblastoma in the antecedents or any other primary tumour at a relative young age.

In addition, we were interested to see if osteosarcoma subtypes reflect a possible hereditary background for malignancy.

Material and methods

Database

Listings of all patients between 1975 and the 20th of May 2000 diagnosed with osteosarcoma were obtained through

the national computerised pathology records system of Foundation PALGA (The Dutch National Pathology Registry). The PALGA registration is obligatory for all pathology labs in the Netherlands. It contains the full conclusions of the pathology report and includes as such all histological and cytological and autopsy data for every patient in the Netherlands. This registration started in 1975 and reached 100% participation of all pathology labs since 1990. This database serves for several population-based questions and forms among others the database source for the Dutch Cancer Registry.

All patients with a reliable diagnosis of osteosarcoma and any other primary tumour, not carcinoma *in situ*, were selected for further investigation.

Selection of syndrome-suspected study group

The syndrome-suspected study group was composed of all osteosarcoma patients with one of the following criteria: (1) a medical history of retinoblastoma; (2) a primary tumour diagnosed before the age of 46 years, since 70% of the Li-Fraumeni patients are at risk to develop a second primary malignancy after a first primary before that age;²³ (3) patients with carcinoma of the skin before the age of 44 years. This age was chosen as a cutoff, since only 4% of all squamous cell carcinomas of the skin and only 10% of all basal cell carcinomas of the skin occur before the age of 44 as has been shown by a study covering the region of south-east Netherlands.²⁴ Of these patients all available patient data and histological material were reviewed.

Review and classification

Subtyping of the osteosarcomas was performed by two review pathologists of the European Osteosarcoma Inter-group (PCWH and EH). Osteosarcomas were classified as conventional, chondroblastic, teleangiectatic, small cell, fibroblastic, osteoclast rich, anaplastic and sclerotic/osteoblastic well differentiated, as defined by the established criteria.^{25–30}

Control groups

As a control for the occurrence of malignancy served 23 252 patients with tonsillectomy diagnosed in the same study period (database interval) as the osteosarcoma patients. Using this control group from the same database, instead of computing an expected number of carcinomas

in the general population, has several important advantages. The selection of patients with osteosarcoma is the same as the selection of the control group, coming from the same group of pathology labs, so that potential regional differences in completeness of adherence of pathology laboratories to the database are levelled out. Moreover, it is not clear how 'person-years' should be calculated, since the survival of the patients with the primary tumours in the database is not known. Patients with lymphoma or malignancy in the head and neck region, in which tonsillectomy is part of the diagnostic work up or treatment, were excluded in order to avoid selection bias. We adjusted the relative risk calculation for age and sex by use of a Mantel-Haenszel procedure.

As control for subtype the histological data from the first two studies of the EORTC, including 570 patients, were used.²¹ The distribution of the subtypes in this group is comparable to that of a similar study group of the Rizzoli Institute.²⁰

Results

Osteosarcoma in the Netherlands

According to the data obtained from PALGA, 938 patients, 513 male and 425 female, were diagnosed with osteosarcoma between 1975 and May 2000. Age varied from less than

Table 1 Localisation of osteosarcoma by gender

	M	F	
Intramedullar osteosarcoma extremity	374	281	
Intramedullar osteosarcoma axial skeleton	87	97	
Surface OS	25	26	
Extra skeletal OS	27	21	
Total	513	425	938

Table 2 Localisation of osteosarcoma in patients with other malignancies

	M	F	
Intramedullar osteosarcoma extremity	9	17	
Intramedullar osteosarcoma axial skeleton	13	20	
Surface OS	2	2	
Extra skeletal OS	0	3	
Total	24	42	66

1 year to 99 years with a mean of 20 years. Distribution per age group is given in Figure 1 and distribution by localisation in Table 1.

Figure 1 (a) Number of osteosarcoma patients by age as found in the nationwide survey ($n=938$). (b) Number of tonsillectomy patients by age ($n=23\,252$).

Patients with multiple primary malignancies including osteosarcoma

A total of 66 osteosarcoma patients (7%) had another malignancy, 24 male (5% of the male osteosarcoma patients) and 42 female (10% of the female osteosarcoma patients) (Table 2). These 66 patients had a total of 73 other malignancies. Multiple basal cell carcinomas in a given patient were counted as one. The nature of these other malignancies is summarised in Table 3. Thirty-five patients had their malignancy prior to osteosarcoma, 31 after. The interval ranged from 0 to 264 months with an average of 92 months prior to the diagnosis of osteosarcoma and 0–231 months with an average of 79 months after the diagnosis of osteosarcoma. In patients with osteosarcoma and another malignancy, the osteosarcomas were more frequently localised in flat bones, bones of the skull and axial skeleton (Table 4). In all, 18% of the patients with intramedullar osteosarcoma of the skull and axial skeleton had other malignancies in contrast to 4% of the patients with osteosarcoma of the long bones of the extremity.

In the control group of 23 252, tonsillectomy patients, 10 142 men and 13 110 women (age distribution in Figure 1), 383 (1.6%) had a malignancy in the observed interval of 120 months before or after tonsillectomy. The crude relative risk of developing a malignancy in osteosarcoma patients is 4.4. After adjustment for age and sex, the relative risk is 2.4 (95% confidence interval 1.88–3.07).

Table 3 Nature of the second neoplasm besides osteosarcoma

Other malignancy	M < 45 years	M ≥ 45 years	F < 45 years	F ≥ 45 years
Hodgkin's disease	2			1
Haematogenic diseases	1		2	
Non-Hodgkin's lymphoma	1		1	2
Basal cell carcinoma skin	1	5		6
Squamous carcinoma skin				1
Malignant melanoma skin			1	
Squamous cell carcinoma nose			1	
Squamous carcinoma pharynx/larynx		2	1	
Adenocystic carcinoma palate			1	
Muco-epidermoid carcinoma parotid			1	1
Hepatocellular carcinoma				1
Adenocarcinoma lung		1		
Squamous carcinoma lung		1		
Signet ring cell carcinoma stomach		2		
Adenocarcinoma large intestine				3
Renal cell carcinoma		2		
Urothelial carcinoma bladder		1		
Prostatic adenocarcinoma		1		
Ductal carcinoma breast			2	5
Squamous carcinoma cervix uteri				1
Endometrioid carcinoma				1
Ovarian carcinoma			1	
Embryonal cell carcinoma ovary			1	
Teratoma testis	1			
Oligodendroglioma	1			
Papillary carcinoma thyroid gland			1	
Fibrosarcoma		1	1	
Leiomyosarcoma			1	1
Rhabdomyosarcoma	1			
Ewing's sarcoma	1		2	
Liposarcoma				1
Nephroblastoma			1	
Retinoblastoma			2	
Unknown			3	1

Syndrome-suspected study group

After selection of all patients with intramedullar osteosarcoma and a history of bilateral retinoblastoma, carcinoma of the skin before 44 years of age or any primary tumour till the age of 45 years, a group of 31 patients remained. One patient with known Rothmund–Thomson syndrome was also included. The data of these 32 patients are summarised in Table 5. In the syndrome-suspected study group without relation to treatment patients with other malignancies

Table 4 Proportion of osteosarcomas by localisation with and without other malignancies

	Osteosarcoma only		Osteosarcoma+ other	
Intramedullar osteosarcoma extremity	655	70%	26	39%
Intramedullar osteosarcoma axial skeleton	184	20%	33	50%
Surface OS	51	5%	3	4,5%
Extra skeletal OS	48	5%	3	4,5%
Total	938	100%	67	100%

represented 2% of the patients with osteosarcoma of the long bones and 2% of the patients with osteosarcoma of the bones of the skull and axial skeleton. Thus, the observed over-representation of osteosarcoma of flat bones and bones of the axial skeleton in patients with other malignancies was not seen anymore in the syndrome-suspected study group.

The patient data and histological material from contributory departments of pathology all over the Netherlands were reviewed. From 20 patients histological material was available for review and analysis (Table 6). Ethics and privacy guidelines concerning the use of patient files made it impossible to obtain additional data on patients and treatment modalities outside the pathology protocol that was sent in with the histological material.

In the total group of 32 of patients, eight patients developed an osteosarcoma at the site of previous radiation therapy, one patient had lymphoma and one myelodysplastic syndrome after chemotherapy for osteosarcoma. In 14 patients (case numbers in bold), we could make sure that there was no relation with therapy between primary and secondary tumour. One of these patients was known with Rothmund–Thomson, one had a basal cell carcinoma and the remaining 12 patients potentially belonged to a Li-Fraumeni (-like), or other not yet defined cancer syndrome family.

Osteosarcoma subtypes in syndrome-suspected osteosarcoma patients

All of the patients in our final selection of osteosarcoma patients with high-grade intramedullar osteosarcoma suspected of a genetic cancer syndrome, and from which material was present for review (Table 7), had an osteosarcoma subtype other than common as opposed to 29% in the control group (Table 8).

Discussion

Data on osteosarcoma in occurrence with other malignancies come to us by large follow-up studies on late effects

Table 5 Syndrome-suspected study group

No.	Primary tumour	Localisation	Therapy	Secondary tumour	Localisation
118	Osteosarcoma	Femur	NA	Squamous cell carcinoma	Larynx
120	Osteosarcoma	Cervical vertebra	S, RT	Adenocarcinoma	Kidney
121	Osteosarcoma	Cervical vertebra	S, RT	Adenocarcinoma	Kidney
153	Morbus Hodgkin	Neck	RT	Osteosarcoma	Clavicle
162	Osteosarcoma	Femur	S, RT	Basal cell carcinoma	Back
173	Teratoma	Testis	S, RT	Osteosarcoma	Vertebra
196	Osteosarcoma	Fibula	NA	Plasmocytoma	Ileum
217	Oligodendroglioma	Brain	S, RT	Osteosarcoma	Skull
247	Unknown	Unknown,	RT	Osteosarcoma	Tibia
299	Rhabdomyosarcoma	Maxilla	Ratchet	Osteosarcoma	Palatum
307	Ewing's sarcoma	Humerus	NA	Osteosarcoma	Humerus
529	Lymphoma	Abdomen	ChT	Osteosarcoma	Maxilla
732	Osteosarcoma	Femur	NA	Ductal carcinoma	Breast
734	Osteosarcoma	Sternum	NA	Ductal carcinoma	Breast
776	Osteosarcoma	Jaw	NA	Morbus Hodgkin	Axilla
790	Adenocystic carcinoma	Palatum	S, RT	Osteosarcoma	Jaw
791	Fibrosarcoma	Breast	NA	Osteosarcoma	Rib
803	Unknown	Unknown	RT	Osteosarcoma	Rib
808	Unknown	Unknown	RT	Osteosarcoma	Clavicle
809	Osteosarcoma	Tibia	NA	Mucinous carcinoma	Ovary
883	Osteosarcoma	Tibia	S; RT	Ductal carcinoma	Breast
897	Osteosarcoma	Femur	NA	Melanoma	Arm
906	Leiomyosarcoma	Cervix	NA	Osteosarcoma	Femur
911	Nephroblastoma	Kidney	NA	Osteosarcoma	Rib
912	Ewing's sarcoma	Humerus	NA	Osteosarcoma	Humerus
971	Osteosarcoma	Femur	S, ChT	Ductal carcinoma	Breast
1035	Osteosarcoma	Femur	S, ChT	Lymphoma	
1039	Osteosarcoma	Femur	S, ChT	MDS	
1058	Osteosarcoma	Fibula	S, ChT	Squamous cell carcinoma	Tongue
1107 ^a	Osteosarcoma	Tibia	NA		
1125	Osteosarcoma	Femur	NA	Leukaemia	
1148	Retinoblastoma	Eye	S, RT	Osteosarcoma	Nose

^aPatient known with Rothmund–Thomson.

NA: information not available; S: surgery; RT: radiation therapy; ChT: chemotherapy.

in patients treated for cancer in childhood. With the exception of the study by Hawkins *et al*,¹⁰ all these studies are multicentre studies.

We present here the incidence of osteosarcoma patients with other malignancies in a population-based study in the time frame of 1975 to May 2000. Of all patients with a reliable diagnosis of osteosarcoma, 7% had other malignancies. The relative risk is 2.4 for developing a second malignancy other than osteosarcoma. 3.4% developed their second tumour after treatment for OS. This equals more or less the finding of 2.6% in the studies of Pratt³¹ and Longhi³². In two other studies this number is, respectively, 1.5 and 5%.^{33,34} In all, 3.6% of the osteosarcoma patients presented with osteosarcoma after a previous malignancy. In large studies on late effects of cancer treatment in childhood this is 0.07–0.34%.^{10,35–37} Especially women seem to be more susceptible to multiple primary tumours. Also in a recent report from the Childhood Cancer Survivor Study,³⁸ the female sex proved to be an independent risk factor for the development of second primary tumour.

Most of the follow-up studies on childhood cancer deal with the effects of treatment. For all these studies together the most frequent malignancy after osteosarcoma is leukaemia (36%). Radiation therapy is the most important causative factor for the development of osteosarcoma.^{10,11} However, alkylating agents and radiation therapy are not the sole causes for malignancies associated with osteosarcoma. Abramson⁸ described an elevated risk for developing osteosarcoma in patients with retinoblastoma not only in the radiation field, but also outside the radiation field and in patients not treated with radiation therapy. This genetic predilection for retinoblastoma patients to develop osteosarcoma was elucidated by the detection of 13q losses (Rb gene location) in osteosarcoma developing after hereditary as well as sporadic retinoblastoma,³⁹ and in some osteosarcomas in nonretinoblastoma patients.⁴⁰

In our 938 osteosarcoma patients, two had a history of retinoblastoma, one developed osteosarcoma of the nose in the field of previous radiation and at the age of 21 years, one had Ewing's sarcoma of the head of the fibula treated with chemotherapy and radiation therapy 13 years after

Table 6 Osteosarcoma subtypes in the syndrome-suspected group

Subtype	No.	Primary tumour	Secondary tumour
Teleangiectatic	120	Osteosarcoma	Adenocarcinoma
Teleangiectatic	121	Osteosarcoma	Adenocarcinoma
Teleangiectatic	808	Unknown	Osteosarcoma
Chondroblastic	153	Morbus Hodgkin	Osteosarcoma
Chondroblastic	776	Osteosarcoma	Morbus Hodgkin
Chondroblastic	911	Nephroblastoma	Osteosarcoma
Fibroblastic	162	Osteosarcoma	Basal cell carcinoma
Fibroblastic	247	Unknown	Osteosarcoma
Fibroblastic	897	Osteosarcoma	Melanoma
Fibroblastic	1039	MDS	Osteosarcoma
Fibroblastic	1107	Osteosarcoma	Osteosarcoma
Fibro/chondroblastic	971	Osteosarcoma	Ductal carcinoma
Osteoclast rich	1058	Squamous cell carcinoma	Osteosarcoma
Osteoma-like	529	Lymphoma	Osteosarcoma
Common	217	Oligodendroglioma	Osteosarcoma
Common	299	Rhabdomyosarcoma	Osteosarcoma
Common	790	Adenocystic carcinoma	Osteosarcoma
Common	1035	Lymphoma	Osteosarcoma
Common	1125	Leukaemia	Osteosarcoma
Common	1148	Retinoblastoma	Osteosarcoma

Table 7 Osteosarcoma subtypes in the syndrome-suspected group without any clear relation with therapy

Osteosarcoma subtype	Case No.		
Teleangiectatic	120,121	2	22%
Fibroblastic	162,897,1107	3	33%
Fibro/chondroblastic	971	1	11%
Chondroblastic	911	1	11%
Osteoma-like	529	1	11%
Osteoclast rich	1058	1	11%
Total		9	

bilateral retinoblastoma. This patient subsequently had a mucoepidermoid carcinoma of the parotid gland at 30 years, an extraskeletal osteosarcoma at 31 years in the field of previous radiation on the fibula and a squamous cell carcinoma of the concha medialis of the nose at 34 years.

A second hereditary cancer syndrome in which osteosarcoma is seen is the Li-Fraumeni syndrome. Based on our selection criteria,¹² patients of all osteosarcoma patients were suspect for having a Li-Fraumeni syndrome, Li-Fraumeni-like syndrome or another yet undefined hereditary cancer syndrome. The way we conducted our research, all data were anonymous. Therefore no family histories could be obtained. This makes the application of the

Table 8 Osteosarcoma subtypes in the European Osteosarcoma Intergroup patients

Osteosarcoma subtype		
Common	404	71%
Chondroblastic	54	9%
Fibroblastic	53	9%
Teleangiectatic	10	2%
Osteoclast rich	11	2%
Other	36	6%
Not subtyped	2	
Total	570	

criteria we used to compose our study group, in a sense, arbitrary. Still, any Li-Fraumeni syndrome patient has a 70% chance of developing any primary invasive cancer (excluding cancer of the skin) before the age of 45 years.²³ By selecting all patients with the development of a primary tumour before the age of 46 years after selecting all patients with a known history of retinoblastoma or a malignancy of the skin before the age of 44 years we believe, we extracted those individuals highly suspected for membership of a Li-Fraumeni family.

As for osteosarcoma subtypes in patients in our syndrome-suspected study group, there appears to be a large fraction of rare osteosarcoma subtypes in this group. In all, 70% of all reviewed osteosarcomas in the syndrome-suspected study group were other than common-type osteosarcoma. When cases without a relation to treatment were left out, all remaining patients had non-common subtype. Of the 81 patients who developed an osteosarcoma after treatment for cancer in a study of the late effects study group by Newton,⁴¹ 57% of the patients treated with radiation therapy had a common type of osteosarcoma. In contrast, in the patients not treated with radiotherapy, the common type was most frequent (90%). In this study, there were also five patients with a family history of cancer. Half of these patients had an osteosarcoma of common type and half of another subtype. Thus, the histological subtyping of osteosarcomas might be predictive as a diagnostic tool in the process of detecting patients with a yet undiagnosed familial predisposition for the development of cancer, more specific yet undiagnosed cases of Li-Fraumeni syndrome. Osteosarcoma can be the first or even the only primary tumour to occur not only in the individual patient, but also in a family with no indication for Li-Fraumeni syndrome at the moment of osteosarcoma diagnosis in one of their offspring.⁴² This has been further proven by the detection of the Li-Fraumeni syndrome-specific p53 germ cell mutation⁴³ in a number of cases of multiple malignant neoplasms in children and young adults without a family history of Li-Fraumeni syndrome.⁴⁴

The absolute numbers we presented here are most likely underestimated. Registration in PALGA covers all the

departments of pathology in the Netherlands only since 1990. The overall survival for osteosarcoma patients is around 55% and patients diagnosed with osteosarcoma in the later years have not yet developed their possible second tumour. This might mean that the initial number of patients suspected for Li-Fraumeni syndrome in our study is smaller than the actual amount of Li-Fraumeni syndrome patients in the total osteosarcoma patient population.

We conclude that although osteosarcoma is a rare tumour, an osteosarcoma patient has a relative risk of 2.4 (95% confidence interval 1.88–3.07) to develop another malignancy. Women are more susceptible than men to osteosarcoma after any other primary tumour. Two of the osteosarcoma patients had retinoblastoma. At a minimum, 1.2% of the osteosarcoma patients are suspected for a hereditary cancer syndrome, and a noncommon subtype of osteosarcoma in a young patient raises the possibility of an individual to belong to a family with hereditary cancer syndrome.

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