Acta Oncologica, 2009; 48: 1165–1172

informa
healthcare

ORIGINAL ARTICLE

Synchronous and metachronous skeletal osteosarcomas: The Norwegian Radium Hospital experience

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Abstract

Background. The purpose of this work was to study clinical and histopathological tumor characteristics of patients treated for synchronous or metachronous skeletal osteosarcoma at The Norwegian Radium Hospital from January 1, 1980 to January 1, 2008. *Patients and methods.* The hospital sarcoma database and patient records were reviewed to identify cases with synchronous or metachronous skeletal osteosarcoma. Patients with more than one skeletal lesion in the absence of pulmonary or other soft tissue tumor manifestations were included in the study, and histopathological slides from these tumors were reviewed. *Results.* Among a total of 297 registered osteosarcoma patients, six with synchronous (2.0%) and 10 with metachronous (3.4%) skeletal osteosarcomas were identified. All tumors were of high-grade malignancy. Treatment at the time of the first osteosarcoma diagnosis was in most cases wide resections and multi-agent chemotherapy according to international protocols, whereas the treatment for metachronous tumors was individualized and in general much less intensive. One patient was diagnosed with Li-Fraumeni syndrome, two other individuals may be suspected to have the same syndrome, and yet another patient had previously been treated for a bilateral retinoblastoma. Thirteen patients are dead, 11 from metastatic osteosarcoma, one from myelodysplastic syndrome, and one from wound infection and methotrexate-related nephrotoxicity; whereas three patients are still alive with no evidence of osteosarcoma. *Conclusions.* The prognosis for patients with synchronous and metachronous skeletal osteosarcoma is poor. However, because long-term survival is seen, aggressive treatment to selected cases, e.g., patients with an osteosarcoma predisposing syndrome and/or late occurring metachronous tumours, is justified. Revealing a possible clonal relationship between these tumors, e.g., by karyotyping, may be of interest for estimating prognosis and guide therapy intensiveness.

Osteosarcomas are malignant primary skeletal tumors most often occurring in adolescents and such neoplasms are slightly more common in males than in females [1–3]. Metastatic spread is predominantly haematogenous, and the lungs are by far the most common site of metastatic disease [3]. After the introduction of chemotherapy for osteosarcoma (OS), extrapulmonary metastases are seen more often [4], and in earlier autopsy studies the frequency of such extrapulmonary OS manifestations was higher than observed clinically [5]. Although imaging studies are far better today, it is still clear that we are not able to detect all micrometastatic disease foci [6]. The frequency of multicentric bone involvement at some point of the OS disease is 30–45% in autopsy studies and 10–30% in clinical studies [4,5,7,8].

In some cases two or more skeletal OS lesions are seen in the same patient, at the same time (synchronous, SOS) or separated in time (metachronous, MOS), without detectable lung or other non-skeletal disease foci [9]. MOS are further divided into early (metachronous tumor developing less than 24 months from first OS diagnosis) and late (metachronous tumor developing more than 24 months from first OS diagnosis) groups [7]. Such SOS and MOS are

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(Received 5 February 2009; accepted 8 May 2009)

ISSN 0284-186X print/ISSN 1651-226X online
DOI: 10.3109/02841860903032809

considered rare and are found at a frequency of about 1–3% of osteosarcoma cases [10,11]. In general, patients with SOS or MOS face a less favorable prognosis than those with only one skeletal osteosarcoma lesion without visceral metastases, but they are not incurable [7,12,13]. It is debated whether such multiple skeletal OS are one primary tumor with metastatic lesion(s), or if they represent separate and clonally unrelated malignancies [9,12,14]. Theoretically, MOS can arise as a consequence of resistant or dormant, distant metastatic tumor cells that are not killed by the chemotherapy administered when the primary tumor is treated. Such tumor cells may for some reason re-enter the cell cycle and, at a later stage, become clinically manifest [10,15]. The proposed estimate that as many as 80% of OS patients have clinically undetectable micrometastases in lungs or other organs at the time of the primary diagnosis [12,15,16] lends some support to such a metastatic theory for metachronous tumors. Likewise, this estimate can be taken in favor of a view stating that the occurrence of SOS is likely to be a sign of metastatic disease. Other arguments and theories favoring a metastatic pathogenesis are summarized by Currall and Dixon [9] and include one dominant lesion, bone-to-bone metastases via venous plexuses or intraosseous embolisation, lymphatic spread, clinical and/or radiological underestimation of lung metastases, and a similar chemotherapy response in the primary tumor and the synchronous/metachronous lesion. If this is the case, one would expect that most patients with such multiple skeletal lesions later will develop further overt metastatic disease. Conversely, different histological sub-typing of tumor pairs, different response to chemotherapy between synchronous/metachronous lesion and primary tumor, no detectable pulmonary metastases, and the presence of a syndrome predisposing to OS can be viewed as arguments supporting that the tumors are clonally independent [12]. A third possibility is that some, but not all, SOS and MOS are clonally related. Knowledge on these matters may be important for prognostication and choice of therapy.

The sarcoma database of The Norwegian Radium Hospital, including about 70% of sarcoma cases in Norway [17], was reviewed to identify patients with SOS and MOS. Clinical data and tumor histopathological characteristics for these patients, including survival, treatment intensity for metachronous tumors, and relevant co-morbidity, are reported and discussed. Furthermore, the number of OS patients with two synchronous skeletal OS foci or at least one metachronous skeletal OS lesion found concurrently with the first non-skeletal metastatic OS focus is also reported.

Patients and methods

All patients diagnosed with OS at our institution after January 1, 1980 are registered in the hospital sarcoma database [17]. This database was used to identify patients with SOS or MOS. Relevant patient records for all cases identified were reviewed. Cases diagnosed between January 1, 1980 and January 1, 2008 were included in the study, as were patients with both single and multiple metachronous lesions. OS patients with skeletal lesions and pulmonary metastases diagnosed concurrently were excluded from further analysis in the present study. However, the number of such patients is also reported. Because the hospital sarcoma database does not include information on the clinical course of all patients following diagnosis of the first metastatic lesion, it was not possible to determine the total frequency of OS patients having skeletal metastases at some (later) point of their disease. The presence or absence of lung metastases was determined using CT scans for all patients, except patient 2 who underwent only a chest x-ray at the time of the diagnosis of the metachronous OS.

The term index OS is used for the first OS lesion diagnosed. Classification of tumors as either synchronous or metachronous based on the time interval between their detection is not entirely consistent in previous reports [7,12]. Herein, tumors were classified as synchronous if both/all tumors were apparent on the initial bone scan of each patient. In those cases where OS lesions developed in areas with scintigraphic findings considered unspecific or clinically irrelevant at the time of the primary diagnosis, initial bone scans were re-evaluated by two experienced nuclear medicine specialists (T.V.B (author) and O.M.A (Acknowledgment)). They were asked to re-evaluate specific scintigraphic lesions questioned at the time of the primary diagnosis. The lesions under scrutiny were graded from 1 to 4 (1 – non-malignant/irrelevant; 2 – probably non-malignant/irrelevant; 3 – probably malignant; 4 – clearly malignant). Furthermore, histopathological characteristics of all tumors included in the study were re-examined and tumor diagnosis, subtype, and grade were re-evaluated by an experienced sarcoma pathologist (author B.B.) according to the WHO classification [18]. Histological response to chemotherapy was evaluated in the surgical specimens according to the criteria used in the on-going EURAMOS1 protocol and classified as good ($<10\%$ viable tumor cells), poor ($\geq 10\%$ viable tumor cells), or not evaluable (see www.euramos.org). It seems that bone marrow micrometastatic disease has prognostic impact in OS patients [15]. Hence, we report micrometastatic disease status for patients where such data were available. The study was

approved by the regional ethical committee, the institutional study board, and informed consent was obtained from patients still alive.

Results

Patient and tumor characteristics for SOS and MOS

A total of 747 patients with a malignant bone tumor diagnosis were identified in the hospital sarcoma database and 297 of these (40%) were diagnosed with OS. Of the 297 OS cases, six had SOS (2.0%), whereas MOS developed in 10 patients (3.4%). Clinical and histopathological data for these 16 patients are summarized in Tables I and II. Ten patients were male and six were female. Femur was the most frequent index tumor localization (four cases). Two patients had multiple synchronous tumors (>two, included index tumor) and two patients had multiple metachronous lesions (>one). The interval between the index and the metachronous OS varied from two to 59 months; seven of 10 metachronous tumors developed less than 24 months after the initial OS diagnosis and were therefore classified as early MOS. Five metachronous tumors were detected following radiological examinations initiated because patients experienced localized pain, two were found during treatment for the index tumor, and three were identified in routine imaging at follow-up. Patient 8 had radiotherapy for a uterine cervical cancer 14 years prior to the diagnosis of sacral OS, and this OS may well have been radiotherapy-induced [19].

One of the patients (11) was diagnosed with Li-Fraumeni syndrome (LFS) and had a germline *TP53* mutation. Patient 3 was diagnosed with an anaplastic astrocytoma between the index and metachronous osteosarcoma, and this may raise the suspicion of LFS, although the family cancer history is unknown. Another patient (6) was surgically treated for a well-differentiated liposarcoma before the diagnosis of the metachronous OS. This patient ultimately succumbed to a myelodysplastic syndrome without signs of OS. Although we do not have knowledge on the family history of this patient, LFS may be suspected. Patient 5 was treated for bilateral retinoblastoma 13 years prior to the OS diagnosis and therefore probably had an *RB1* mutation known to predispose to OS [3].

OS patients with multiple skeletal OS lesions and visceral metastases

In the same time period as the above-mentioned cases were diagnosed at our hospital, the number of OS patients with more than one skeletal OS lesion and simultaneous non-skeletal metastases at primary diagnosis was five (1.7%). Furthermore, 10 patients (3.4%) were diagnosed with one or several OS lesions simultaneously with non-skeletal metastases at some point after completion of treatment for the primary OS.

Treatment

All patients except four received multi-agent chemotherapy for their index OS (Table II). Treatment was administered according to the following protocols: SSGII/T-10 [20,21], SSGVIII [22], ISG/SSGI [23], ISG/SSGII [24], EURAMOS1 (on-going study of resectable OS in patients <40 years) [25], and EURO-B.O.S.S. (on-going study of bone sarcomas in patients aged 41–65) [25]. All protocols include(d) high-dose methotrexate (HD-MTX), doxorubicin, and cisplatin, whereas ifosfamide was used in all protocols except SSGII/T-10. Patient 1 was scheduled for such multi-agent chemotherapy, but succumbed to a combination of methotrexate-related renal failure and postoperative wound infection following the first cycle of HD-MTX. Three patients did not receive chemotherapy at all: patients 5 and 8 because they were judged to have a poor prognosis due to multiple synchronous tumors, and patient 7 because of significant cardiovascular morbidity related to a congenital, inoperable ventricular septum defect. Most patients received multi-agent chemotherapy both in a neoadjuvant and in an adjuvant setting. Two patients (1 and 13), however, had primary surgery and therefore only adjuvant chemotherapy. Except patients 5 and 8 who had more than 10 skeletal lesions at primary diagnosis, all patients had surgery of their index OS. Patients 5 and 6 had palliative and adjuvant, respectively, radiotherapy for their index tumors.

For the second synchronous tumor, the treatment was chemotherapy and surgery for three patients and no OS-specific therapy in three patients. The treatment for the metachronous tumors was individualized and in most patients much less intense compared to therapy given for the index OS. Patients 1 and 12 had metachronous tumors occurring so early that they were affected by chemotherapy administered for the index tumor. Only three patients received chemotherapy dedicated for their metachronous tumors; patients 4 and 11 are still alive whereas patient 10 died from lung metastases nine months after diagnosis of the metachronous tumor. In total for patients with metachronous tumors: one had surgery only, four had surgery combined with other treatment modalities, two had no surgery but other forms of therapy, and three (included 1 and 12) had no active osteosarcoma treatment at all.

Histopathology, bone scan re-evaluation, and bone marrow status at index OS diagnosis

A histopathological diagnosis was obtained and re-evaluated in all index tumors and in 13 of 16

Table I. Clinical data and histopathological characteristics of tumors in patients with synchronous and metachronous osteosarcoma

					Localization		Histopathology		
Pat nr	Sex/age at primary diagnosis	SOS/MOS	Year of index diagnosis	Time between tumors (months)	Index tumor	Tumor 2	Index tumor	Tumor 2	Tumor grade Index tumor/ Tumor 2
1	M/62	MOS	1981	2	Femur, L	Os ileum	Fibrobl./ chondrobl.	NE	4/4
2	M/6	MOS	1989	13	Femur, L	Sacrum	Osteobl./ chondrobl.	Osteobl./ fibrobl./ chondrobl.	4/4
3	M/40	MOS	1994	59	Mandibula, L	1. L5 2. L1 and os ileum, L	Osteobl.	1. Osteobl. 2. –	4/4
4	F/11	MOS	1981	26	Femur, R	Femur, L	Osteobl./ chondrobl.	Osteobl.	4/4
5	M/14	SOS	1983	0	Tibia/Femur, L	Multiple (>10)	Osteobl.	Osteobl	4/4
6	F/44	SOS	2000	0	Mandibula	Scapula, R	Chondrobl.	NE	4/NE
7	F/13	SOS	1993	0	Tibia, R	Calvarium	Telangiectatic	–	4/-
8	F/51	SOS	2007	0	Sacrum	Multiple (>10)	Osteobl.	–	4/-
9	F/6	MOS	1981	17	Fibula, R	L4	Osteobl.	Osteobl.	4/4
10	M/17	MOS	2001	1. 10 2. 12	Os ileum, R	1. Costa 6, R 2. Costa 1, R	Chondrobl.	1. Chondrobl. 2. –	4/4
11	M/11	MOS	2000	43	Femur, R	Ulna, L	Osteobl.	Osteobl.	4/4
12	M/16	MOS	1982	2	Humerus, R	Multiple (5)	Osteobl.	–	4/NE
13	F/17	SOS	2006	0	Calvarium	Humerus, R	Osteobl./ telangiectatic	Osteobl./ fibrobl.	4/4
14	M/19	SOS	1989	0	Fibula, L	Humerus, L	Chondrobl./ fibrobl.	Osteobl.	4/4
15	M/17	MOS	1981	13	Humerus, L	Os ileum, L	Osteobl.	Osteobl.	4/4
16	M/51	MOS	2005	11	Os ileum, R	Costa 4, R	Fibrobl.	Fibrobl./ osteobl.	4/4

NE: not evaluable; -: not performed; M: male; F: female; SOS: synchronous; MOS; metachronous; L:left; R: right.

Table II. Treatment data and survival for patients with synchronous and metachronous osteosarcoma

		Treatment		Histological response to chemotherapy			
Pat nr	SOS/MOS	Tumor 1	Tumor 2	Tumor 1	Tumor 2	Status at last follow-up	Survival (months)
1	MOS	HD-MTX Surgery	No surgery	– (primary surgery)	NE	D-NED	0
2	MOS	SSGII/T-10 Surgery	None	Good	–	DOD	3
3	MOS	SSGVIII Surgery	RT	Good	–	DOD	23
4	MOS	SSGII/T-10 Surgery	MTXx1 Surgery	Poor	Poor	A-NED	295
5	SOS	RT	None	–	–	DOD	5
6	SOS	ISG/SSGI Surgery RT	ISG/SSGI Surgery	Poor	Good	D-NED	48
7	SOS	Surgery	None	–	–	DOD	5
8	SOS	None	None	–	–	DOD	4
9	MOS	SSGII/T-10 Surgery	Surgery RT	Poor	–	DOD	22
10	MOS	ISG/SSGII Surgery	MTXx2 Surgery	Poor	Poor	DOD	9
11	MOS	ISG/SSGI preop./ SSGVIII postop. Surgery	HD-MTXx4, Eto/Ifox1, Doxo/Etox1, HD-Ifox1 Surgery	Poor	Poor	A-NED	54
12	MOS	SSGII/T-10 Surgery	(SSGII/T-10) No surgery	Poor	–	DOD	16
13	SOS	Surgery	EURAMOS1 Surgery	– (primary surgery)	Poor	A-NED	31
14	SOS	SSGVIII Surgery	SSGVIII Surgery	Poor	Poor	DOD	45
15	MOS	SSGII/T-10 Surgery	RT INF	Poor	–	DOD	8
16	MOS	EURO-B.O.S.S Surgery	Surgery	Poor	–	DOD	14

HD: high-dose; MTX: metotrexate; Eto: etoposide; Ifo: ifosfamide; RT: radiotherapy; INF: interferon; NE: not evaluable; –: not performed; SOS: synchronous; MOS; metachronous; L: left; R: right; D-NED: Dead with no evidence of osteosarcoma; DOD: Dead of disease/sarcoma; A-NED: Alive without evidence of osteosarcoma; Survival is from diagnosis of tumor 2.

metachronous/second synchronous tumors (Table I). All tumors were classified as OS of high-grade malignancy. The histopathological sub-typing of the tumors was as follows: seven index tumors were classified as osteoblastic, two as chondroblastic, one as fibroblastic, one as telangiectatic, and five tumors as mixed variants. Patients 7, 8, and 12 did not have histopathological verification of their metachronous/second synchronous lesions, whereas for patients 1 and 6 the metachronous lesions were not possible to sub-type. In the other 11 metachronous/synchronous OS, the histological subtype was concordant with the index tumor in six cases and discordant in five cases.

Re-evaluation of bone scans was done in nine patients (Table III). Two patients (6 and 14) were re-classified from metachronous to synchronous, whereas three patients (10, 12, and 15) were considered not to have initial bone scintigraphic lesions indicative of synchronous tumors. Furthermore, patients 5, 7, and 8 had initial bone scans suggestive of synchronous tumors that were never verified histologically. The re-evaluation of the scintigrams from these three patients confirmed that lesions highly suggestive of synchronous OS were present. Also, in patient 3, the re-evaluation of the scan taken 59 months from the primary diagnosis confirmed findings highly suggestive of OS.

Seven patients had bone marrow specimens sampled at the time of the index OS diagnosis (Table IV). Five of these (3, 7, 13, 14, and 16) had micrometastatic bone marrow disease, whereas patients 6 and 10 had bone marrow samples scored as negative. Four of the five patients with primary micrometastatic bone marrow disease are dead from OS, whereas one (13) is still alive with no evidence of OS. The two patients with no micrometastatic bone marrow disease are both dead, one of them (6) without evidence of OS.

Table IV. Micrometastatic bone marrow status at the time of the index osteosarcoma diagnosis

Pat nr	SOS/ MOS	Micrometastatic bone marrow status at the time of the index osteosarcoma diagnosis
1	MOS	n.a.
2	MOS	n.a.
3	MOS	+
4	MOS	n.a.
5	SOS	n.a.
6	SOS	−
7	SOS	+
8	SOS	n.a.
9	MOS	n.a.
10	MOS	−
11	MOS	n.a.
12	MOS	n.a.
13	SOS	+
14	SOS	+
15	MOS	n.a.
16	MOS	+

SOS: synchronous; MOS: metachronous; n.a.: not available.

Patient outcome

At the time of writing, three patients are alive, all without signs of OS (4, 11, and 13). For most of the other 13 patients, the presumed cause of death was based on investigations performed when they were still alive. Metastatic disease including pulmonary metastases from OS was the presumed cause of death in 11 of these patients, myelodysplastic syndrome in one patient (6), and a combination of methotrexate-related nephrotoxicity and wound infection in one patient (1).

Discussion

Synchronous and metachronous skeletal osteosarcomas are rare entities which carry a poor prognosis, but in recent reports it has been emphasized that long-term survival is possible if the patient receives adequate treatment [7,12]. The relative incidence of

Table III. Results of bone scan re-evaluation in nine patients with synchronous and metachronous osteosarcoma

Patient nr.	Localization of 2nd lesion	Scintigraphic grading of 2nd lesion	Histologically confirmed osteosarcoma development in 2nd lesion	Re-classification from MOS to SOS based on initial scintigram
3	L5/Os ileum	4/3	Yes/NP	-
5	Multiple	4	NP	-
6	Scapulae	4	Yes	Yes
7	Calvarium	4	NP	-
8	Multiple	4	NP	-
10	Costa 6	1	Yes	No
12	Costa 5	2	NP	No
14	Humerus	4	Yes	Yes
15	Skull	2	NP	No

SOS: synchronous; MOS: metachronous; NP: not performed; -: originally classified as synchronous
Scintigraphic grading: 1 – non-malignant/irrelevant, 2 – probably non-malignant/irrelevant, 3 – probably malignant, 4 – clearly malignant.

SOS and MOS of 2.0% and 3.4%, respectively, found in our material, is in the expected range based on earlier reports [10,12]. Our results also show that the simultaneous detection of pulmonary and skeletal metastases at primary diagnosis or first metastatic diagnosis in patients with OS is relatively rare (5.1%). Nonetheless, not taking micrometastatic disease into consideration, the skeleton, second only to the lungs, seems to be the most frequent organ involved in metastatic disease in OS [5].

In two of the patients with MOS, the metachronous tumor was found two months after the diagnosis of the index tumor, and the classification of these as MOS is not obvious. In fact, these two tumors would have been assigned to different groups based on different criteria in earlier publications [7,12,26]. Furthermore, although the initial clinical evaluation of some uncertain scintigraphic findings concluded that they were not clinically relevant, the disease course nonetheless showed that some of these minor scintigraphic abnormalities turned out to be skeletal OS lesions. Also, in five of six patients with SOS, one of the OS lesions was larger and more illustrious than the other lesions. A possible interpretation of these findings is that the number of patients with metastatic disease at the time of the primary OS diagnosis was underestimated. If diagnosed today, MRI would have been performed in most of these cases to further explore such uncertain/unspecific scintigraphic findings, thereby reducing the uncertainty. There is no method to determine the frequency of possible underestimation of pulmonary metastases in the patients included in this study. Except at the time of diagnosis of the metachronous tumor of patient 2, all patients went through a chest CT looking for pulmonary metastases when any OS lesion was found. However, because many of the patients were diagnosed and treated several years ago, the sensitivity of their CT scans was not as high as it would have been today.

Histological sub-typing was concordant in six and discordant in five of the 11 evaluable tumor pairs. Although it is tempting to claim that this finding corresponds to a connection and no connection, respectively, it is no more than a weak indication. Metastases may look different than the primary tumor and two unrelated tumors may be histologically of the same sub-type. In the five patients where response to chemotherapy was evaluated for tumor pairs, four had a concordant response. The interpretation of these findings when it comes to a possible relationship between the tumor pairs is difficult; a different response to chemotherapy between two tumors does not prove that they are unrelated, because a metastasis may be genetically dissimilar to its primary tumor and therefore respond in a different manner.

The time interval between metachronous skeletal tumors is worth noticing. It has been reported that patients with early metachronous tumors (<24 months interval) have a poorer prognosis than those with late metachronous tumors (>24 months interval) [7]. Two of the three patients with late metachronous tumors in our series are still alive four and a half (11) and nearly 25 (4) years after the diagnosis of their MOS, whereas none of the patients with early metachronous tumors are alive. A possible interpretation is that most of the early tumors are metastatic, whereas among the late tumors the proportion of clonally independent tumors is higher.

Micrometastatic bone marrow disease at the time of the primary osteosarcoma diagnosis has been shown to have a certain prognostic value [15]. The fact that patient 13 had positive micrometastatic bone marrow status at the time of the primary diagnosis, lends some support to a theory suggesting that the SOS in this patient were clonally dependent. However, because sub-clinical metastatic disease is thought to be common in OS patients at the time of the primary diagnosis [12], the mentioned theory remains unresolved. Furthermore, because this patient is still alive 30 months after the diagnosis of SOS, one could alternatively speculate that the two OS lesions were in fact clonally independent. Patient 6 had negative micrometastatic bone marrow status at the time of the primary OS diagnosis and succumbed 48 months later – without any evidence of OS. It is likely that the patient, given metastatic disease at primary diagnosis, would have had evidence of OS disease at the time of death. When held together, these findings may therefore indicate a clonal independence between the two OS lesions.

Early occurring metachronous tumors, rapid disease progression ultimately involving also lungs, multifocal (>one) metachronous skeletal lesions, unspecific primary bone scan findings later manifesting as OS lesions, and possibly also similar histological subtyping may indicate metastatic OS. Most of our patients seem to fall into this category, and although their chest CT scans were normal, this by no means excludes the possibility of pulmonary metastases [6]. The presence of an OS predisposing syndrome, absence of bone marrow micrometastases, and/or late occurring solitary metachronous tumors, such as in patients 3, 4, 6, and 11, may indicate unrelated primary tumors. Some synchronous tumors may also be unrelated, as might be the case in our patient 13. Nonetheless, the above-mentioned arguments provide, at best, only circumstantial evidence for the presence or not of a clonal relationship between index OS and synchronous/metachronous lesions. Cell culture and

karyotypic analysis could, if performed and successful, have provided more information on possible clonal associations between index OS and synchronous/metachronous lesions. A problem is the karyotypic complexity often seen in these neoplasms [27], but the finding of the same marker chromosome in two skeletal OS would strongly suggest their clonal relationship.

Two of the three patients that received chemotherapy for their metachronous tumor are alive several years from diagnosis of their metachronous OS, as is one of the patients with synchronous tumors. Although the herein reported material is small, this fact emphasizes, in accordance with earlier reports [7,12], that some patients with MOS and SOS are curable, and that selected cases should be treated intensively. Our results may be interpreted in two different ways: the selection of patients for chemotherapy in the setting of a metachronous tumor was good, or, too few patients received chemotherapy for their metachronous tumor. Hence, even a few more patients could have become long-term survivors with more aggressive treatment.

Acknowledgment

We thank MD PhD Olav Magne Aas for his help with re-evaluation of bone scintigrams.

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

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