Osteosarcoma prediagnosed as another tumor. A report from the Cooperative Osteosarcoma Study Group (COSS)

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Research Article

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Abstract

Purpose: The course of osteosarcoma patients primarily treated as such has been well described. Little, however, is known about patients who were primarily treated assuming a different tumor diagnosis.

Methods: The database of the Cooperative Osteosarcoma Study Group COSS was searched (4.445 primary high-grade central osteosarcomas registered prior to 01/01/21). A different tumor entity had to have been assumed for at least one month after the initial diagnostic procedure before the correct diagnosis of osteosarcoma was finally made. Identified patients were analyzed for demographic, tumor-, and treatment-related factors as well as for survival outcomes.

Results: 37 patients were identified. They were a median of 19.7 (2.7 - 60.4) years old at first presentation and were more likely to be females than males (23:14). Bone cysts (n=8), giant cell tumor of bone (n=6), and osteoblastoma (n=6) were the most frequent of 29/37 (78%) benign, chondrosarcoma and its variants (n= 6) the most frequent of 8/37 (22%) malignant original diagnoses. Tumors affected the extremities in 23 (62%), the trunk in 11 (30%), and the craniofacial bones in 3 (8%). Only one patient received systemic treatment while assuming the different diagnosis (1/37, 3%). The median time until the correct diagnosis of osteosarcoma was made was 8 months (range: 1 month – 14.1 years). At that time, 6/37 (16%) presented with metastatic disease. All patients went on to receive chemotherapy, 17/37 (46%) neoadjuvantly. Histologic response was only evaluated in 13/17 (76%) patients and was good (<10% viable tumor) in only 4/13 (31%) patients. In 31/37 (84%) patiens, a surgically complete resection of all macroscopically identified tumor manifestations could be achieved. Five-year overall and event-free survival rates at 5 years were 50.2% (standard error: 8.6%) and 42.6% (8.5%), respectively.

Conclusion: Osteosarcoma may initially be misdiagnosed and hence subjected to inappropriate treatment including misguided surgery. Once diagnosed correctly, some of the affected patients may still be cured if finally treated according to modern osteosarcoma standards.

Introduction

Osteosarcoma treatment has been well established for many decades. A combination of intensive chemotherapy and surgery can cure approximately 60–70% of patients with apparently localized extremity disease and above 20% of those with axial tumors or with primary metastases (1–3). Prospective trials, however, characteristically exclude pretreated patients. This includes those pretreated under the correct diagnosis, but also those who first received treatment assuming they were suffering from a completely different disease. Searching the literature, we were not able to detect a single analysis focusing on this particular group of patients. It is therefore unknown if certain conditions are more likely to lead to misdiagnoses and if and to which extent they will be able to survive following their protracted course to the correct diagnosis and to correct therapy.

The Cooperative Osteosarcoma Study Group (COSS) has been running a comprehensive osteosarcoma registry for more than four decades (4–6). In addition to those patients eligible for trials, it is open for all

other patients suffering from osteosarcoma. We searched the COSS-database for patients with high-grade, central osteosarcoma who had started treatment under the assumption of a different tumor. Affected patients were analyzed for presenting signs and symptoms, treatments received under the distinct diagnoses, and outcomes.

Patients And Methods

The database of the Cooperative Osteosarcoma Study Group COSS was searched for all of 4.445 patients registered prior to 01/01/21 with a primary high-grade central osteosarcoma who had received at least one month of pre-treatment (surgery, chemotherapy, or radiotherapy) for their primary tumor under assumption of a different diagnosis. The analysis was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All registered patients and/or their parents, whichever appropriate, were required to give their informed consent into treatment, data capture, and unlimited follow-up. All study and registry protocols were approved by the appropriate Ethics committees. Once the correct diagnosis had been made, patients were to be treated according to the various COSS regimens active at time of enrolment, generally with neoadjuvant and adjuvant multidrug chemotherapy and surgery (4–6).

Affected patients were analyzed for presenting patient and tumor related factors and treatments at time of the original, erroneous diagnosis as well as for that of the final osteosarcoma diagnosis, the interval between both, treatments, and outcomes. Tumor response to osteosarcoma therapy, if available, was coded according to Salzer-Kuntschik et al (7), with a good response assumed when tumor viability was below 10%. Survival outcomes were calculated using the Kaplan-Meier method (8). The starting point was that of the osteosarcoma diagnosis. Overall survival was calculated from this date until death from any cause. Event-free survival was calculated until the date of diagnosis of any renewed osteosarcoma manifestation or death from any cause, whichever occurred first. Only patients considered to have achieved a macroscopically complete surgical remission of all diseased sites were considered to have been made disease-free, all others were coded as having suffered an event at day 1 after recurrence. Secondary malignancies were not to be considered as events, but to be analyzed separately.

Results

Thirty-seven COSS patients pretreated assuming a tumor diagnosis distinct from osteosarcoma were identified. The erroneous diagnosis had been benign in 29/37 (78%; bone cyst 8 (aneurysmatic 7, unspecified 1), giant cell tumor of bone 6, bone forming and fibro-osseous tumors 8 (osteoblastoma 6, ossifying fibroma 1, osteoid osteoma 1), chondroid lesions 4 (chondromyxoidfibroma 2, chondroblastoma 1, synovial chondromatosis 1), fibrolipoma 1, and not clear 2). Malignancies were assumed in 8/37 (22%; chondrosarcoma 6 (conventional 5, mesenchymal 1), malignant giant cell tumor 1, carcinoma of unknown primary (CUP) 1) cases.

The study cohort consisted of 14/37 (38%) males and 23/37 (62%) females. None of the affected patients was reported to suffer from a known tumor predisposition syndrome or had a history of prior malignancy. The median age at the first (incorrect) diagnosis was reported as 19.7 (range: 2.7–60.4) years. Twenty-three (62%) tumors were located in the limbs (tibia 9 (proximal 6, distal 2, diaphysis 1), femur 7 (distal 5, diaphysis 1, proximal 1), fibula 3 (all proximal), humerus 3 (proximal 2, distal 1), foot 1). Eleven (30%) tumors affected the axial skeleton (pelvis 8, ribs 2, clavicle 1), three (8%) were located craniofacially (base of skull 1, maxilla 1, mandibula 1). Primary metastases, to distant bones, were only reported for one (3%) tumor, the one assumed as CUP.

All patients had been subjected to a diagnostic biopsy or primary surgery. In total, 36/37 (97%) received an operation intended to remove the lesion. Radiotherapy or chemotherapy was administered to one (3%) patient each. In total, 35/37 (95%) of all patients were considered cured by first-line therapy.

The correct diagnosis of osteosarcoma was finally made at the second disease manifestation in 22/37 (59%), the third in 11 (30%), the fourth in two (5%), and the fifth and sixth in one (3%), patient each. By then, it was a correct assumption in 9/22 (41%) and an unexpected finding in 13/22 (59%) among 22/37 (59%) with appropriate information. The latency period from the first incorrect diagnosis to the diagnosis of osteosarcoma was reported as 8 months (range: 1 month – 14.1 years). It was longer than one year in 15/37 (42%) and longer than five years in 2/37 (5%) affected patients. Patients were 22.1 (5.4–60.4) years old when the osteosarcoma diagnosis was made.

Information about the osteosarcoma subtype was available for 31/37 (84%) patients. Among these, 9/31 (29%) tumors each were considered osteoblastic and chondroblastic, 6/31 (19%) teleangiectatic, and 5/31 (16%) fibroblastic. One tumor each (3%) was classified as undifferentiated pleomorphic sarcoma-like and osteoblastoma-like. The absolute size of the primary tumor at time of correct diagnosis was only known for 12/34 (35%) of osteosarcomas with local involvement. In these, it was a median of 6 (1.6–13) cm. Its relative size in relation to the involved bone was known for 13/34 (38%) of these and was reported as less than one third of the involved bone in 11/13 (85%) and more in 2/13 (15%). At the time of the osteosarcoma diagnosis, 31/37 (84%) affected patients still had localized disease, 3/37 (8%) metastases only, and 3/37 (8%) had both a local recurrence and metastases. Metastases involved the lungs in four/37 (11%), distant bones in one/37 (3%), and both in one/37 (3%). They consisted of more than one lesion in all but one case, a solitary lung metastasis.

Among patients with involvement of the primary site at correct diagnosis, treatment included surgery of this site in 32/34 (94%) tumors. In the subgroup of 20/21 (95%) operated extremity primaries, it was reported as ablative in 12/20 (60%), limb-salvage procedures were performed in 8/20 (40%). Local radiotherapy of 40, 51, and 71 Gy was given to 3/37 (8%) patients, all as an adjunct to surgery. As a result of local therapy, a complete macroscopic remission of all disease sites was achieved in 31/37 (84%), one of these with known microscopic residuals.

All 37/37 (100%) patients proceeded to chemotherapy. Its duration was reported for 34/37 (92%) and lasted a median of 252 (range: 18–609) days. The use of pre- and postoperative chemotherapy was

documented for 17/37 (46%) patients, that of postoperative chemotherapy only in 19/37 (51%). One further patient was known to have received preoperative chemotherapy, but postoperative therapy was unknown. Drugs used were documented for all 37/37 (100%) and included doxorubicin in all 37/37 (100%), high-dose methotrexate and cisplatin in 34/37 (92%), and ifosfamide in 29 (78%) patients. A variety of further drugs were administered to 8 (22%), including one case of autologous bone marrow transplantation. No patient was known to have received targeted or immunotherapy. Data on tumor response to preoperative chemotherapy was available for 13/37 (35%) patients. In these, it was good in 4/13 (31%) and poor in 9/13 (69%).

Median follow-up from osteosarcoma diagnosis was 4.3 (range: 0.3–32.1) years for all patients and 15.7 (0.3–32.1) years for survivors. The corresponding event-free observation period was 2.1 (one day – 32.1) years. During this period, 21/37 (57%) patients developed in an event as defined (six without surgical remission (including one without disease progression after radiotherapy), ten metastatic, three local, two combined, one death of unknown causes), 16/37 (43%) remained event-free. There were no secondary malignancies. At last follow up, 18/37 (49%; 16 1st, 1 2nd complete remission, one with irradiated tumor residual) patients were still alive and 19/37 (51%; five without ever having achieved a remission, ten 1st, three 2nd recurrence, one death of unknown causes while in first remission) had died.

Median overall survival from osteosarcoma diagnosis for all 37 patients was 85.7% (standard error: 5.9%) at 2, 50.2% (8.6%) at 5, 47.1% (8.6%) at 10, and 43.2% (8.7%) at 15 years. The corresponding values for event-free survival were 57.8% (8.3%) at 2, 42.6% (8.5%) at 5 and 10, and 38.3% (8.6%) at 15 years, respectively (Fig. 1). Results by presenting and therapeutic variables are given in table 1.

Discussion

Diagnostic and therapeutic delays caused by erroneous diagnoses may still occur in osteosarcoma. Diagnostic diligence including reference pathology may help reduce the incidence of such cases. Despite inappropriate initial treatment, some affected patients may still have a realistic chance to achieve cure.

The unparalleled size of the COSS-registry allowed us to amass a relevant cohort of patients with osteosarcomas who had originally received therapy assuming a divergent diagnosis. We can only assume that not all of these were erroneous, but that some patients indeed developed an osteosarcoma arising in the same location as a previous tumor of divergent histogenicity. This is probably most likely for tumors with particularly long interim periods between both events. Most of the tumors we were able to analyze were, however, clearly osteosarcomas from the very beginning and misdiagnosed at initial presentation.

The unselected nature of our analysis is a clear advantage. We must nevertheless assume that we are not describing anything close to the true incidence of misdiagnoses. Centers may have been reluctant to register affected patients and to thus make their own mistakes public. In other, registered patients, pretreatments may have been concealed. Medico-legal concerns may have been another reason for not reporting everything.

Osteosarcoma was camouflaged by a wide variety of primary diagnoses. If assessed as malignant, distinguishing chondro- from osteosarcoma seems to have posed the most challenging distinction. This distinction is, however, most relevant, as systemic therapies are largely ineffective against chondrosarcoma, while they are an essential part of osteosarcoma therapy (2). Aneurysmatic bone cysts and giant cell tumor of bone were the main benign mimics of osteosarcoma. Experienced bone pathologists should be able to reliably distinguish these as well as the variety of other lesions from a life-threatening malignancy such as osteosarcoma. Reference pathology should therefore be encouraged in all bone tumors, independent of whether they are assumed to be malignant or benign (9).

The median latency period between the original diagnosis and that of osteosarcoma was eight months, but much longer time-spans occurred. It is of note that the latency was longer than one year in almost 40% of patients and longer than five years in two or 5% of these. There is no interval that could distinguish two clearly distinct neoplasms from one single, misdiagnosed malignancy. We can only assume that the former were among those with the longest lag-times.

The age at original presentation, a median of 19.7 years, was some years higher than that of osteosarcoma in general (1), but no age was safe. It is not unusual to include osteosarcoma into the differential diagnosis in school-age children, adolescents, and even young adults. The infrequency of osteosarcomas in other age groups, however, may have impeded its inclusion into the differential diagnosis in older adults. Our study cohort consisted of more females than males, which is rather unexpected for osteosarcoma (1). We have no unequivocal explanation for this finding other than clinicians might have been less aware of a potential osteosarcoma in females. In general, the rate of non-extremity osteosarcomas is considered rather low, certainly much lower than the frequency detected in our cohort (2, 3). Here, this atypical region of presentation obviously prevented physicians from including osteosarcoma into their differential diagnosis. Again, a correct diagnosis requires an appropriate index of suspicion. The interpretation of tumor size is not straightforward and hindered by the paucity of data in our cases. On the one hand, osteosarcomas can be expected to progressively grow over time until detection. On the other hand, relevant parts of the tumor are prone to be removed during surgery performed under the assumption of a different diagnosis. This would explain why most lesions were considered small when the correct diagnosis was made. It is quite evident that more metastases were present when osteosarcoma was finally diagnosed than when another tumor was still assumed. This probably represents a clear sign of disease progression in the ensuing interval. It cannot be excluded, however, that some of the metastases were already originally present but had not been searched for.

While still assuming the first (usually erroneous) diagnosis, systemic therapy was administered for one patient only. This is no surprise, as benign tumors would pose no indication for such treatment and the assumed malignancies (mis-)diagnosed in our cohort are also largely considered largely chemo-refractory (2). On the other hand, chemotherapy was generally as intensive as for other osteosarcomas once the correct diagnosis had been made (3). This was not influenced by whether the osteosarcomas were still localized at time of their diagnosis or had spread detectably. Preoperative chemotherapy, a standard in modern osteosarcoma treatment, was, however, not quite as routinely administered as in

common practice. This may be explained by surgical procedures which were performed while the diagnostic process had not yet been finalized. Other than preventing to assess the response to chemotherapy, this primary surgery is, however, unlikely to have had any negative effects on prognosis (1, 10). In those few patients treated preoperatively, the response rate to upfront chemotherapy seems to have been rather low. The limited number of patients prohibit us from concluding if this was a true finding or due to chance.

Given the somewhat higher rate of axial primaries, the overall prognosis of the analyzed cohort seems to have been in the lower range of that of previously untreated patients (1–3). It is of note that those osteosarcomas initially misdiagnosed as other malignant tumors did worse than those misdiagnosed as benign. The former may have presented with more dramatic symptoms or have been more likely to involve unfavorable sites. There was also a clear prognostic disadvantage for those patients in whom metastatic spread was present when osteosarcoma was finally unveiled. This reflects the situation with primary metastases in general (1). Too few tumors were eligible for response assessment to draw definitive conclusions, but the data points in the same direction as usual with good responders doing better.

Not all patients who would otherwise have been considered candidates for limb-salvage surgery might still have been considered as such following unsuitable surgical procedures. It is, however, remarkable that limb-salvage surgery was still performed for many extremity tumors upon osteosarcoma diagnosis. It is particularly important to include previous surgical fields into the surgical planning, as exemplified by involvement of the former primary site in five of 16 individuals with osteosarcoma recurrences during later follow-up. Incorrect diagnoses might lead to inappropriate surgical attempts, thereby predisposing to local failure. However, while the local failure rate seems to have been somewhat higher than expected (11), the overall risk of recurrence was almost that which we would have expected had the osteosarcoma been diagnosed primarily (1, 3). Given the resulting lag-time, this may come as a surprise as osteosarcomas usually seem to progress rather rapidly. It may have been that the most aggressive tumors were more likely to be diagnosed correctly from the very beginning, while it was those with a slower evolution and fewer symptoms that were more likely to be misdiagnosed. Whatever the case: If still amenable to surgery, cure was often still possible even when the osteosarcoma was only unveiled following unsuitable approaches at local treatment. Our results clearly demonstrate that combined local and systemic therapy is still indicated when the correct diagnosis of osteosarcoma is only made after pretreatment under another assumed tumor diagnosis.

In summary, erroneous diagnoses seem particularly likely with somewhat atypical osteosarcoma presentations. The likelihood of detectable metastatic spread may increase in the time leading to the correct diagnosis. Ablative surgery may be indicated more frequently than usual due to prediagnostic, unsuitable operations. Systemic therapy is still possible and usually requires little to no alterations from standard. The extra latency period leading to the correct diagnosis should not deter from providing state of the art osteosarcoma care. Have a high index of suspicion: If something does not fit, rethink!

Declarations

Disclosures

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Table

Table 1 Survival outcomes by presenting and therapeutic factors.

1 patients with preoperative therapy and available response data only

	n	event-fee			overall		
		2year (%)	5year	p	2year	5year	p
All patients	37	57.8 (8.3)	42.6 (8.5)	-	85.7 (5.9)	50.2 (8.6)	-
Age at erroneous diagnosis							
< 20 years	15	72.20 (11.9)	50.3 (13.4)	.527	92.9 (6.9)	57.1 (13.2)	.504
≥ 20 years	22	48.1 (10.9)	42.8 (10.9)		81.0 (8.6)	45.5 (11.1)	
Sex							
male	14	67.5 (13.4)	50.6 (14.4)	.237	91.7 (8.0)	58.3 (14.2)	.597
female	23	52.2 (10.4)	37.9 (10.3)		82.6 (7.9)	45.9 (10.6)	
Tumor site							
extremity	23	59.2 (10.5)	49.3 (10.8)	.425	86.4 (7.3)	52.8 (10.9)	.791
trunk or head	14	56.3 (13.8)	32.1 (13.0)		84.6 (10.0)	46.2 (13.8)	
Original diagnosis							
benign	29	67.2 (9.0)	55.4 (9.7)	**<.001**	88.9 (6.0)	61.8 (9.5)	**.010**
malignant	8	25.0 (15.3)	0		75.0 (15.3)	12.5 (11.7)	
Diagnostic procedures							
one	22	51.1 (11.2)	35.8 (10.8)	.241	85.0 (8.0)	40.0 (11.0)	.251
≥ two	15	66.7 (12.2)	51.9 (13.2)		86.7 (8.8)	65.0 (12.7)	
Interval between diagnoses							
≤ one year	22	59.1 (10.5)	45.6 (10.6)	.962	81.8 (8.2)	54.5 (10.6)	.380
> one year	15	55.2 (13.8)	36.8 (14.0)		92.3 (.7.4)	42.0 (14.3)	
Metastases at osteosarcoma diagnosis							
none	31	66.2 (8.7)	47.8 (9.4)	**.027**	89.7 (5.7)	57.4 (9.3)	**.017**
detected	6	16.7 (15.2)	16.7 (15.2)		66.7 (19.2)	16.7 (15.2)	
Response[1]							
<10% viable	4	25.0 (21.7)	0	.069	100	0	.282
≥10% viable	9	62.5 (17.1)	46.9 (18.7)		87.5 (11.5)	43.8 (18.8)	
Complete surgical remission							
achieved	31	69.0 (8.6)	50.8 (9.4)	-	93.1 (4.7)	57.3 (9.3)	.057
none	6	-	-		50.0 (20.4)	16.7 (15.2)	

Figures

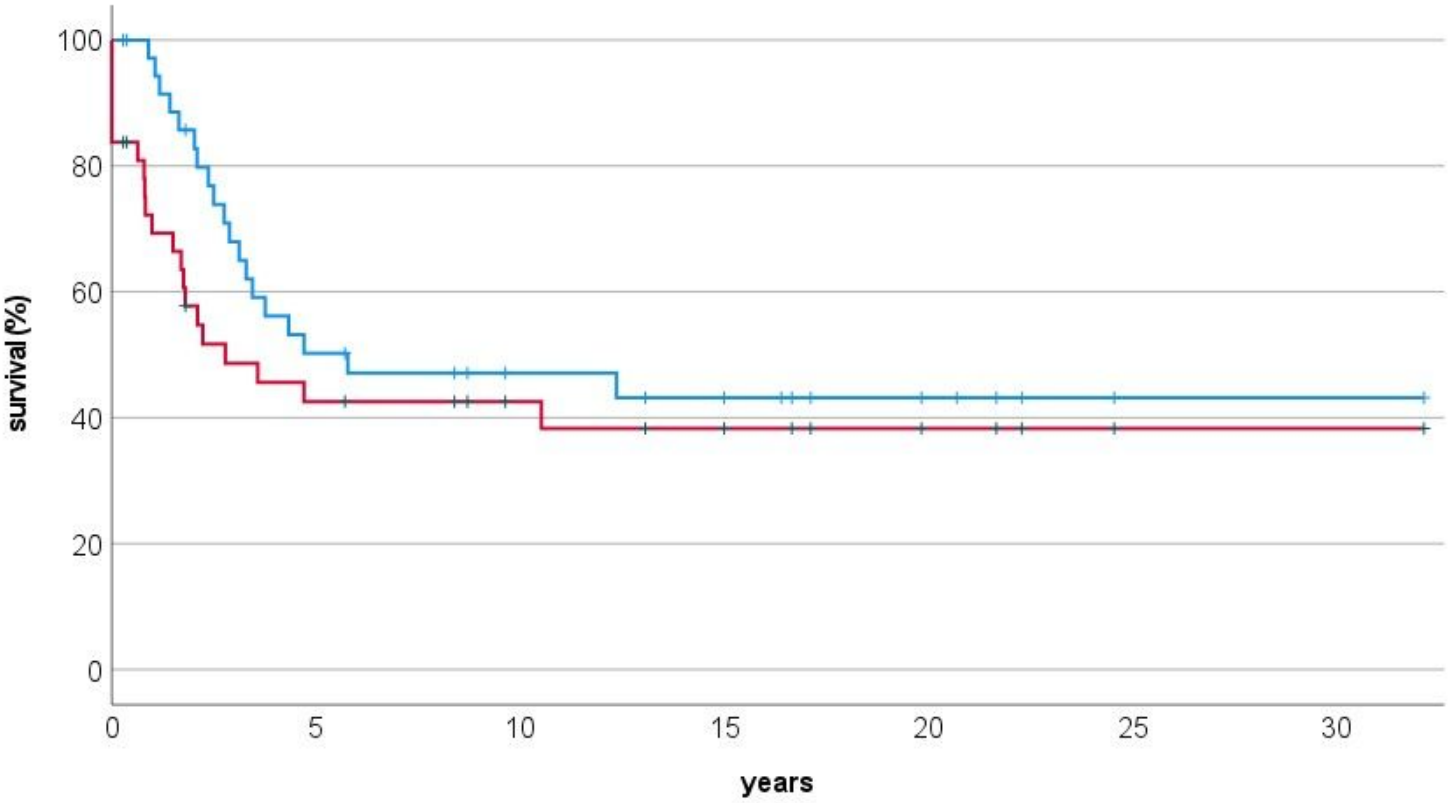

Figure 1

Overall (blue) and event-free (red) survival for all 37 patients from date of osteosarcoma diagnosis