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Osteosarcoma after the age of fifty: A clinicopathological study

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ABSTRACT

Introduction: Osteosarcoma, a primary malignant bone tumor, has a well-recognised double peak of incidence in early adolescence and after 50 years. This study investigates the clinical features and prognostic factors of patients older than 50 years with osteosarcoma.

Materiel and methods: From January 2000 to December 2012, in one bone tumor reference center, 32 patients aged more than 50 years at the diagnosis (mean age: 62.4 years (50–85), sex ratio: 13 males, 19 females) diagnosed with osteosarcoma were included. Patients younger than 50 years at diagnosis or with a non-histologically proved osteosarcoma were excluded. For each patient, we registered medical history, tumor location, systemic and local extension, treatment, and survival.

Results: 62% were located in the extremities and 28% in the axial skeleton. 6 were secondary sarcomas. Mean delay between first symptoms and biopsy was 7.4 months (range from 0 to 28 months). Ten patients had a systemic osteosarcoma with one or more pulmonary metastases. Six patients were treated with palliative care (18.8%). Eighteen patients received neodajuvant chemotherapy, sixteen of them received postoperative chemotherapy. Twenty-five patients had surgery. Postoperative complications were reported in eight cases (25%). Overall survival for all 31 patients was 25% at 5 years and 6.2% at 10 years. Survival without metastases was 15.6% at 5 years and nil at 10 years. Median survival time for the 22 localised osteosarcoma patients was 4 years (0.9–12.6) versus 1.2 years (0.3–12.3) for the 10 systemic osteosarcoma patients ($p = 0.01$).

Conclusion: Metastases at diagnosis, age, axial location are worse prognostic for survival.

Introduction

Osteosarcoma, a primary malignant bone tumor, has a well-recognised double peak of incidence in early adolescence (75%) and elderly in the seventh and eight decades (20%) [1–4]. Global incidence is 3 cases per million per year [5,6]. This primitive osseous tumor is principally localised on long bones metaphysis (90%) [5].

During first part of the twentieth century, five-year survival was less than 20% with only one treatment, amputation. The deceases were due to pulmonary metastases [7,8]. After 1980s, neoadjuvant chemotherapy and surgical resection led to a ten-year survival rate of 60–70% for localised osteosarcoma. Whereas metastatic osteosarcoma patient's five-year survival remains 25–30% [9].

As a result of the rapid population aging, osteosarcoma has increased in the elderly [2,10]. Balducci et al. [11] assessed that in 2030, 70% of all cancer would happen in patients aged more than 65 years. Some authors concluded that the older the patient is, the less his survival rate is [12–17]; whereas others found no correlation between age and survival [18–20]. While a standard treatment is well defined for young patients, no standard strategy has been established for the older [21–24]. The efficacy of chemotherapy in elderly is still controversial [3,14,25–29].

Clinical and histopathological features of osteosarcoma in adolescent patient have been well described, but there are only a few reports of the clinical and radiographical features of osteosarcoma in elderly patients. Publications [2,3,14,26–31] indicated that most osteosarcoma in patients over the age of 50 years are secondary lesions.

The aim of this study was to investigate the clinical features and prognostic factors of a heterogeneous group of patients older than 50 years with osteosarcoma.

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Materiel and methods

This is a retrospective study carried out in one bone tumor specialised center. From January 2000 to December 2012, we included all patients with an osteosarcoma aged more than 50 years at diagnosis. Patients younger than 50 years at diagnosis or with a non-histologically proved diagnostic were excluded.

For each patient, we registered in the medical history a Paget's disease or a previous irradiation, the discovery mode (pain, mass or fracture), the time between initial symptoms and biopsy, the biopsy type (Tru-cut® [32,33] or surgical), the tumor location and his systemic and local extension with Broders'histology grade [34] and general check-up. The treatment was also reported: chemotherapy, surgery with histological margin and tumor necrosis percentage post chemotherapy grade [19], radiotherapy and complications. At last follow-up, surviving patients were accounted for.

Statistics

Differences between groups were assessed using Chi-squared test. Overall and disease free survival was calculated using Kaplan-Meier product limit method and the impact of prognostic factors was assessed using a log-rank test univariate analysis. A p-value <0.05 was considered significant. Overall survival was calculated from date of diagnosis until death or the last follow-up visit. Disease free survival was defined as the period until the local or systemic disease recurred. Statistical analysis was done with XLSTAT version 2014 (Addinsoft). Confidence intervals (CI) of 95% were calculated for the statistical parameters.

Results

From January 2000 to December 2012, 32 patients aged more than 50 years were histologically diagnosed with an osteosarcoma (Table 1). Mean age was 62.4 years (range from 50 to 85). There were 13 males and 19 females. The most common location in the extremities was the distal femur in 11 patients, followed by proximal femur in 6, proximal or distal tibia, proximal humerus in 3 and calcaneus in one. In the axial bones, 5 patients had tumor in the pelvis, 2 in the scapula. In 27 cases, a soft tissue extension was noted. There were 6 patients with secondary osteosarcoma, 5 of which were associated with radiotherapy, one with pelvis Paget's disease. Diagnosis was discovered after pain in 22 patients, an increasing size mass in 6 patients, a traumatism without fracture in one patient and a pathologic fracture in one patient.

Mean delay between first symptoms and biopsy was 7.4 month (range from 0 to 28 months) except for one patient with a painful multiple year evolution. Biopsy was realised with a Tru-cut® in 6 patients and surgically in 26 patients. Broders' grade histology was II for 3 patients and III for 29 patients (Table 2). Ten patients had a systemic osteosarcoma with one or more pulmonary metastases. One patient had an extensive pelvis osteosarcoma with a palliative treatment and had no thoracic scanner. Twenty-one patients had a localised osteosarcoma. An external whole-body bone scan was done for 15 patients without other location. For the 17 other patients, no scintigraphy was found in the medical report.

One patient was lost just after the diagnosis.

Palliative care was decided in multidisciplinary staff meeting for six patients with a high grade pelvis osteosarcoma (18.8%).

Fifteen patients underwent the recommended therapy which included neodajuvant chemotherapy, surgery and adjuvant chemotherapy. Eighteen patients received neodajuvant chemotherapy with a unique protocol for all patients: API-AI (doxorubicine/cisplatins/ifosfamide; doxorubicine/ifosfamide). Only the number of courses varied. Twenty-five patients received surgery: five underwent amputation and the twenty others received limb-salvage surgery. In all patients, the status of surgical margin was wide R0 with a circumferential resection margin inferior to 1 mm in 4 cases. Among the eighteen patients who received neoadjuvant chemotherapy, there was seven good responders with tumoral necrosis > to 90% (grade III and IV [19]), ten bad responders and one deceased before surgery. The conservative surgery was resection without reconstruction (acromion, scapula, collarbone) for three patients, resection and reconstruction by massive prosthesis for fourteen, one resection and spacer, two resection and reconstruction by allograft and osteosynthesis. Sixteen of these eighteen patients received postoperative chemotherapy adapted to histologic response, chemotherapy tolerance and pulmonary extension.

For one patient, therapy was surgery with an amputation and adjuvant chemotherapy. Surgical biopsy concluded to an unclassifiable osteosarcoma. Diagnosis was done after amputation.

Six patients had only surgery (2 amputations and 4 limb-salvage surgeries) without chemotherapy.

Postoperative complications were reported in seven cases (28%). Complications were infection treated surgically and with antibiotics in four cases (one hip arthroplasty infection at 8 days, one knee prosthesis infection at 12 days, and 2 scar infections at 1 month), multiples metastasis in the scar at 19 months in one case, and one massive knee prosthesis mechanical complication which needed surgery at 2 months in the last case.

At diagnosis, osteosarcoma was systemic with pulmonary metastases in 10 patients. Among these patients, two underwent

Table 1
Description of the patients.

Mean age (min-max) (years)			32 patients 62.4 (50–85)	%
Gender	Male		13	40
	Female		19	60
Site	Extremity	Distal femur	10	31.3
		Proximal femur	6	18.8
		Proximal humerus	1	3.1
		Diaphysis of femur	1	3.1
		Proximal tibia	3	9.5
		Distal tibia	1	3.1
		Others	1	3.1
	Trunk	Pelvis	5	15.6
		Scapula	2	6.2
		Others	2	6.2
Primary or secondary		Primary	26	91.2
		Secondary	6	18.8

Table 2
Histologic description of the osteosarcoma.

		32 patients	%
Broders' histology grade	Grade III	29	90.5
	Grade II	3	9.5
Histologic type	Osteoblastic	18	56.3
	Fibroblastic	7	21.8
	Chondroblastic	2	6.2
	Telengiectasic	2	6.2
	Others	3	9.5

pulmonary surgery with adjuvant chemotherapy, two only had adjuvant chemotherapy, five were on palliative care and one was lost.

Secondary metastases happened in thirteen patients with a mean of 29.7 months (range of 3–96): 10 pulmonary and 3 multiples bone locations. Patients with pulmonary metastases were treated surgically and with adjuvant chemotherapy in 4 cases, only with chemotherapy in 2 cases, and with palliative care in 4 cases. Multiples bone metastases were treated by palliative radiotherapy.

Six patients developed local recurrence after surgery with a mean delay of 11.7 months (range of 4–24). Recurrence surgical resection was made in 5 cases followed by local irradiation in 2 cases. Palliative care was decided for one patient with well-oriented analgesia.

At last follow-up (Table 3), eight patients were alive and in remission without systemic manifestations. Two patients were lost: one just after the diagnosis due to a treatment refusal and one at three years postoperative disease free due to moving. Overall survival (Fig. 1) for all 31 patients was 25% at 5 years and 6.2% at 10 years. Survival without metastases was 15.6% at 5 years and nil at 10 years. Median survival time for the 31 patients was 3.3 years (range from 0.3 to 12.6). Median survival time for the 22 localised osteosarcoma patients (Fig. 2) was 4 years (0.9–12.6) versus 1.2 years (0.3–12.3) for the 11 systemic osteosarcoma patients (Fig. 3) ($p = 0.01$). Median survival delay for living patients at the last follow-up was 4 years (3–12.6).

Survival was different depending on the initial symptoms: if it was a pathologic fracture, median survival was 3.7 years (1.5–5.4); if it was a mass, median survival was 5.8 years (1.2–12.6); if it was pain, and median survival was 2.5 years (0.3–12.3). No significant difference was found between these different groups (pain versus mass: $p = 0.08$; pain versus fracture: $p = 0.6$).

Location was associated with a different prognosis. Median survival of the 9 axial osteosarcoma patients was 1 year (0.3–8.5) and for the 23 extremities osteosarcoma patients, it was 4 years (0.9–12.6) ($p = 0.02$).

No significant difference was observed between amputation and limb-salvage surgery in terms of survival.

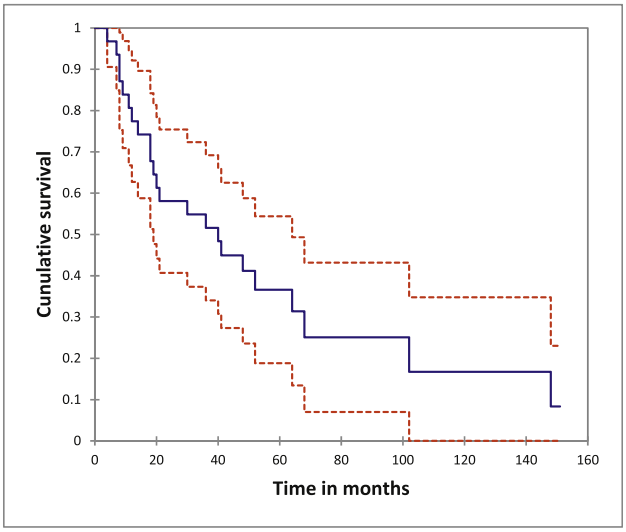

Fig. 1. Kaplan-Meier survival curve for all patients (solid line is median survival, dotted lines represent upper and lower 95% CI).

Median survival for the twelve patients who received chemotherapy was 4 years (0.3–12.6) versus 1.5 years (0.7–8.5) for the eleven patients with a treatment without chemotherapy ($p = 0.03$).

Discussion

In the present study, we reviewed 32 osteosarcoma patients older than 50 years treated in one bone cancer center to demonstrate clinical features and prognostic factors. The site of primary lesions, metastases at diagnosis, definitive surgery and chemotherapy were significant prognostic factors.

Osteosarcoma over the age of 50 years is not that uncommon (approximately 13% of patients with osteosarcoma over the age of

Table 3
Survival of patients (one patient lost with a distal femur primitive systemic osteosarcoma).

Variable		n	Median overall survival (min-max) (years)	Log-rank p value
Site	Extremities	22	4 (0.9–12.6)	0.02
	Trunk	9	1 (0.3–8.5)	
Type	Primitive	25	3.4 (0.3–12.6)	0.28
	Secondary	6	3.1 (0.6–8.5)	
Initial metastasis	Present	9	2.4 (0.3–12.3)	0.01
	None	22	4.2 (0.9–12.6)	
Surgery	Present	25	4.3 (0.9–12.6)	0.0002
	None	6	0.7 (0.3–1.2)	
Surgery type	Amputation	5	3.2 (1.5–4.3)	0.63
	Limb-salvage	20	4.6 (0.9–12.6)	
Chemotherapy	Present	20	4 (0.3–12.6)	0.03
	None	11	1.5 (0.7–8.5)	
Treatment	Chemotherapy+surgery	19	4.3 (0.9–12.6)	0.34
	Surgery alone	6	3.5 (1.2–8.5)	

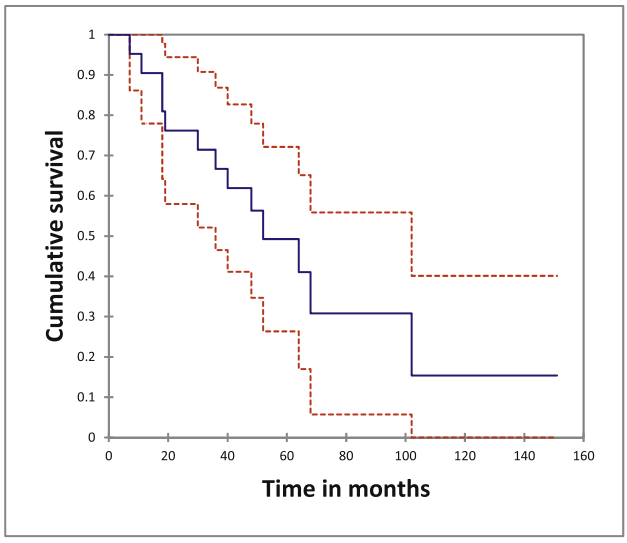

Fig. 2. Kaplan-Meier survival curve for patients with a localised osteosarcoma at the diagnosis (solid line is median survival, dotted lines represent upper and lower 95% CI).

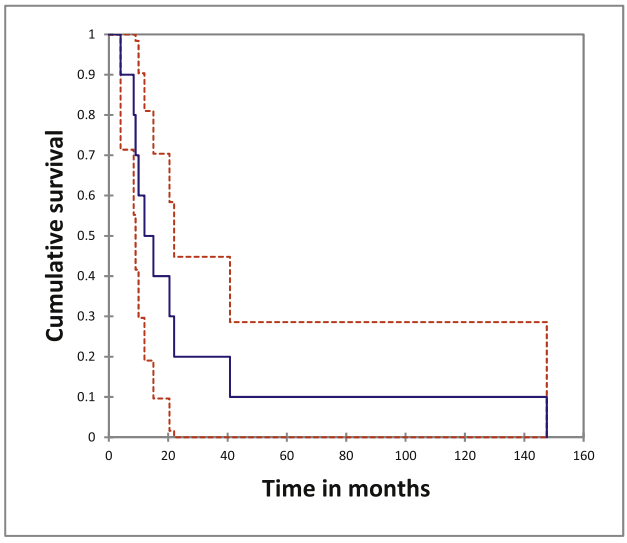

Fig. 3. Kaplan-Meier survival curve for patients with a systemic osteosarcoma at the diagnosis (solid line is median survival, dotted lines represent upper and lower 95% CI).

50 years) [35]. Age is a well-known bad prognosis factor. Song and al [36]. compared survival in two groups: inferior or superior to 40 years. Five year survival without metastases was 40.1% in the older group and 61.5% in the younger patients. In our study, 5-year survival was 25%, similar to other studies [3,13,14,27,37]. Elderly patients seem to wait a longer time between first symptoms and first medical advice in comparison with younger patients. Time between symptoms and diagnosis was shown to be higher in the elderly by Longhi and al [27]. who reported 4 months (0-73) for elderly and 10 weeks for adolescents. This is also observed in our study with a mean waiting time of 7.4 months (0-28).

In young patients, extremities are the most frequent locations. It decreases when the patient is older [12,37]. The incidence of axial osteosarcoma in elderly patients has been reported as 13.7–49% [2,3,13,14,26,27,27,29]. In the present study, 31.2% patients had a tumor at an axial site. Their survival was 2.3 years (0.3–8.5), significantly different overall survival of the 22 patients with an extremities location, which was 4.2 years (0.9–12.6) ($p = 0.02$). This result confirms the previous articles about the severity of axial location.

In elderly, osteosarcoma can be secondary to another disease, especially Paget's disease (8–32% of elderly osteosarcoma) or previous irradiation (3–8.5% of elderly osteosarcoma) [14,27,38,39]. Only 3% of the total patients were recorded as having osteosarcoma in association with Paget's disease and 15.6% in association with previous radiotherapy. No association between secondary or primary osteosarcoma and survival was significant statistically; neither in the different studies nor in our study (Table 3).

Metastases at the diagnosis have also been frequently observed in elderly patients, with an incidence between 5 and 33% and with a poor outcome [3,13,14,26–30]. This is confirmed in our study with 31.2% of the patients with systemic osteosarcoma at diagnosis and a significant poorer outcome with an overall survival of 2.8 years (0.3–12.3) versus 4.2 years (0.6–12.6) for patients with a localised osteosarcoma ($p = 0.01$).

In some studies, surgery type is correlated with the survival. Patients who underwent limb-salvage surgery have had a better survival than those with an amputation [13,14,27,40]. In our series, there was no significant difference between amputation and limb-salvage surgery but this can be biased by the histologically clean margin in all cases (Table 3).

The role of chemotherapy in elderly patients has remained controversial. Some reports stated that chemotherapy in the elderly is beneficial, while others did not. Antman et al. [41] reported that relatively lower effectiveness of chemotherapy was observed in adults with advanced disease. This may have arisen from two reasons: one is the biological feature of osteosarcomas in the elderly who have a lower sensitivity to standard chemotherapy than those in younger patients. The other reason is that chemotherapy was not given to patients who refused the treatment, to patients whose health conditions were not good enough to tolerate intensive chemotherapy.

According to the results of the present study and previous reports concerning osteosarcoma in the elderly, metastases at diagnosis and definitive surgery are critical factors for survival.

One of the main limitations of the present study is its retrospective nature. Precise analyses concerning the chemotherapy dose and intensity were lacking.

Conclusion

Our results described herein show that patients over the age of 50 years should be treated similarly to those in the younger age group with aggressive chemotherapy and complete surgical resection whenever it is possible. Prospective studies of treatment for patients in this age group are required to identify the most effective, tolerable chemotherapy.

Acknowledgments

None.

Conflict of interest

None.

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