Osteosarcoma: What did we learn from the paediatric experience for adolescents and young adults?

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Abstract

The term 'osteosarcoma' (OS) defines a primary malignant tumour of bone, characterised by the production of osteoid tissue or immature bone by malignant proliferating sarcomatous cells. Due to the variable biological features of different osteosarcoma, several varieties are included in the osteosarcoma family, with different grades of malignancy (Table 1). Of these variables, high grade primary central osteosarcoma is the most common form and accounts for more than 80% of cases. About 85% of these patients have tumours located in the extremities, and about 15–20% of patients are metastatic at diagnosis. This tumour represents 0.2% of all malignant tumours with an incidence of three new cases/year per million population, and the majority of cases are in children and adolescents younger than 20 years of age. Therefore, it is a very rare tumour and during the course of their activity, orthopaedic surgeons or medical oncologists see about one patient with this tumour every 5 years. Thus, the interest in osteosarcoma for these specialists is quite limited. From a cultural point of view, however, this is an important tumour: (1) for the oncologist, because most current strategies using adjuvant and neoadjuvant treatments in other more common tumours (for instance breast cancer) have been formulated on the basis of results obtained in osteosarcoma; (2) for the orthopaedic surgeon because some of the new methods of surgical reconstruction devised for osteosarcoma may also be used in other orthopaedic pathologies. The present report is limited to primary high grade osteosarcoma of the extremity and will consider separately different presentations (localised, metastatic at diagnosis, relapsed).

Table 1
Classification of osteosarcoma [1]

Grade	Tumours	
	Central or intramedullary	Surface
Low	Low grade central	Parosteal
Intermediate		Periosteal
High	High grade central: – Common/mixed – Osteoblastic – Chondroblastic – Fibroblastic Telangiectatic Small cell Epithelioid Anaplastic	Juxtacortical

High grade osteosarcoma of the extremity localised at diagnosis

Results achieved in patients treated by surgery alone

In 1879 Gross [2] suggested amputation to extirpate the primary tumour. This operation was preferred to limited surgery because of the malignant nature of the disease. Up to the beginning of the 1970s amputation remained the mainstay of osteosarcoma treatment. The intent of such surgery was to eradicate the origin of a malignant process with a high propensity to seed, primarily to the lung, which was usually responsible for the patient's death. However, results obtained were very disappointing. As shown in Table 2 , also in cases without detectable metastases at presentation, 85–90% of patients died within a few months from metastases. This meant that although undetectable at diagnosis, micrometastases were already present in the majority of patients with an apparently localised tumour.

At the Rizzoli Institute [3] among 107 patients treated with surgery alone between 1959 and 1970, the cure rate was 10% with a mean time to relapse of only 7 months (range:1–33 months). From these data we learnt that even with the use of very aggressive surgery alone it is almost impossible to cure osteosarcoma.

Table 2
Rate of 5-year event free survival (EFS) and amputations in patients with osteosarcoma of the extremity treated only by surgery in historic and recent series

Center [Ref]	Years	No. of cases	Amputation (%)	5-year EFS
Rizzoli Institute[a] [3]	1959–1970	107	92	10
M.D. Anderson Hospital[a] [4]	1950–1974	173	100	14
Sloan Kettering[a] [5]	1949–1965	145	100	18
Mayo Clinic[a] [6]	1963–1968	57	100	20
Rizzoli Institute[b] [7]	1972–1988	58	76	11
MIOS[b,c] [8]	1982–1984	72	100	14
UCLA[b,c] [9]	1980–1984	27	100	20

[a] Historic series. [b] Recent series.
[c] The data of MIOS and UCLA studies refer to control arms in two randomised trials (surgery versus surgery plus adjuvant chemotherapy).

The association of radiotherapy with amputation

Osteosarcoma has been found to be a highly radioresistant lesion. Viable tumour cells have been observed in amputation specimens after doses of 8,000 CgY [10]. Before 1970, when this tumour was almost uniformly fatal, a strategy of primary radiotherapy followed by delayed amputation evolved into an effort to avoid mutilating surgery in patients who would die of their disease (Cade's method) [11]. High dose radiotherapy (8,000 –10,000 CgY) was administered initially and ablative surgery used only for those patients without metastases 4 to 6 months after completion of radiotherapy. However, primary radiotherapy gave few responses and also palliation, the ostensible goal of delayed surgery, was poor [12]. At the Rizzoli Institute we treated 16 patients with Cade's method. In eight of them who developed lung metastases after 6 months, it was still necessary to perform an amputation for the local sequelae of radiotherapy.

Therefore, Cade's method, in our experience, was also useless in avoiding amputations in patients who would die from metastases.

Patients treated with adjuvant chemotherapy

Oncologists have carefully studied adjuvant treatments (chemotherapy, immunotherapy, interferon) in osteosarcoma. The reason is that this tumour represents an excellent clinical model to test the effectiveness of combined treatments because of the following prerogatives: (1) the almost constant poor prognosis, also in cases without metastases at presentation, if treated by surgery alone despite good local control achieved by amputation; (2) the short interval between amputation and occurrence of metastases; (3) the site of first metastases, which are nearly always located in the lungs, and thus easily detected by x-rays.

However, up to 1972, osteosarcoma was considered a chemoresistant tumour. At the beginning of the 1970s Cortes and colleagues [13] and Jaffe and colleagues [14] achieved about 30% response in lung metastases from osteosarcoma using respectively Doxorubicin (DOX) or high dose Methotrexate (HDMTX). The same authors in 1974 published in the New England Journal of Medicine the first two papers on adjuvant chemotherapy for osteosarcoma. Cortes [15] by using DOX obtained in 88 patients a 5-year event-free survival of 39% and Jaffe [16], with HDMTX in 12 patients reported a 5-year event-free survival of 33%. As indicated in Table 3 these good results of adjuvant chemotherapy were confirmed in several mono-institutional and multicentric trials. If a general consensus that adjuvant chemotherapy improved outcome of patients with osteosarcoma of the extremities localised at diagnosis was accepted, it was not clear which adjuvant chemotherapy regimen was best, i.e. which drugs, which dosage, and for how long. Table 3 gives a schematic overview of the most important adjuvant trials performed employing as chemotherapeutic agents either only one drug or a combination of two or more drugs. Although there are no randomised studies that compare the efficacy of mono chemotherapy regimens with those of polychemotherapy, the data referred seems to show that the more recent and more complex regimens including a combination of drugs (HDMTX and DOX or HDMTX, DOX plus other drugs) are generally more effective than the regimens that use a single drug (DOX or HDMTX). At Rizzoli Institute, between 1972 and 1992, we treated 248 patients with four different protocols [17]. Surgery was limb salvage in 25%

Table 3
Primary high grade non metastatic osteosarcoma of the extremities (results achieved in several uncontrolled mullticentric or monocentric studies with adjuvant chemotherapy)

Center	No. of cases	Drug used	Amputation (%)	5-year EFS (%)
ALGB[a] [11]	90	DOX	100	39
INT Milan [18]	29	DOX	100	45
Gainesville Univ. [19]	51	DOX	97	49
NCI [20]	39	HDMTX	100	42
Dana Farber [16]	12	HDMTX	100	42
Dana Farber [21]	68	DOX-HDMTX	72	59
COSS 77[a] [22]	58	DOX-HDMTX-CPM	100	51
MIOS[a] [19]	77	DOX-HDMTX-BCD	100	61

[a] Multicentric studies.
DOX: Adriamycin; HDMTX: High dose Methotrexate; CPM: Cyclophosphamide; BCD: Bleomycin–cyclophosphamide-Dactinomycin; CDP: Cisplatinum.

of cases and the 5-year EFS 43%. From the above cited studies we learnt that adjuvant chemotherapy considerably improves outcome of osteosarcoma and that, probably, multidrug regimens are more effective than monodrug regimens.

Patients treated with neoadjuvant chemotherapy

Considering that about 50% of these patients could be cured by adding adjuvant chemotherapy to surgery, orthopaedic surgeons started to ask themselves whether it was also possible to improve the quality life by avoiding amputation, at least in selected cases. Unfortunately, osteosarcomas of the extremity are usually (more than 90%) located in portant bones (femur, tibia, humerus), i.e. bones that cannot be resected and later reconstructed. At the beginning of the 1980s, custom-made prostheses were the only method available to rebuild these 'portant bones', but the manufacturing of custom-made prostheses required at least 2 months. In patients who could undergo conservative surgery, Rosen and colleagues [23] thought of covering this period of time with chemotherapy. This was the main reason that led to the introduction of neoadjuvant chemotherapy. Only later did neoadjuvant chemotherapy acquire a scientific rationale as: (a) reduction of tumour volume making conservative surgery easier or feasible; (b) immediate start of treatment that allowed for earlier treatment of the microscopic disease (we must not overlook the fact that in those days, for fear of wound infections, postoperative chemotherapy was postponed at least a month after surgery); (c) providing the opportunity of histologically verifying, on the resected specimen, the effect of preoperative chemotherapy and, if necessary, change the drugs in postoperative treatment. In different studies of neoadjuvant treatment [24–33] chemotherapy was performed with different combinations of drugs. In many studies [24,26,30,32, 34] salvage chemotherapy different from preoperative therapy was performed in poor responder patients. In all but one [24] of these studies, in spite of the change in postoperative treatment, outcome of poor responders remained significantly worse than that of good responders.

Results of the most important neoadjuvant studies show that all treatments were: (a) performed using several drugs; (b) that the drugs most often employed were HDMTX, DOX, Cisplatinum (CDP) and ifosfamide (IFO); (c) that the rate of amputation ranged from 3% to 71%; (d) that the rate of 5-year event-free survival (EFS) ranged between 43% to 76%; (e) that the 5-year EFS (that in osteosarcoma is very close to the cure rate because relapses after 5 years are less than 5%) results to be higher in good responder patients to preoperative chemotherapy than in poor responder patients and in monoinstitututional trials than in multicentre trials. (f) that changing postoperative treatment in poor responder patients does not improve their outcome.

At Rizzoli Institute, between 1983 and 1999, 900 patients were treated according to five different protocols previously reported. Limb salvage was 86%, 'good histologic response' (tumor necrosis >90%) was achieved in 62% of patients and the 5-year EFS was 58%. Therefore, from these neoadjuvant studies, we learnt that results are, in terms of cure rate, no worse than those previously achieved with adjuvant chemotherapy, that often it is possible to avoid

amputations, that histologic response to preoperative treatment has an important prognostic significance (see later), that changing postoperative treatment on the basis of histological response generally does not improve prognosis.

Adjuvant or neoadjuvant chemotherapy?

Over the last 10 years, osteosarcoma of the extremities localised at diagnosis is nearly always treated with neoadjuvant chemotherapy. Can we really be certain that neoadjuvant treatment is better than the old adjuvant treatment? All the potential advantages of neoadjuvant treatment, as considered 15 years ago and reported before, are today no longer valid. In fact: (a) surgical reconstructions today use prostheses or other methods that are promptly available; (b) chemotherapy is usually started 3–5 days after surgery without waiting a month or longer as in the past; (c) in the more recent protocols, active drugs in OS (i.e. DOX, HDMTX, CDP, IFO) are generally all used from the start and thus evaluation of histological response on the resected specimen only has prognostic significance but no postoperative treatments are based on this evaluation.

On the other hand, when neoadjuvant treatment is used, we run the risk of leaving in site, for 2 or more months, a tumour that might not be completely responsive to chemotherapy, with the possible consequence of selecting chemoresistant clones of malignant cells that could metastasise. It must not be forgotten that 20–30% of osteosarcomas respond poorly to preoperative treatment. On this topic, adjuvant versus neoadjuvant chemotherapy, only one controlled study was performed. The Paediatric Oncology Group [34] conducted a trial where patients were randomised to receive immediate surgery followed by adjuvant chemotherapy or neoadjuvant treatment. The chemotherapy protocol was the same (HDMTX, DOX, CDP, BCD). The study, performed between 1986 and 1993, had great difficulty in recruiting cases (100 patients from 37 Institutions in 8 years). The rate of limb salvage and the rate of 5-year EFS were the same in the two groups (50% versus 55% and 61% versus 69%). The greatest criticism that can be made of this recent study is the high percentage of radical resection surgery carried out in both groups. Despite the results of this study, it is not possible to express with certainty the superiority of neoadjuvant treatment in comparison to the adjuvant. Although there are no doubts that for surgeon it is easier to operate an osteosarcoma previously treated with chemotherapy, we believe that the choice of treatment should be based on each single case, in accordance with clinical and radiological findings. For instance, it could be a nonsense in a small osteosarcoma of the fibula, a bone that does not require reconstruction, to deliver 3 months of chemotherapy before surgery, with the risk of non response and the risk that the tumour could metastasise during this time.

Prognostic factors

Several papers report prognostic factors in osteosarcoma. According to our experience (Table 4), previously reported [35–37] on 1148 patients with osteosarcoma treated at the Rizzoli Institute with adjuvant or neoadjuvant chemotherapy between 1972 and 1999, the prognostic factors that kept their negative significance in multivariate analyses were: (1) high serum values of alkaline phosphatase at presentation; (2) tumour volume of more than 200 ml; (3) adjuvant treatment instead of neoadjuvant; poor histological response to preoperative chemotherapy; (4) inadequate surgical margins. Most of these data were confirmed in other trials.

Table 4
Patients treated at the Rizzoli – 5-year EFS (multivariate analyses[a])

Variable		Relative risk	Wald test
Serum alk. phos	Normal	1	
	Elevated	2.31	$P < 0.0005$
Tumour volume	< 200 ml	1	
	> 200 ml	1.26	$P < 0.004$
Chemotherapy	Neoadjuvant	1	
	Adjuvant	1.66	$P < 0.0005$
Tumour necrosis	Good	1	
	Poor	1.87	$P < 0.024$
Surgical margins	Adequate	1	
	Inadequate	1.34	$P < 0.024$

[a] Cox's regression with iterative model of Wald.

Amputation or limb salvage

The rate of limb salvage in neoadjuvant studies ranges between 27% and 98%. It is interesting to outline that the percentage of limb salvage as well the rate of 5-year EFS is significantly higher in mono-institutional studies than in multicentric studies, as recently published in our meta-analyses study [38]. The results of this paper show that in 1523 patients

Table 5
Rate of local recurrence according to different variables in the Rizzoli series (61 out of 1,148 patients treated with adjuvant or neoadjuvant chemotherapy)

Protocol		Rate of Local Recurrence	Amputation
Gender	Male	4.9%	
	Female	6.2%	$P < 0.42$
Age	< 14 years	5.6%	
	> 14 years	5.3%	$P < 0.92$
Pathologic fracture	yes	7.9%	
	no	5.2%	$P < 0.39$
Serum value of A.P.	Normal	4.3%	
	Elevated	4.4%	$P < 0.6$
Tumour site	Femur	5.8%	
	Tibia	4.7%	
	Fibula	3.4%	
	Humerus	7.2%	
	Other extremity bone	0%	$P < 0.88$
Tumour size	< 150 ml	5.7%	
	> 150 ml	5.9%	
Histology	Osteoblastic	6.5%	
	Chondroblastic	5.6%	
	Fibroblastic	6.1%	
	Unclassified	1.2%	
	Others	5.4%	$P < 0.27$
Surgery	Amputation	2.8%	
	Limb Salvage	6.3%	
	Rotation plasty	5.6%	$P < 0.3$
Surgical margins	Adequate	3.6%	
	Inadequate	23.5%	$P < 0.0001$
Chemotherapy	Adjuvant	3.7%	
	Neoadjuvant	5.9%	$P < 0.24$
Response to preop. treatment	Good	4.1%	
	Poor	8.7%	$P < 0.006$

treated in multi-institutional trials and 1133 patients treated in mono-institutional trials the rate of amputation and the rate of 5-year EFS were respectively 45% versus 16% ($P < 0.0001$) and 55% versus 65% ($P < 0.0001$). For this reason we believe that treatment of patients with osteosarcoma should be performed in a few selected institutions with vast experience in treatment of musculoskeletal tumours.

The problem of local recurrence

There are few published data on the incidence of local recurrences (LR) in osteosarcoma. These seem strictly correlated to surgical margins and histological response to preoperative treatment [39]. Our experience on patients treated with neoadjuvant chemotherapy and reported in Table 5 gives an incidence of 4.2% of LR for amputated patients and of 6.5% in patients treated with limb salvage. This difference is not statistically significant. According to surgical margins the rate of LR was 4% in cases with adequate surgical margins (radical or wide) and 56.6% for patients with inadequate surgical margins (marginal, intralesional or contaminated ($P < 0.0001$). According to histologic response to preoperative treatment the rate of LR was 4.1% for good responder patients and 9.8% for poor responders ($P < 0.017$). It is important to note that

prognosis of patients who develop LR is very poor, significantly worse than the outcome of patients who relapse for metastases [40].

Mortality and important side-effects due to chemotherapy

Among the damages due to chemotherapy the most important are: (1) deaths, mostly due to DOX myocardiopathy. The rate of this terrible event, that can manifest even after 10–15 years from the end of treatment [41], is about 1%; (2) sterility in males [42]; (3) risk of a second malignancy [43]. Regarding this last point, according to the Rizzoli experience, 26 patients with osteosarcoma treated with combined chemotherapy developed a second malignant neoplasm (2.2%) 1 to 25 years (median = 8 years median) after the start of treatment. Of these patients only two had a family history of cancer (Li-Fraumeni syndrome). The second tumours were leukaemia (10), breast cancer (7), lung cancer (2), CNS tumours (2), soft tissue sarcoma (1), parotid cancer (1) and colon cancer (1). The relative risk of developing a second tumour was 1.5% at 5 years, 4.2% at 10 years, and 4.5% at 15 years. The rate of second malignancies was significantly higher in females than in males ($P < 0.02$). No second neoplasms were seen in 176 patients that at the time of diagnosis of OS were 10 years old or younger. The latent period was significantly shorter in haematological malignancies than in solid tumours (2.5 versus 9.4 years, $P < 0.01$).

What we learnt from this group of tumours

Today, by combining surgery and adjuvant or neoadjuvant chemotherapy, it is possible to cure 60–65% of these patients. However, this cure rate has not improved in the last 15–20 years.

Relapsed patients

There are no reliable data on the outcome of patients who relapsed after adjuvant or neoadjuvant treatments. According to our experience of 488 patients who relapsed, 325 were followed and treated at the Rizzoli whereas 123 moved to other hospitals for treatment. Of this last group of patients we only know the type of first relapse and final outcome, but not the exact treatment performed after recurrence. The following analyses therefore concern only patients followed by us. In these 325 patients post-relapse treatment was the following: (a) only symptomatic treatment in 2%; (b) surgery in 62% patients (in 60% surgery was followed by second-line chemotherapy); (c) only second-line chemotherapy in 31%; (d) other treatments in 5%.

The present outcome of these patients is the following: 65 patients (20%) are alive and free of disease from 1 to 23 years (mean 9.5 years) after the last treatment. The number of relapses and treatments in these patients was one in 43 (66%), two in 15 (23%), three in four (6%), four in two (3%) and five in one; 247 (76%) died of tumour; three died for toxicity of second-line chemotherapy; and 10 are still alive with uncontrolled disease. The overall 5- and 10-year survival for the 1148 patients reported here were respectively 66% and 62%.

For patients who were treated at the Rizzoli after relapse, the 5-year post last recurrence result was correlated with: (a) time to relapse; (b) site of first metastases; (c) and in patients who relapsed with lung metastases with the number of pulmonary lesions. In more detail the rate of 5-year post last relapse EFS was 3% for 76 patients who relapsed again within one year of their first relapse, 18% for 152 who relapsed in the second year ($P < 0.002$), and 37% for 108 who relapsed in the third year or later ($P < 0.0008$). According to site of first metastases the rate of 5-year post-relapse survival (PRS) was 27% for patients who relapsed in the lungs and 4% for those who first relapsed in bone or other sites ($P < 0.003$). In patients who relapsed in the lung, the 5-year PRS was 39% for patients who had only one or two nodules and 13% for patients with three or more nodules ($P < 0.0001$). None of the patients who relapsed with local recurrence and metastases, metastases in lung and bones, metastases outside lung and bones, are presently alive. Therefore, about 20% of patients who relapsed were probably cured.

It is interesting to note that the final outcome of patients who had local recurrence was significantly worse than that of patients who had only systemic relapse [24,39]. From these data we learnt that about 20–25% of patients who relapse after adjuvant or neoadjuvant treatment could still be cured but that the cure rate is very low in patients who relapse outside the lungs or have a local recurrence.

Patients with lung metastases at presentation

About 15–20% of patients with osteosarcoma of the extremity present metastases at the time of diagnosis. These patients are usually treated with thoracotomy as

well as chemotherapy. The cure rate of these patients, as reported in Table 6, ranges between 11% and 56%.

Table 6
Patients with lung metastasis at presentation

Study	Years	No. of cases	5-year Overall Survival
Sutow *et al.* [40]	1972–1978	19	0%
Meyers *et al.* [44]	1975–1984	62	11%
Beron *et al.* [45]	1977–1982	16	56%
Kaste *et al.* [46]	1977–1997	32	29%
Marina *et al.* [47]	1962–1990	31	30%
Thompson [48]	1982–1997	85	50%
Mialou [49]	1987–2000	87	18%
Harris [50]	1987–1990	26	46%

At the Rizzoli Institute, between 1993 and 2000, 66 patients with osteosarcoma metastatic only to the lung were treated. These patients received chemotherapy, then were restaged, and, if possible, were operated for the primary tumour and the metastatic pulmonary nodules at the same time. This was possible in 62 patients. At a follow up of 3 years, 24 (36%) remained continuously free of disease, one patient died from chemotherapy toxicity and 42 relapsed.

Patients with multicentric osteosarcoma

Patients with multiple bone locations of OS, with or without metastases in other sites, have a very dismal prognosis, although only a very few cases have been reported. At the Rizzoli Institute, the only consistent series, between 1986 and 2002, 42 patients with synchronous multifocal osteosarcoma were treated with neoadjuvant chemotherapy and surgery to all involved sites [51]. This was possible only in 16 patients. Only three of these patients survived and were free of disease at 5, 6 and 17 years. Therefore we learnt that prognosis of multicentric osteosarcoma is very poor.

Conflict of interest statement

No conflict of interest with this abstract.

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