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ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Telangiectatic osteosarcoma: a review of 87 cases

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Abstract
Purposes Telangiectatic osteosarcoma (TOS) is a rare subtype of osteosarcoma. We analyzed (1) oncologic outcome in a large homogeneous series and (2) the role of prognostic factors on prognosis, local recurrence and metastasis.
Methods Eighty-seven patients (47 males, 54 %) were retrospectively analyzed. All except 4 had extracompartmental disease, and ten patients had lung metastasis at diagnosis. Pathologic fracture was present in 27 cases (31 %). Seventy-eight patients were treated with neoadjuvant chemotherapy; nine had surgery as first treatment. Limb-salvage surgery was performed in 71 cases, amputation in 14, and rotationplasty in one. One patient died before surgery. Possible prognostic factors were statistically evaluated.
Results Overall survival was 60.7 % at 10 years of follow-up. Fifty-one patients were disease-free (58.6 %), 2 were alive with disease (2.3 %), 31 died with disease (35.6 %), and 3 died of other causes (3.4 %). Ten local recurrences were observed (11 %). Twenty-five patients (29 %) developed lung (22) or bone (3) metastases. No statistical difference was found considering age, metastases at diagnosis, gender, pathologic fracture, tumor volume, compartmental status, number of neoadjuvant chemotherapy agents and treatment. Induced necrosis was significant at both univariate and multivariate analysis ($p < 0.0001$).
Conclusions TOS does not have a poor prognosis as previously reported in literature, with a survival of about 60 % at 10 years. Most of patients can be cured with neoadjuvant chemotherapy plus surgery (limb sparing surgery is possible and safe). Tumor response to chemotherapy as induced necrosis was the only significant prognostic factors on survival, even if small tumor volume at diagnosis correlates with better prognosis at univariate analysis.
Level of evidence IV.

Keywords Bone sarcoma · Chemotherapy · Pathologic fracture · Prognostic factors · Statistical analysis

Introduction

Osteosarcoma (OS) is the most common non-hematopoietic, primary malignant tumors of bone affecting adolescents and young adults, with an estimated incidence of 4 to 5 per million population (Fletcher et al. 2002). Histologically, OS can be classified into several types: osteoblastic, chondroblastic, fibroblastic, rich in giant cells, epithelioid, small cells and telangiectatic, depending on the dominant element. Telangiectatic OS (TOS) is a rare subtype that represents from 2 to 12 % of all cases of OSs (Picci 2014; Farr et al. 1974; Matsuno et al. 1976; Huvos et al. 1982; Rosen et al. 1986; Bacci et al. 2001a, b; Weiss et al. 2007; Durnali et al. 2013), and this means that there must be substantial difference in interpretation of the diagnosis in the reported series. It is distinguished histologically from conventional OS by spaces, often blood-filled, separated by septa containing highly malignant cells, with a predominately lytic radiographical pattern (Dorfman and Czerniak 1995;

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Vanel et al. 1987). Prognosis of patients with TOS has been debated in the literature for decades. Since the introduction of neoadjuvant chemotherapy, long-term overall survival has improved from less than 20 % to about 60 % (Picci 2014; Farr et al. 1974; Matsuno et al. 1976; Huvos et al. 1982; Rosen et al. 1986; Bacci et al. 2001a, b; Weiss et al. 2007; Durnali et al. 2013). The prognosis of TOS was initially thought to be poor, but the scenario has progressively changed and at present, conventional OS and TOS share the same treatment and the same prognosis (Rosen et al. 1986; Bacci et al. 2001a, b; Weiss et al. 2007). The aim of our study was to evaluate the results of the treatment of patients with TOS in a homogeneous series from a single institution. Moreover, identification of variables that influence prognosis for TOS may permit stratification of these patients into subgroups with better or worse risk of local recurrence, metastasis and death due to this disease. Discovery of such prognostic factors would allow identifying at-risk patients with the aim of improving the therapeutic results. Further objective of this study was to analyze the clinical and treatment-related factors that influenced the outcome of patients with TOS treated in a single institution.

Materials and methods

We retrospectively studied all patients with histologically verified TOS treated at our Institution between January 1985 and December 2008. We decided to consider patients up to 2008 in order to have a minimum of 5 years of follow-up. All pathology materials and imaging studies for these patients were reviewed. Patients who fulfilled the histologic and radiographic diagnostic criteria of TOS as defined by the World Health Organization Classification were included in this study (Matsuno et al. 1976). These criteria are summarized as follows: (1) predominantly lytic bone mass with minimal sclerosis on radiographs, (2) grossly cystic medullary mass with no or minimal solid or sclerotic component, and (3) histologic features consisting of bone-forming tumor with notable blood-filled spaces separated by septa lined by and/or containing malignant tumor cells with prominent nuclear atypia and limited osteoid deposition. Eighty-seven consecutive patients with histologically proven TOS were included. Information regarding the clinical characteristics, treatment and outcome of TOS patients was collected. Imaging studies used to define the extension of the primary tumor included radiography, bone scintigraphy, computed tomography (CT) and magnetic resonance imaging (MRI) (some methods varied with time and, hence, availability). Computed tomography scan of the chest was also available after 1991.

Patients age and gender, tumor site, volume and extension, pathological fracture and metastases at diagnosis, type of local treatment, number of chemotherapy agents, tumor response to neoadjuvant chemotherapy and surgical margins were evaluated for their distribution in the patient cohort and for possible correlations with outcome (Table 1). Tumor volume was measured on coronal, transverse, and sagittal MRI or CT scans of the lesion; the maximum height, width, and depth were recorded; and the volume was calculated using the formula of an ellipsoid mass volume $= [(\pi/6) \times \text{height} \times \text{width} \times \text{depth}]$. If CT or MRI were not available, tumor volume was measured on two-plane radiographs. The outermost boundaries of tumor density visible on two-plane radiographs of the lesion site were marked, and the greatest dimensions for width (in anteroposterior (AP) view, depth (in lateral view), and length (in AP and lateral view) were measured (Shin et al. 2000). Metastasis was assumed whenever other than skip lesions were detected on initial staging, except when the suspicion was later excluded by surgery with negative histology. Margins of tumor resection were defined according to Enneking (1986) as 'adequate' if radical or wide and 'inadequate' if margins were marginal, intralesional, or contaminated, regardless of histologic response, i.e., when margins still contained tumor cells even if completely necrotic. About chemotherapy, patients were treated with different protocols (Bacci et al. 1993, 2001a, b, 2002, 2006; Ferrari et al. 1999, 2012) in agreement with the current therapeutic approach of the year of treatment (Table 2). Briefly, with protocol IOR/OS-1, patients received two drugs preoperatively: methotrexate (MTX) and cisplatin (CDP); with protocols IOR/OS-2, IOR/OS-3, ISG-OS1 and ISG/OS-Oss, three drugs: MTX, CDP, and doxorubicin (ADM); and with protocols IOR/OS-4, Pilot ISG and ISG/SSG-1, four drugs: MTX, CDP, ADM, and ifosfamide (IFO). The preoperative treatment protocols IOR/OS-2 and IOR/OS-3 differed in the doses of MTX. Considering the results of the randomized study ISG/OS-1 (Ferrari et al. 2012) where the addition of IFO to MTX, CDP and ADM from the preoperative phase did not improve the rate of good responders and increased the hematological toxicity, newer protocols included IFO only for patients showing a poor histological response. Few patients were treated with one or two drugs only due to specific clinical setting. Cisplatin was delivered intraarterially or intravenously, whereas all other drugs were delivered intravenously. Postoperative chemotherapy was performed with the same drugs used preoperatively in the IOR-OS/4 and ISG/SSG-1 protocols. In the other protocols, salvage chemotherapy was performed by changing all the drugs used postoperatively (IOR/OS-1) or by adding new drugs to the regimen used preoperatively (IOR/OS-2, IOR/OS-3, and ISG/OS-Oss). For the purpose of this study, we grouped patients receiving none (nine patients received postoperative chemotherapy only), one or two (14 patients) and three or more (64 patients) neoadjuvant chemotherapy

Table 1 Characteristics of 87 patients with telangiectatic osteosarcoma and univariate statistical analysis

Characteristic	No. of patients (%)	Exact *p*
Age at diagnosis, y		
Median	16.6	
Range	4.7–59.8	
<14	31 (35.6)	0.233
≥14	56 (63.4)	
Sex		
Men	47 (54.1)	0.735
Women	40 (45.9)	
Primary tumor site		
Extremities		
Femur	38 (43.6)	
Tibia	19 (21.8)	
Humerus	20 (22.9)	
Fibula	4 (4.6)	
Radius	1 (1.1)	
Heel	1 (1.1)	
Cuneiform	1 (1.1)	
Trunk		
Ischium	1 (1.1)	
Pubis	1 (1.1)	
Cup	1 (1.1)	
Disease stage		
Localized	77 (88.6)	0.074
Metastatic	10 (11.4)	
Tumor compartmental status		
Intracompartmental	4 (4.6)	0.168
Extracompartmental	83 (95.4)	
Tumor Volume n = 67		
<150 cm^3	40 (59.7)	0.044
>150 cm^3	27 (40.3)	
Pathologic fracture		
Yes	27 (31)	0.863
No	60 (69)	
Neoadjuvant chemotherapy		
Yes	78 (89.7)	0.154
Not	9 (10.3)	
No. of active chemotherapeutic agents n = 78		
<3	14 (18)	0.277
≥3	64 (82)	
Histologic response to neoadjuvant chemotherapy n = 78		
Huvos grade I/II	16 (20.5)	0.0001
Huvos grade III/IV	62 (79.5)	
Type of primary surgery		
Resection	71 (81.6)	0.205
Amputation (+1 rotationplasty)	15 (17.3)	
No surgery	1 (1.1)	

* *p* values were obtained by the log-rank test on Kaplan–Meier curves survival analysis

agents (Table 2). Tumor response to neoadjuvant chemotherapy was assessed histologically according to the 4-grade system of Huvos and coworkers (Huvos et al. 1977; Rosen et al. 1982). Functional outcome has been evaluated according to the Musculoskeletal Tumor Society (MSTS) functional rating system (Enneking et al. 1980).

The presence of local recurrence, metastasis, or death was assessed, and the patients subdivided as follows: (1) continuously disease-free (if the patient was continuously disease-free to the latest routine follow-up); (2) disease-free after treatment of local recurrence or metastasis; (3) alive with disease, patients with local recurrence or metastasis; and (4) dead of disease or dead of other disease, patients who died from the tumor or other unrelated causes, respectively. Survival was defined as the time interval from the date of diagnosis to the date of last follow-up or the date of death from any cause. Event-free survival (EFS) was defined as the time interval from the date of diagnosis to the date of the first event or the date of last follow-up for patients who had no events. An event included recurrent or progressive disease and death from any cause. Survival and EFS distributions were estimated by the Kaplan and Meier curves survival analysis (Kaplan and Meier 1958; Petrie 2006); differences in survival were determined with the log-rank test. The effect level of clinical characteristics on survivorship was evaluated using both the univariate Kaplan–Meier analysis and the multivariate Cox regression analysis with stepwise forward procedure (Petrie 2006). The data were recorded in a Microsoft Excel ® 2003 spreadsheet (Microsoft Inc, Redmond, WA) and analyzed using MedCalc ® Software Version 11.1 (MedCalc Software, Mariakerke, Belgium).

Results

Patients age and gender

There were 47 males (54 %) and 40 females (46 %), with a mean age of 20 years (range 5–60 years). Several cut-off limits have been reported in literature and age limits for analyzing it as prognostic factor was arbitrarily choose based on the major significance at the univariate analysis. The age of 14 years was found the most significant value of survival and therefore has been used to group patients in univariate and multivariate analysis.

Tumor site, volume and extension

The most common location was the distal femur, followed by the tibia and the proximal humerus (Fig. 1). No case of multifocal bone involvement was observed. The cut-off limit of 150 cc tumor volume was used to evaluate tumor

Table 2 Protocols of neoadjuvant chemotherapy and number of chemotherapy agents used for each patient enrolled in the study

Protocol	Period	Preop treatment	Postop treatment
IOR/OS-1	1983–1986	HdMTX-CDP versus LdMTX-CDP	GR: MTX-CDP-ADM PR: ADM-BCD
IOR/OS-2	1986–1989	MTX-CDP-ADM	GR: MTX-CDP-ADM PR: MTX-CDP-ADM-IFO-ETO
IOR/OS-3	1990–1993	MTX-CDP-ADM	GR: MTX-CDP-ADM PR: MTX-CDP-ADM-IFO
IOR/OS-4	1994–1995	HdMTX-CDP-ADM-IFO	GR: HdMTX-CDP-ADM-IFO PR: HdMTX-CDP-ADM-IFO
PILOT ISG	1996–1997	HdMTX-CDP-ADM-IFO	GR: HdMTX-CDP-ADM-HdIFO 3 cycles PR: HdMTX-CDP-ADM-HdIFO 4 cycles
ISG/SSG-1	1997–2000	HdMTX-CDP-ADM-IFO	GR: HdMTX-CDP-ADM-HdIFO 3 cycles PR: HdMTX-CDP-ADM-HdIFO 4 cycles
ISG/OS-1	2000–2006	HdMTX-CDP-ADM	GR: HdMTX-CDP-ADM PR: HdMTX-CDP-ADM-HdIFO
ISG/OS-Oss	2007–2011	HdMTX-CDP-ADM	GR: HdMTX-CDP-ADM PR: HdMTX-CDP-ADM-IFO

Drugs	No. of patients (%)
MTX	5 (6.4)
ADM	1 (1.3)
CDP	1 (1.3)
MTX + ADM	4 (5.1)
MTX + CDP	3 (3.9)
MTX + ADM + CDP	27 (34.6)
MTX + ADM + CDP + IFO	37 (47.4)

MTX Methotrexate, *CDP* cisplatin, *ADM* doxorubicin, *IFO* ifosfamide, *ETO* etoposide, *BCD* bleomycin, *Hd* high dose, *Ld* low dose, *GR* good responder, *PR* poor responder

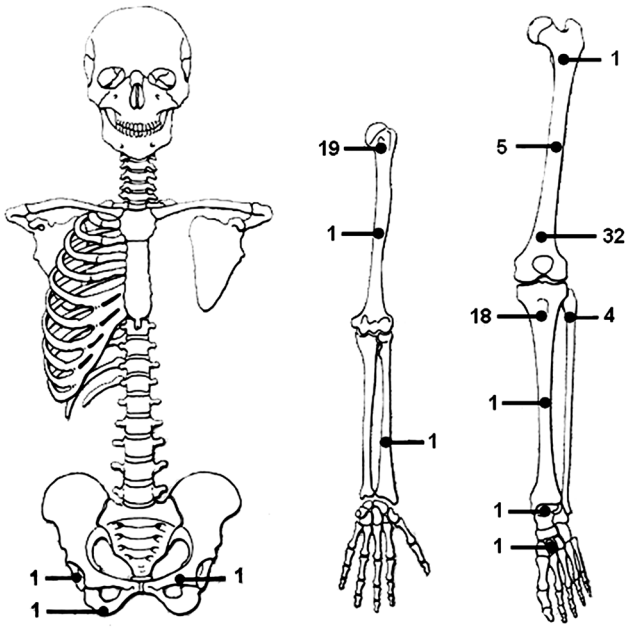

Fig. 1 Location of telangiectatic osteosarcoma in 87 patients

volume as a prognostic factor in univariate and multivariate analysis. TOS was intracompartmental in 4 cases (4.6 %) and extracompartmental in the other 83 cases (95.4 %).

Pathological fracture and metastases at diagnosis

Twenty-seven patients (31 %) presented with a pathological fracture that occurred at the femur (10 patients), the humerus (14 patients), the tibia (2 patients) and the radius (1 patient). Lung metastases at diagnosis were identified in 10 patients.

Type of local treatment

Eighty-six patients (98.9 %) had surgical treatment; one patient with tumor of the ischiopubic branch did not undergo surgery because she refused hind-quarter amputation. Among surgical procedures, amputation was performed in 14 patients (16 %), rotationplasty considered an ablative procedure in one patient (1.2 %) and resection in

71 patients (limb-salvage procedures, 83 %). Eighty-three patients (97 %) had adequate surgery, while three patients (3 %) had inadequate surgical margins (two wide but contaminated margins and one marginal margin).

Number of chemotherapy agents and tumor response to neoadjuvant chemotherapy

According to the grade of chemotherapy-induced necrosis, the patients were divided for the statistical analysis into two groups: poor responders (Huvos grade I/II, 16 patients; 21 %) and good responders (Huvos grade III/IV, 62 patients; 79 %).

Functional results, assessed according to MSTS system, were evaluated in 71 cases (all patients treated with surgical resection and reconstruction) at last follow-up: the average score was 24.4 points (range 8–30 points). Results were excellent (from 23 to 30) in 48 cases (67.6 %), good (from 16 to 22) in 17 cases (23.9 %), fair (from 8 to 15) in the remaining 6 cases (8.5 %). At a mean follow-up of 8 years (range 5–22 years), 45 patients (51.7 %) remained continuously disease-free, six were disease-free after treatment of tumor relapse (6.9 %) and two were alive with disease (2.3 %); 31 patients were dead of disease (35.6 %) and three dead of other disease (cardiac arrest, stroke, motor vehicle accident). The overall survival was 63.5 % at 5 years, 60.7 % at 10 years, and 58.0 % at 15 years (Fig. 2). The overall metastasis rate excluding patients with metastases at diagnosis was 29 % (25 patients: 22 with lung and 3 with bone metastases); the local recurrence rate was 11 % (10 patients). The EFS rate to metastases was 69.3 % at 5 years and 67.5 % at 10 years (Fig. 3); the EFS rate to local recurrence was 86.4 % at 5 years and 82.4 % at 10 years (Fig. 4).

Only two factors were significantly predictive of survival at the univariate analysis. Good responders had a better overall survival ($p < 0.0001$) than poor responders. Patients with tumor volume at diagnosis <150 cc had a better prognosis than patients with larger tumors ($p = 0.044$). Although close to significance, metastases at diagnosis in this cohort did not correlate with survival ($p = 0.074$) and we think that with the accumulation of a larger patient series, the statistical difference may reach the significance. No statistical difference was found between patients with age more or less than 14 years ($p = 0.233$), males or females ($p = 0.735$), pathological fracture or no fracture at diagnosis ($p = 0.863$), less or more than three neoadjuvant chemotherapy agents ($p = 0.277$), ablative procedures or limb-salvage surgery ($p = 0.205$), and intracompartmental or extracompartmental tumor ($p = 0.158$) (Table 1). Using the Cox proportional hazard model, multivariate analysis was performed to determine the following variables on survival: chemotherapy-induced necrosis, tumor volume, metastases at diagnosis, age and pathological fracture. As reported in Table 3, the grade of induced necrosis after neoadjuvant chemotherapy retained its significance and represents the only independent prognostic factor on survival. Conversely, the tumor volume lost its statistical significance at multivariate analysis.

About survival to local recurrence, we found no statistical difference between patients with age more or less than 14 years ($p = 0.489$), males or females ($p = 0.092$), pathological fracture or no fracture at diagnosis ($p = 0.505$), tumor volume at diagnosis lessor more than 150 cc

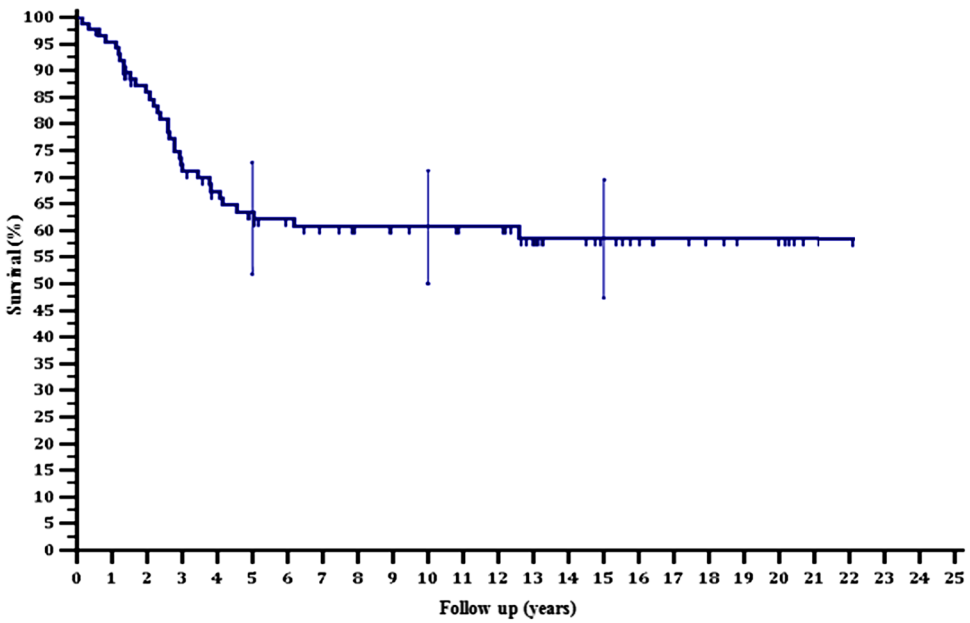

Fig. 2 Kaplan–Meier curve of survival: overall survival of the patients with telangiectatic osteosarcoma was 63.5 % at 5 years, 60.7 % at 10 years, and 58.0 % at 15 years

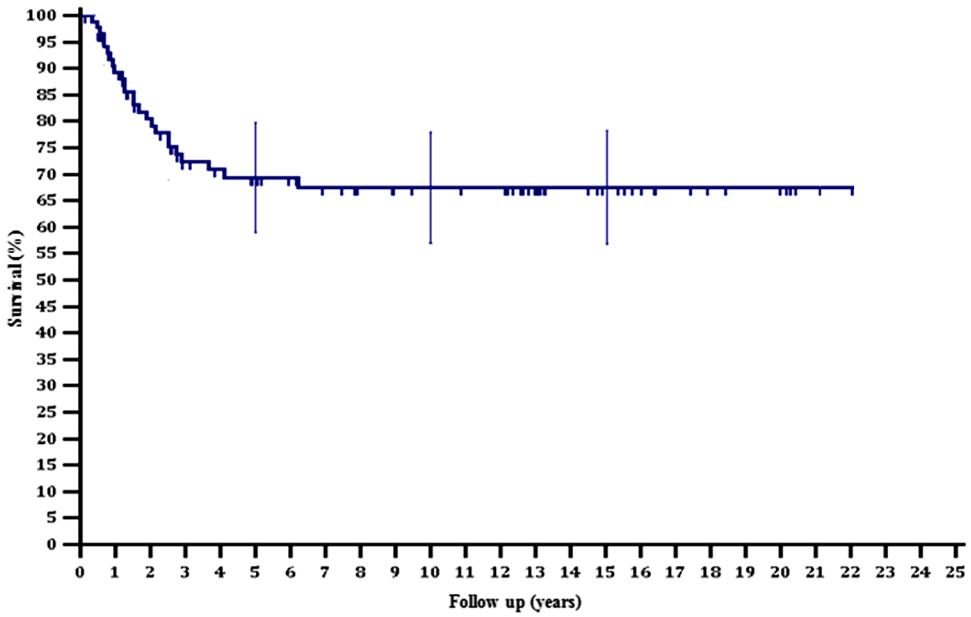

Fig. 3 Kaplan–Meier curve of survival: EFS to metastases was 69.3 % at 5 years and 67.5 % at 10 years

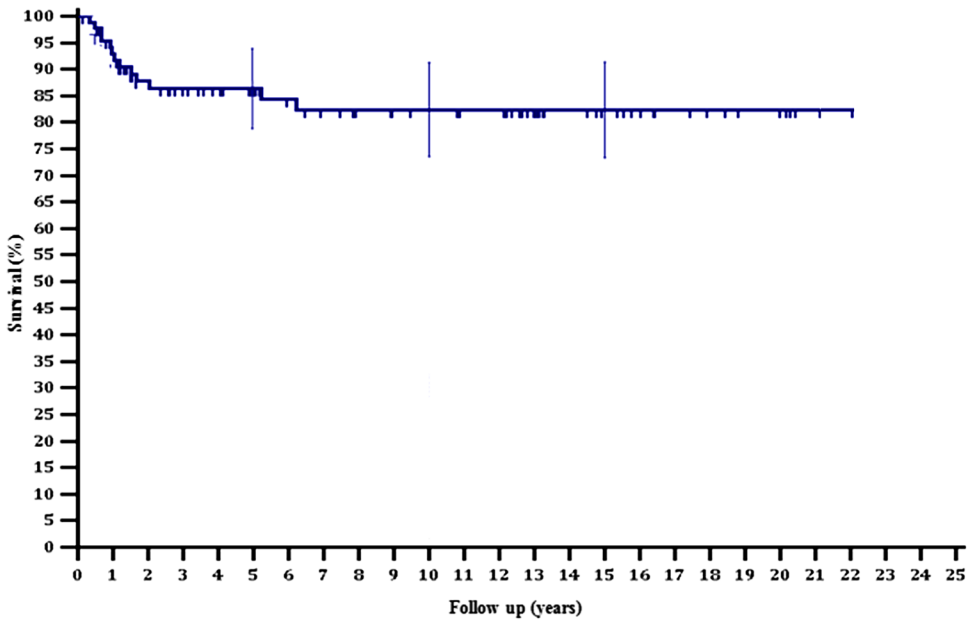

Fig. 4 Kaplan–Meier curve of survival: EFS to local recurrences was 86.4 % at 5 years and 82.4 % at 10 years

Table 3 Multivariate analysis

Predictor variables	*p*	OR	95 % CI OR
Huvos	0.0004	0.2351	0.1053–0.5250
Volume	0.4778	1.3932	0.5603–3.4643
Metastases at diagnosis	0.6693	1.3107	0.2360–3.3887
Age ≤ 14 years	0.1689	0.3962	0.2720–1.6693
Pathologic fracture	0.4074	1.1064	0.4999–2.4486

($p = 0.687$), less or more than three neoadjuvant chemotherapy agents ($p = 0.290$), ablative procedures or limb-salvage surgery ($p = 0.704$), wide or inadequate margins ($p = 0.235$), intracompartmental or extracompartmental tumor ($p = 0.448$).

Discussion

TOS is a rare variant of OS, accounting for about 8 % of cases of OS seen at our Institution (Picci 2014), 2.5 % in the Mayo Clinic series (Matsuno et al. 1976), and 5 % in the Gustave Roussy series (Vanel et al. 1987) and in the Sloan Kettering Cancer Center series (Huvos et al. 1982). The current study, to our knowledge, is one of the largest single-center series of patients with TOS to date. The

Table 4 Summary of most relevant studies on telangiectatic osteosarcoma and relative overall survival compared with other subtypes

	Years	No. pts TOS	5-years overall survival				Adverse prognostic factors in TOS subgroups
			TOS	ObOS	ChbOS	FbOS	
Current study	1975–2008	87	64 %	66 % (all subtypes)			Histologic response (PR)
Durnali et al. (2013)	1995–2011	13	–	–	–	–	TOS had lowest survival time
Weiss et al. (2007)	1978–2005	24	67 %	58 % (all subtypes)			Local progression during cht <3 cht agents
Bacci et al. (2006)	1972–2000	47	68 % (EFS)	56 % (EFS)	64 % (EFS)	76 % (EFS)	Histologic response[a]
Smeland et al. (2003)	1990–1997			63 – 74 %			
Bacci et al. (2001a, b)	1990–1994	24	87 %	69 % (all subtypes)			Histologic response[b]
Ferrari et al. (2001)	1986–1992	25	76 % (EFS)	54 % (EFS)	57 % (EFS)	82 % (EFS)	Histologic response[c] Tumor volume Age
Bacci et al. (1994)	1983–1990	28	–	–	–	–	
Glasser et al. (1992)	1976–1986	17	73 % (EFS)	67 % (EFS)	72 % (EFS)	93 % (EFS)	Histologic response
Mervak et al. (1991)	1975–1983	17	47 %	–	–	–	

TOS Telangiectatic osteosarcoma, *ObOS* osteoblastic osteosarcoma, *ChbOS* chondroblastic osteosarcoma, *FbOS* fibroblastic osteosarcoma, *GR* good responder, *PR* poor responder

[a] Authors reported 87 % of GR in TOS patients

[b] Authors reported 96 % of GR in TOS patients compared to 68 % in conventional osteosarcoma

[c] Authors reported 92 % of GR in TOS patients compared to 68 % (ObOS), 48 % (ChbOS) and 64 % (FbOS)

main strength of our study is that patients were treated at the same institution, and data on the investigated variables are available for almost all patients. The main limitations of this study are the retrospective type of the analysis and the distribution of the treated patients over a 23-year period. Considered the rarity of this pathologic entity, it would not be possible to concentrate a study on patients treated over a short period of time and again the rarity of the disease would make a prospective study practically unfeasible.

Since the use of neoadjuvant chemotherapy, long-term overall survival of osteosarcoma has improved to about 60 % (Bacci et al. 1993, Bacci et al. 2001a, b, 2002, 2006; Ferrari et al. 1999; Rosen et al. 1982; Mavrogenis et al. 2015). According to some studies, the histological type is a strong predictor of local recurrence-free survival, metastasis-free survival and overall survival (Bacci et al. 1993, 2006; Rosen et al. 1982; Mirabello et al. 2009). In a study based on the National Cancer Institute's population-based Surveillance, Epidemiology, and End Results (SEER) Program between 1973 and 2004, the 5-year survival rates by osteosarcoma pathology (including the pathologic types with >10 reported cases and excluding osteoblastic, periosteal and parosteal OS) were analyzed in three group of age. The authors reported a 5-year survival rates of 66.7 % (chondroblastic), 65.5 % (fibroblastic), 65.3 % (telangiectatic), 61.2 % (central) and 41.6 % (small cell) in patients younger than 24 years old, whereas it was 54 % (chondroblastic), 73 % (fibroblastic), 59 % (telangiectatic) in patients aged between 61 and 85 years old and was 55.3 % for chondroblastic osteosarcoma in older patients (Mirabello et al. 2009). The 5-year overall survival of patients affected by TOS in the most relevant studies in literature has been compared with those of other subtypes (Table 4). Although previous studies reported that patients with TOS fared much worse than patients with conventional OS (Matsuno et al. 1976; Huvos et al. 1982; Durnali et al. 2013; Bispo Júnior and Camargo 2009; Petrilli et al. 1991), this observation does no longer appear to be true: papers evaluating osteoblastic versus non-osteoblastic OS concluded that chondroblastic, telangiectatic or fibroblastic subtypes had a more favorable prognosis than the osteoblastic type (Hudson et al. 1990; Bacci et al. 2003). Other reports demonstrated that the subtype did not prove to be a prognostic factor (Farr et al. 1974; Rosen et al. 1986; Bacci et al. 2001a, b; Weiss et al. 2007; Durnali et al. 2013; Hauben et al. 2002). In this study, the 5-year overall survival was 64 % that is similar with the 5-year overall survival (66 %) of 789 patients with OS (all subtypes) treated at our institution (Bacci et al. 2006).

The variables of age (Bielack et al. 2002; Spanier et al. 1990; Raymond et al. 1987; Xie et al. 2012) and gender (Durnali et al. 2013; Raymond et al. 1987; Goorin et al. 1987) have been shown to be prognostic factors in some series of OS using univariate analysis alone. Regarding gender, some studies (Durnali et al. 2013; Petrilli et al. 1991; Bielack et al. 2002; Saeter et al. 1997) stated that male gender was a poor prognostic factor. Regarding age, a better prognosis for younger patients has been reported

(Winkler et al. 1984), whereas other authors (Ferrari et al. 2001; Carsi and Rock 2002; Saeter et al. 1991) found a better prognosis for older patients. It is interesting to observe that comparison between studies is biased by different cut-off values. In the present study, gender and age (cut-off value of 14 years) were not found to be significant prognostic variables, in agreement with other studies on OS (Hudson et al. 1990; Bacci et al. 2003; Hauben et al. 2002; Bielack et al. 2002; Spanier et al. 1990; Raymond et al. 1987; Xie et al. 2012; Goorin et al. 1987; Saeter et al. 1997; Winkler et al. 1984; Ferrari et al. 2001; Carsi and Rock 2002; Saeter et al. 1991) and with all previous series on TOS with available comparison between age and survival (Bacci et al. 2001a, b; Bispo Júnior and Camargo 2009).

The metaphysis of long bones (distal femur, proximal humerus and proximal tibia in decreasing order of frequency, Fig. 1) was the most common site for TOS in this study. The literature shows that the distal femur and proximal tibia are the most frequent sites, followed by the humerus (Pakos et al. 2009). Some studies on OS have demonstrated different results about tumor site and survival (Durnali et al. 2013; Bacci et al. 2006; Bispo Júnior and Camargo 2009; Bielack et al. 2002; Xie et al. 2012; Goorin et al. 1987; Pakos et al. 2009; Bramer et al. 2009), but few studies have investigated the TOS site as a prognostic variable (Bacci et al. 2001a, b; Weiss et al. 2007). Weiss et al. (2007) reported the same prognosis between TOS located in the femur or other bones and Bacci et al. (2001a, b) reported that the disease-free survival rate was not related with the tumor volume or site. Our data are in agreement with these; we did not find site of TOS a significant factor for survival.

The volume of bone sarcoma is a very old debated problem because it is difficult to evaluate the importance of tumor volume in a small child as well in a young adult. We think that multivariate analysis including age and tumor volume is the best way to obtain a correct comparative analysis. Analyzing selective series on TOS, the tumor volume seems not to be a statistical prognostic factor (Bacci et al. 2001a, b; Weiss et al. 2007; Durnali et al. 2013). In the present series, 40 patients had a tumor volume measured less than 150 cc. These patients presented better survival at the univariate analysis ($p = 0.044$), but in our multivariate analysis, this prognostic variable did not maintain its significance.

Stage at diagnosis was considered to be an important predictive factor on survival in OS (Bramer et al. 2009). In a recent study on TOS, the tumor compartmental status did not reveal statistically significant differences (Weiss et al. 2007). Also in our study, a statistically significant difference between intracompartmental and extracompartmental tumors was not observed, even if 95.5 % of patients had extracompartmental tumor at diagnosis, making it difficult for a statistical analysis.

The incidence of pathological fractures among patients with TOS (17–43 %) (Matsuno et al. 1976; Huvos et al. 1982; Rosen et al. 1986; Bacci et al. 2001a, b; Weiss et al. 2007; Vanel et al. 1987) is higher than in conventional OS (6–17 %) (Bispo Júnior and Camargo 2009; Hudson et al. 1990; Scully et al. 1996, 2002). A very high rate of pathological fracture (61 %) also was observed in a recent retrospective study of 36 patients with TOS (Murphey et al. 2003). In recent reports, patients with pathologic fracture of primary OS treated with limb salvage and neoadjuvant chemotherapy did not seem to have a significantly differ on survival at long-term and higher risk of local recurrence or metastasis (Durnali et al. 2013; Xie et al. 2012; Scully et al. 2002; Colomina et al. 2013). In agreement with previous studies on TOS (Bacci et al. 2001a, b; Weiss et al. 2007; Colomina et al. 2013), we did not observe a worse prognosis for cases with a pathological fracture at the initial diagnosis. Satisfactory results can still be achieved in the majority of patients with pathologic fracture treated with limb-salvage surgery if safe surgical margins can be obtained (Ruggieri et al. 2010). Bramer et al. (2007) reported the management of pathologic fractures in a large series of bony sarcoma, concluding that patients with a pathological fracture should be conservatively treated with stabilization of the fracture (e.g., by means of a splint) and appropriate analgesia, followed by chemotherapy (according to the standard protocol) and then surgical resection of the tumor with wide margins, as usual.

Clinically detectable primary metastases have been reported to be independent adverse prognostic factor for survival of patients with all types of OS (Durnali et al. 2013; Bielack et al. 2002; Meyers et al. 1993; Bacci et al. 1998). Weiss et al. (2007) reported similar survival rates for patients with localized and metastatic disease at diagnosis in a cohort of 22 patients with TOS. In this study, the presence of metastases at diagnosis was close to significance; probably, it would have reached significance with a larger sample size.

Due to the efficacy of neoadjuvant chemotherapy, surgical treatment has now attained a high limb preservation rate: whereas up to the late seventies, 80 % of patients with an extremity osteosarcoma ended up with an amputation, nowadays limb-saving surgery is possible in 90 % of patients (Picci 2014; Farr et al. 1974; Matsuno et al. 1976; Huvos et al. 1982; Rosen et al. 1982, 1986; Weiss et al. 2007; Durnali et al. 2013; Bacci et al. 1993, 2001a, b, 2002, 2006; Ferrari et al. 1999; Bielack et al. 2002; Raymond et al. 1987; Winkler et al. 1984; Saeter et al. 1991). In this series, no significant difference was found comparing ablative to limb-salvage procedures. Adjuvant and neoadjuvant chemotherapy, introduced in the early

1970s, have significantly improved the long-term survival rate for patients with osteosarcoma (Picci 2014; Farr et al. 1974; Matsuno et al. 1976; Huvos et al. 1982; Rosen et al. 1982, 1986; Bacci et al. 2001a, b; Weiss et al. 2007; Durnali et al. 2013; Bielack et al. 2002; Winkler et al. 1984). During the last 40 years, several different protocols with different number and type of agents have been used (Picci 2014; Farr et al. 1974; Matsuno et al. 1976; Huvos et al. 1982; Rosen et al. 1982, 1986; Bacci et al. 1993, 2001a, b, 2002, 2003, 2006; Weiss et al. 2007; Durnali et al. 2013; Ferrari et al. 1999; Bielack et al. 2002; Goorin et al. 1987; Saeter et al. 1997; Winkler et al. 1984). In 22 patients with TOS, Weiss and coworkers (Weiss et al. 2007) reported that their strongest predictor of event-free survival and overall survival was the number of active chemotherapeutic agents, with a significantly better outcome in patients who received 3 or more drugs. Considering that no other studies specifically compared the number of active agents as prognostic factor, we decided to use the same cut-off in our series. The results of our study contradict those of Weiss and coworkers; no statistical difference was found in patients who received less or more than 3 chemotherapeutic agents. Bacci et al. (2001a, b) compared the efficacy of the same protocols of chemotherapy between 24 patients with TOS and 269 contemporary patients with conventional OS. They concluded that TOS was more sensitive to chemotherapy that conventional OS. A lot of previous studies have shown tumor response to preoperative chemotherapy to represent the most important prognostic factor for patients with localized OS of the extremities (Matsuno et al. 1976; Huvos et al. 1982; Rosen et al. 1982, 1986; Bacci et al. 2001a, b; Weiss et al. 2007; Bispo Júnior and Camargo 2009; Petrilli et al. 1991; Hudson et al. 1990; Bacci et al. 2003; Hauben et al. 2002; Bielack et al. 2002; Saeter et al. 1991; Bieling et al. 1996; Pakos et al. 2009; Bramer et al. 2009). Also in our series, the overall survival rate was significantly higher in good responders than in poor responders.

Our study has some limitation. First, Type II statistical error remains possible for some of the end points we considered. However, we believe that the long-term follow-up increases the power of our analysis and allows us to assess prognostic factors on survival at long term. Second, because of the relatively small number of patients in some of our subgroups, we could not analyze all confounding variables with a multivariate regression model; in fact, we had the choice to reduce the number of variables to increase the value of our analysis. Third, while we report a relatively large cohort of patients with TOS, there is heterogeneity of chemotherapy over the year; this may be considered a limitation. However, the rarity of TOS renders a prospective clinical trial of this tumor difficult and the statistically significance of tumor response to neoadjuvant chemotherapy supports the results of this study.

Conclusion

Our analysis of a large cohort of patients with TOS allowed to compare the efficacy of chemotherapy to that observed in classic osteosarcoma and allowed as well the evaluation of prognostic factors. Survival of TOS was similar to that of classic OS, even if TOS has a higher incidence of pathologic fractures. The only significant prognostic factors at univariate analysis were tumor response to chemotherapy and tumor volume. Multivariate analysis confirmed the prognostic value of induced necrosis only. Age, gender, primary tumor site, metastasis or pathological fracture at diagnosis, and number of chemotherapy agents were not significant prognostic factors.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent to be included in scientific studies was obtained from all individual participants included in the study at the time of admission.

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