Extraskeletal Bone Sarcomas
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Citation

Abstract
Extraskeletal bone tumors are rare and high grade tumors including osteosarcoma, chondrosarcoma and Ewing's sarcoma of the soft tissues and its variants. A retrospective study of 25 cases of these tumors was made in our institution in the 1983 - 2000 period. The study of 25 cases revealed that these tumors affect adults (median age 51.2, range 17-73 years). The most common tumor locations were the thigh (12 cases, 48%) and the arm-elbow (6 cases, 24%). As a classification for diagnostic type of tumors: 14 were chondrosarcomas (56%), 8 were osteosarcomas (32%) and 3 were Ewing sarcomas (12%). The median follow-up was 47.07 months with a range from 24 months to 156 months. All the cases were treated with preop. chemotherapy and postoperative radiotherapy (with the exception of the myxoid chondrosarcoma). Globally, the preoperative duration of symptoms ranged from 2 weeks to 6 years (median 6 months). Local recurrences after wide and compartimental margin surgery developed in 7 cases (12%), three cases of chondrosarcoma and four cases of extraskeletal osteosarcoma; and distant metastases developed in seven cases (6 osteosarcomas and 1 Ewing's sarcoma). The two year overall survival rates were: extraskeletal chondrosarcoma 50%, osteosarcoma 36.5% and Ewing sarcoma 66.6%. The two year disease-free survival was: 42.8% chondrosarcoma, 25% osteosarcoma and 33.3% Ewing sarcoma. The interest of this series is the fact that tumors are high grade and cure may be achieved by wide or compartimental local excision of the tumor at an early stage of the disease (combined with radiation and chemotherapy).

INTRODUCTION
Extraskeletal primary bone sarcomas are rare and high-grade tumors that include osteosarcoma (OS), chondrosarcoma (CHO) and Ewing sarcoma (EW) of the soft tissues and its variants.

Osteosarcoma of the soft tissues is a malignant mesenchymal tumor whose cells produce osteoid substance. Unlike skeletal osteosarcoma it is observed during adult and advanced age and particularly in women. The sites most involved are the thighs, the muscles of the pelvic girdle and the shoulder. Radiographically, there may be areas or nodules of faced radiopacity, due to tumoral osteogenesis. Microscopically, skeletal osteosarcoma (OS) is prevalently osteoblastic, but chondroblastic and/or fibroblastic areas may be present. Differential diagnosis must include osteoproducive benign lesions (i.e. myositis ossificans) and malignant lesions (i.e. sarcomas with osteogenesis of a metaplastic nature). The prognosis is very severe, as pulmonary metastasis frequently occurs. The treatment is the same as for skeletal OS: preoperative chemotherapy, wide or radical surgery, and maintenance chemotherapy.

Chondrosarcoma of the soft tissues is very rare. Instead, almost all the cases of CHO are constituted by myxoid forms and by mesenchymal chondrosarcoma.

Extraskeletal myxoid chondrosarcoma (named chordoid sarcoma) is a rare tumor that affects men more than women and it is almost exclusively observed during adult and advanced age. It is specially observed deeper in the lower limb. The radiographic picture is completely unspecific, locking images of calcification or ossification. Histologically, it has a lobular structure, more or less cellular; nonetheless this differentiation hardly ever achieves the stage of well-differentiated hyaline cartilage. Differential diagnosis must include myxoid liposarcoma, myxoma and chordoma. The prognosis is the same as that for skeletal chondrosarcoma, but it has a considerable tendency to recur locally and it is capable of metastasizing. The most suitable type of treatment appears to be wide surgical excision.

Mesenchymal chondrosarcoma is rare in the soft tissues, even more rare than in the skeleton. There is no predilection for sex, and unlike myxoid chondrosarcoma it is observed during young and adult age (15-40 years) and deeper in the lower limb and neck. Clinically, again unlike myxoid chondrosarcoma, it has a rather rapid growth. Radiographic
appearance is often sprayed by calcifications, with angiography the tumor is injected intensely, in virtue of its rather rich and dilated capillary circulation. Histologically, the pattern is intense vascularization and dilated sinusoidal with balloon-oval cells by the presence of foci of cartilaginous differentiation. Differential diagnosis above all involves hemangiopericytoma. Prognosis is very severe (high malignancy). Its growth is rapid and its tendency to metastasize is also high. The treatment includes surgery, chemotherapy and radiation.

Synovial chondrosarcoma are exceptional cases in which a synovial chondromatosis causes a chondrosarcoma, or in which a chondrosarcoma originates in the joint. It is a soft and compact cartilaginous tissue filling the joint cavity, eroding the capsule, invading the soft tissues, digging into and infiltrating the joint bones. It is difficult to establish whether it was truly a chondrosarcoma or an aggressive and tumor-like synovial chondromatosis.

Ewing sarcoma of the soft tissues remains a rare tumor, it shows predilection for the male sex, and for those aged between 15 and 45 years. Histologically, the aspect is the same as that of Ewing sarcoma of the bone: uniform fields of small and round cells. Differential diagnosis must include neuroblastoma,

embryonal or alveolar rhabdomyosarcoma, and for patients aged over 30-50 years malignant lymphoma and metastasis of small cell carcinoma. Prognosis and treatment seem to be very similar to what is indicated for Ewing sarcoma of the skeleton.

MATERIAL AND METHODS

Retrospective studies of 25 cases of this heterogenic group of tumors were made in our Hospital in the 1983 - 2000 period (Table I). The study of 25 cases revealed that these tumors affect adults (median age 51.2, range 17-73 years). The most common tumor locations were the thigh (12 cases, 48%) and the arm-elbow (6 cases, 24%). Three tumors were superficial (hand and foot locations, 12%), 3 pelvic locations (12%) and 1 perone location (4%).

As a classification for diagnostic type of tumors: 14 were chondrosarcomas(56%), 8 were osteosarcomas (32%) and 3 were Ewing sarcomas (12%) (Table III) and staging with the AJCC classification (Table II and III).

Figure 1
Table 1: Details of patients.

Figure 2
Table 2: Classification UICC/AJCC 2002 (VI edition).
Fourteen extraskeletal chondrosarcomas are distributed in 6 myxoid chondrosarcomas: 5 male and 1 female patients, median age 58.3 years (ratio 47-70 years) with a median follow-up of 49.5 months (ratio 24-95 months), 5 thigh and 1 arm locations; 5 mesenchymal chondrosarcomas: 4 females and 1 male patient, median age 33.6 years (ratio 17-56 years) with a median follow-up of 30.2 months (ratio 26-36 months), 3 thighs, 1 arm and 1 foot locations and 3 synovial chondrosarcomas: 2 male and 1 female patients, median age 47.6 years (ratio 43-55 years) with a median follow-up of 30.6 months (ratio 28-36 months), 2 knee-thigh and 1 hip-thigh locations.

The 6 cases of myxoid chondrosarcoma were treated initially with wide and compartmental surgery (three wide surgeries and three compartmental surgeries without adjuvant and coadjuvant treatment). The 5 cases of mesenchymal chondrosarcoma were treated initially with wide and compartmental surgery (four compartmental surgeries and one wide surgery) accompanied with coadjuvant chemotherapy and radiation. The 3 cases of synovial chondrosarcoma were treated initially with wide surgery associated in this kind of tumor, in one case with coadjuvant chemotherapy and in another case with postoperative radiation; in one case supracondylar amputation is performed and in another case hemipelvectomy is preformed for tumor local persistence.

Eight extraskeletal osteosarcomas were revised: 6 male and 2 female patients, median age 58 years (ratio 28-73 years) with a median follow-up of 73.12 months (ratio 24-156 months), 3 arm-elbow, 2 pelvic, 1 arm-shoulder, 1 thigh and 1 perone locations. All of the cases of osteosarcomas were treated initially with preoperative or neoadjuvant chemotherapy after surgery (1 case of initial leg supracondylar amputation, 4 cases of initial wide surgery and 1 initial compartmental surgery were performed) and postoperative or coadjuvant chemotherapy and postoperative radiotherapy (except the case of initially amputation performed). The two cases of pelvic locations were treated with chemotherapy and radiation only (surgery is not possible in these particular cases).

Three extraskeletal Ewing sarcomas were studied: 3 female patients, median age 51.6 years (ratio 46-62 years) with a median follow-up of 29 months (ratio 24-33 months), 2 foot and 1 pelvic locations. All the cases were treated initially with neoadjuvant chemotherapy after surgery (2 cases of initial infracondylar amputations in foot locations and abstention of surgery in pelvic location) and coadjuvant chemotherapy and local radiation.

Globally, the preoperative duration of symptoms ranged from 2 weeks to 6 years (median 6 months). The median follow-up was 47.07 months with a range from 24 months to 156 months.

One case of osteosarcoma presented a history of previous...
radiation and 2 cases of osteosarcoma presented a history of prior trauma.

RESULTS

TREATMENT COMPLICATIONS

In the 25 cases presented, the following treatment complications were observed: 2 superficial infections, 2 toxicity chemotherapy, 2 ulcerated tumors with recurrence and 1 thromboembolism.

LOCAL RECURRENCE

Local recurrences after wide and compartimental margin surgery developed in 7 cases (12%). Three cases of chondrosarcoma and four cases of extraskeletal osteosarcoma.

In the cases of myxoid, mesenchymal and synovial chondrosarcoma, eleven cases were alive with no evidence of recurrence (78.5%). Three cases of recurrences: one synovial chondrosarcoma of the knee one year after wide resection, the recurrence was treated with compartimental surgery and it had a new recurrence two years later the first wide surgery and its was treated with a above-the-knee amputation associated with postoperative chemotherapy. This patient was alive with one or more recurrences and two cases of mesenchymal chondrosarcomas treated initially with wide surgery and ampliation of surgery at compartimental where the recurrence was present at two and one year (one arm location and one thigh location).

In the cases of extraskeletal osteosarcomas, four cases were alive with no evidence of recurrence (50%), and another four cases of recidivated extraskeletal osteosarcomas were treated; two cases of extraskeletal osteosarcoma in the arm-elbow developed a recurrence one year and two years later respectively after wide resection and they were treated with an above-the-elbow amputation and compartimental surgery respectively associated with postoperative chemotherapy (alive with lung metastasis). Another case presented recurrence in arm-shoulder location two years after wide resection, and it was treated with compartimental surgery (alive without metastasis). One case of recurrence of extraskeletal osteosarcoma of the thigh, one case developed a recurrence 18 months after wide resection and it was treated with a supracondylar amputation associated with postoperative chemotherapy (alive without metastasis).

In the cases of extraskeletal Ewing sarcomas, none were recidivated.

METASTASIC DISEASE-EXITUS

None of the cases of extraskeletal chondrosarcomas and its variants were metastasized.

In cases of extraskeletal osteosarcoma, five cases (62.5%) presented lung metastasis (two cases at diagnosis time) and three cases (37.5%) died after 134 months (peroneal location), 80 months and 29 months (pelvic location), respectively. The two cases with metastatic lung disease were arm-elbow locations treated with wide surgery initially and subsequent amputation above-the-elbow in one particular case after recurrence. The other case was treated with wide resection initially. These cases were alive with metastasic disease (25%) and achieved local control after 156 months and 89 months respectively.

In extraskeletal Ewing sarcoma cases, one case (33%) of foot location developed regional lymph nodes metastasis and it is alive after 14 months at diagnosis. One pelvic case died after 33 months and another foot location case was alive without metastasis disease after 14 months.

SURVIVAL RATES FOR TYPE OF TUMORS

The two year overall survival rates were: extraskeletal chondrosarcoma 50%, osteosarcoma 36.5% and Ewing sarcoma 66.6%. The two year disease-free survival were: 42.8% chondrosarcoma, 25% osteosarcoma and 33.3% Ewing sarcoma.

STATISTICAL ANALYSIS

This retrospective study is based in a short series of patients and a rare and heterogenic group of tumors. The statistical analysis included the study of several variables: tumor location(Table IV), type of tumor (Table V), staging system (Table VI) and surgical treatment (Table VII) with one curve of global overall survivor (Table VIII). This study is presented following a Kaplan-Meier system of survivorship curves.
The statistical significance only was demonstrated in the case of surgical treatment. None of the rest of variables included in this study (diagnostic tumor, staging system, and tumor location) are significative statistically.
**DISCUSSION**

This group of tumors rarely occur and they are included in the XII group of the W.H.O. classification (WHO book) (extraskekeletal bone tumors) in the cases of osteosarcomas and chondrosarcomas and the group of lesions of uncertain origin in the case of Ewing sarcoma-PNET group.

As for osteosarcoma patients, there is a poor type of tumor prognosis due to the aggressive biological behavior of this kind of tumors (high tendency to local recurrence and general dissemination). The staging of these tumors is grade II-C or high (IV) in the American Joint Committee System Staging (variation 1997) (Sugarbaker book,5) : >5 cm tumors, superficial or deep, with or without lymph and lung metastases. In previous studies of extraskeletal osteosarcoma (,) the thigh was the most common tumor location; in our series, the most common location is the arm-elbow and pelvic tumors (worse prognosis for a location that prevents surgical treatment). The extraskeletal osteosarcoma was described in more locations: hand(,), urinary bladder, prostate, kidney, breast, lung, thyroid, retroperitoneum (,), frontal region(,) and cardiac intramuscular(;) presentations. Etiology of the cases is controversial, several theories were performed: association with Li-Fraumeni Syndrome(,) and myositis ossificans(,), prior trauma(,), radiation-induced (,), thorotrast-induced (,) and heterotopic ossification after an electrical burn (,). Microscopically tumors contain varying amounts of neoplastic osteoid of bone (Figure 1), sometimes together with islands of malignant-appearing cartilage (,).
Figure 10
Figure 2: Extraskeletal osteosarcoma of the arm. Radiological appearance.

Bone scan reveals uptaking in the lesion (\textsuperscript{15}) CT scan revealed mineralized soft tissues, and MRI presentation shows hipointense images in T1-weighted spin echo and hiperintense in T2-weighted spin echo and STIR sequences. Telangiectatic variant are least common histological variety in this group (\textsuperscript{16}). As for the diagnosis of these, it was made by needle biopsy (tru-cut technique in all the cases), but with appropriate clinicoradiologic correlation extraskeletal osteosarcoma may not be recognized easily by FNAB (\textsuperscript{17}), unlike skeletal osteosarcoma. Like the osteosarcoma of bone, extraskeletal osteosarcoma showed a striking variation in histological appearance and focally resembled malignant fibrous histiocytoma (\textsuperscript{1}), fibrosarcoma, soft tissue aneurismal bone cyst (\textsuperscript{16}) and malignant schwannoma. The prevailing sites of metastases were the lung, the regional lymph nodes and bone (none in our series of patients). The treatment included in all the cases neoadjuvant chemotherapy, surgery (wide, compartimental or radical) and coadjuvant chemotherapy with local postoperative radiation.

Extraskeletal osteosarcoma is a high grade malignant tumor associated with a 5-year survival rate of 37% of the cases. Local recurrences and distant metastasis are common and usually occur by 3 years after excision in Mayo Clinic series (\textsuperscript{18}). In comparison, in our series the 2-year survival rate is 36.5 % and the 2-year free of disease survival rate is 25%. Additional larger series will be required before drawing definite conclusions.

Chondrosarcoma of the soft tissues is a rare tumor. The near totality of CHO is instead constituted by myxoid forms, mesenchymal chondrosarcoma and by synovial sarcoma.

Extraskeletal myxoid chondrosarcoma is an uncommon neoplasm, according for less than 2% of all soft tissue sarcomas. It affects adult males with an age in the fifth decade at the time of diagnosis. The tumor usually arises in the deep soft tissues, especially in the lower extremities (Figure 3) (\textsuperscript{19}).

Figure 11
Figure 3: Extraskeletal myxoid chondrosarcoma. Thigh location. MRI T1-weighted image.

It is a rare low-grade soft tissue sarcoma (staging of these tumor varies in II-B, II-C or III in the AJCC system), with locally aggressive and metastasizing potential (\textsuperscript{20}). It is specially observed deeper in the lower limbs. In myxoid CHO, the cells that resemble epithelial, can very closely mimic some malignant breast tumors in thoracic locations (\textsuperscript{21}). A diagnosis of extraskeletal myxoid chondrosarcoma was rendered based on histological findings (\textsuperscript{22}). Differential diagnosis included other myxoid neoplasm such as bony myxoid chondrosarcoma, myxoid liposarcoma, chordoma and parachordoma (\textsuperscript{22}). Differential diagnosis with
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extaskeletal chondroma: asymptomatic and harmless clinical course, the lack of connection between the tumor and the underlying bone, the slow tumor development, the absence of a sex predominance and the characteristic tumor histological picture. Typically well-circumscribed, extraskeletal myxoid chondrosarcomas are commonly encapsulated by a rim of fibrous tissue. The abundant myxoid matrix gives the cut surface a gelatinous appearance. The degree of cellularity is variable; less well-differentiated, highly cellular tumors generally have less extracellular matrix and behave more aggressively (Figure 4) (22).

Figure 12
Figure 4: Histological pattern of extraskeletal myxoid chondrosarcoma. Hematoyline-eosine x 200.

Pulmonary metastases are not unusual in this tumor, only two patients have been reported with multiple bone metastases (33).

In our series no adjuvant therapy is necessary, none of the cases were disseminated. Resistance to standard soft tissue sarcoma chemotherapy has been demonstrated (33). Myxoid CHO are a better prognosis respect to synovial CHO and mesenchymal CHO (33).

Mesenchymal chondrosarcoma is rare in the soft tissues (making up less than 2% of all chondrosarcomas) (33), even more rare than in the skeleton. There is no predilection for sex, and unlike myxoid chondrosarcoma it is observed during young and adult age (15-40 years) and deeper in the lower limb (Figure 5) and neck.

Figure 13
Figure 5: MRI of mesenchimal chondrosarcoma of the thigh.

The extraskeletal mesenchymal chondrosarcoma was described in more rare locations: jaw (36), intraspinal (37), cauda equina (38), pleura (39), labium majus (40), orbit (41), heart (42), intracranial (43), femoral vein (44) and vagus nerve (45). Clinically, again unlike myxoid chondrosarcoma, it has a rather rapid growth. Radiographic appearance is often sprayed by calcifications, with angiography the tumor is injected intensely, in virtue of is rather rich and dilated capillary circulation. Histologically pattern is intense vascularization and dilated sinusoidal with balloon-oval cells by the presence of foci of cartilaginous differentiation (38), typically characterized by tumor compartmentation (undifferentiated tumor cells in the small-cell areas were negative for vimentin and cytoprotein S-100, whereas other tumor cells expressed collagen type II-A and vimentin indicating a chondroprogenitor cellular phenotype in these small areas)(38), citogenetic studies of mesenchymal chondrosarcoma are few and to date, no specific or recurrent aberrations have been found (46,47,48). Differential diagnosis above all involves hemangioperyicitoma. Prognosis is very severe (high malignancy) (46). Its growth is rapid and its tendency to metastasize is also high (lung, bone and skin metastases (46)). The treatment includes surgery, chemotherapy and radiation.

Synovial chondrosarcoma are exceptional cases in which a synovial chondromatosis causes a chondrosarcoma (49,50), or in which a chondrosarcoma originates in the joint. It is a soft and compact cartilaginous tissue filling the joint cavity, eroding the capsule, invading the soft tissues, digging into
and infiltrating the joint bones (Figure 6).

**Figure 14**

Figure 6: Synovial chondromatosis of the hip. MRI T1-weighted image.

Malignant transformation to chondrosarcoma shows no specific MR features to distinguish these cases with malignant change of primary synovial chondromatosis alone. Synovial chondrosarcoma is considered very rare and it is not always clear whether the sarcoma develops by malignant transformation of synovial chondromatosis or whether it arises de novo. Differentiation of the two conditions based on clinical and radiographic features is not possible and it can be difficult based on histological criteria. The indispensable criteria to diagnose malignant transformation are: 1) histological diagnosis of synovial chondromatosis established before diagnosis of chondrosarcoma, 2) histological diagnosis of chondrosarcoma on the same anatomic site as the synovial chondromatosis, 3) diagnosis of chondrosarcoma and synovial chondromatosis on the same resection specimen. The most important histological features were loss of the “clustering” growth pattern typical of synovial chondromatosis, myxoid change in the matrix, areas of necrosis, and splinting at the periphery of chondroid lobules (Figure 7). It is difficult to establish whether it was truly a chondrosarcoma or an aggressive and tumor like synovial chondromatosis. This condition was described in the hip joint, knee joint, radiocarpal joint, ankle joint, and metacarpophalangeal joint.

**Figure 15**

Figure 7: Histological appearance of synovial chondrosarcoma. Hematoxyline-eosine x400.

**Figure 16**

Figure 8: Histological pattern of extraskeletal Ewing sarcoma. Hematoxyline-eosine x400.

Extraskeletal Ewing sarcoma (EES) is a rare soft tissue tumor that is morphologically indistinguishable from the more common Ewing sarcoma of bone (Figure 8). It must be distinguished from other small, blue round cell tumors (SBRCTs). The most frequent sites of occurrence are the chest wall, lower extremities, and paravertebral region. Less frequently, the tumor occurs in the pelvis and hip region, the retroperitoneum, and the upper extremities. It is usually found in young adults (younger than 30 years) and has a slight predominance in male patients. Ewing sarcoma is the second most common primary osseous malignancy in childhood and adolescence, and most of the success in survival with multimodality treatment has been in that age group. Survival rates in patients with childhood nonmetastatic ES/PNET have improved from 10% in 1967 to 50% in 2000. The improvement in survival is primarily associated with the combination of surgery and...
chemotherapy. Little has been published about the outcome of adults with extraosseous (soft tissue) ES/PNET.

Four studies to date, regarding both skeletal and extraskeletal adult ES/PNET (Figure 9), have been published evaluating survival and predictors of survival. Two studies have demonstrated age as a poor predictor of outcome, and 2 studies have not seen age as an adverse risk factor. Our extraskeletal Ewing series shows a higher median age (51.6 years) and the curious location (2 foot cases and 1 pelvic case).

Figure 17
Figure 9: Histological appearence of PNET sarcoma. Hamatoxyline-eosine x 200.

CONCLUSIONS

- Extraskeletal bone tumors are tumors predominantly high-grade tumors (except the factomyxoid chondrosarcoma).

- The treatment includes preoperative chemotherapy, surgery and postoperative chemotherapy and radiotherapy in the cases of OS, EW and mesenchymial CHO. CHO was treated with radical, wide and compartmental margins surgery.

- The prevailing sites of metastasis were the lung and the regional lymph nodes. No bone metastasis was registered.

- Cure may be achieved by wide or compartmental local excision of the tumor at an early stage of the disease (combined with radiation and chemotherapy in the cases of OS, EWand myxoid CHO).

- Myxoid CHO have better prognosis than synovial CHO and mesenchymal CHO.

- In myxoid CHO, the cells that resemble epithelial cells, can very closely mimic some malignant breast tumors in thoracic locations.

- Differential diagnosis with extaskeletal chondroma: asymptomatic and harmless clinical course, the lack of connection between the tumor and the underlying bone, the slow tumor development, the absence of sex predominance and the characteristic tumor histological picture.

- Pulmonary metastasis is not usual in extraskeletal myxoid chondrosarcoma, only two patients have been reported with multiple bone metastasis.

- Biopsy was made in all cases for punction biopsy with the tru-cut technique

- Extraskeletal osteosarcoma is the poor type of tumor prognosis (three cases of exits, three cases of local recurrence and five cases of lung metastases)

- Additional larger series will be required before drawing definite conclusions.

References

9. Puzas JE, Miller MD, Rosier RN. Pathologic Bone


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