Prognosis factors in muscle-skeletal tumors (Osteosarcomas and soft tissue sarcomas)

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Abstract: - A characteristic of patients with soft tissue sarcomas and osteosarcoma is the aggressive tendency of invasion of the surrounding tissue and precocious hematogenous dissemination, mostly within the lung. Metastases are incurable despite the currently available advanced therapies. The evaluation of prognostic factors and the follow-up of metastases are major research areas that enable cancer patients to have maximum therapeutic benefits, increased quality of life and survival. We conducted a survey from January 2000 to December 2005 on patients diagnosed with sarcomas (osteosarcomas and soft tissue sarcomas) admitted in Cluj-Napoca Oncology Institute and "Leon Daniello" Pneumology Clinical Hospital. We analyzed risk factor and evolution of the diseases with survival function calculated since sarcoma diagnosis, and the other calculated since pulmonary metastases.

Key-Words: - osteosarcomas, soft tissue sarcomas, prognosis factors, survival

1. Introduction

Malignant tumors are divided into sarcomas (originating from conjunctive tissue) and carcinomas (originating from epithelial tissue). Bones are made up from cartilage tissue, bone tissue, fiber and marrow elements. Each part can develop malignant and benign cellular lines [1, 2]. Soft tissue sarcomas refer to the extraskeletal conjunctive tissue tumors which includes the portion of the body between the epidermis and parenchymal organs. These include tumors of locomotory organs (muscles, tendons) and a large variety of support structures (fibrous tissue, fat tissue and synovial tissue). The diagnosis of skeletal malignant tumors will need a clinical, radiological (x-ray, CT) and histology evaluation [1, 2]. Malignant tumors are rare as they represent only 0.2% of total primitive cancers. Soft tissue sarcomas represent 0.7% of total cancers and 6.5 of cancers among kids with ages under 15. Bone tumors disseminate exclusively hematogenous because bones have a poor lymph system. When lymphatic involvement is demonstrated, the prognosis is unfavorable (upon autopsy, only 10% demonstrate lymphatic affliction). A characteristic of patients with soft tissue sarcomas is the aggressive tendency of invasion of the surrounding tissue and precocious hematogenous dissemination, mostly within the lung. This represents 33% of metastatic locations (according to Chiricuta, 52%), followed by bone and liver [2]. The lung is the place of election of metastases as 80% of pulmonary metastases appear within the 2 years of treatment. The average survival rate since the apparition of pulmonary metastases is 6 to 12 months (without their resection)

2. Problem Formulation

We analyzed the main clinical and lab prognosis factors which can improve the understanding of the pathogenesis of muscle-skeletal tumors. The purpose of this paper consists in establishing an algorithm of approach in the management of muscle-skeletal tumors in belated stages (with pulmonary metastases) in order to extend survival and improve the quality of life. The identification of some unfavorable prognosis factors (validated) at the time of diagnosis and application of certain differentiated treatments, adapted to the risk class, could allow and increased curability rate. The sarcoma diagnosis was demonstrated histological before entering into the study. The diagnosis of pulmonary metastases was based on x-ray and/or CT images which were interpreted by a radiologist, oncologist, and pneumologist as suspect of secondary determination. Inclusion criteria: Pleurisy with positive cytology, Exudative pleurisy with no other explanation, multiple pulmonary nodules with radiological image or CTs interpreted by clinicians or from a radiological point of view with metastatic etiology with or without bioptic confirmation, Radiology images on X-ray of CT stating solitary pulmonary nodule. Exclusion criteria: patients with clinical or radiological lesions that suggest sarcoma but which did not have histopathologic confirmation;

patients with Kaposi's sarcoma and HIV/AIDS, patients who did no show pulmonary metastases detectable by radiology or fiber-bronchoscopy at the date the study began even if they demonstrated respiratory symptoms, patients with no follow-up (at least one more visit after the pulmonary metastasis diagnosis was established).

3 Method

Patients were evaluated using: anamnesis and clinical exam, complete blood tests (with the evaluation of renal and hepatic functions), cardio-logic evaluation (EKG) and echocardiography, abdominal ultra sounds, bone scintigraphy, pulmonary x-rays from two angles of incidence (front and profile) and pulmonary CT, all used to diagnose pulmonary metastases. Fiber-broncho-scopy was performed when the patient's state allowed it. We diagnosed two main types of sarcomas – osteosarcomas and soft tissue sarcomas. We evaluated the main symptoms and signs of patients, the time period between the emergences of symptoms and establishment of diagnosis, and the interval of time until the emergence of pulmonary metastases (reported in months) from the date the diagnosis of sarcoma was established, the emphasize of pulmonary metastases, and types of pulmonary metastases. The response to chemotherapy treatment was evaluated as follows: complete response (disappearance of tumor and metastatic lesions confirmed clinically and radiological), partially favorable response with a tumor regression of 2/3, poor response, defined as a regression ratio greater than 1/3 but lower than 2/3, and no response at all with a regression less than 1/3. In order to monitor the evolution, we evaluated patients periodically, every two months. This evaluation included> x-ray and CT of primary tumor, thoracic x-ray and CT (+/ - abdominal x-ray and CT when requested by the localization of the primary proximity tumor). We performed a statistical analysis by following the variables below: patient related variables (age, gender, environment, time span between symptoms and diagnosis), tumor related (tumor dimension, localization, LDH values, histology), metastasis related (type of pulmonary metastases – micro-opacities, macro-opacities, unique nodule, lymphan-gitis, pleurisy), treatment related (evaluation of the therapeutic response). The statistical analysis was performed using standard methods. Survival was calculated either by confirmation of death or by absence at the next visit (months away from the diagnosis of the primary tumor). We also calculated the arte of survival from the date of pulmonary metastasis diagnosis (in months). Survival curbs were calculated from the beginning of treatment. We divided the batch into two subgroups, patients with osteosarcomas and patients with soft tissue sarcomas. Although prognosis factors are similar, it is our belief that they represent two distinctive entities in regard to prognosis and evolution under treatment

4 Results

Demographic characteristics of the batch of patients with osteosarcomas and evaluation of host related prognosis factors

Gender is a factor that does not influence survival. We noticed a slight predominance among patients of female gender both with osteosarcomas (54.84%) and with soft tissue sarcomas (52%), without it significantly influencing statistical survival of patients with osteosarcomas (p=0.984) or patients with soft tissue sarcomas (p= 0.121).

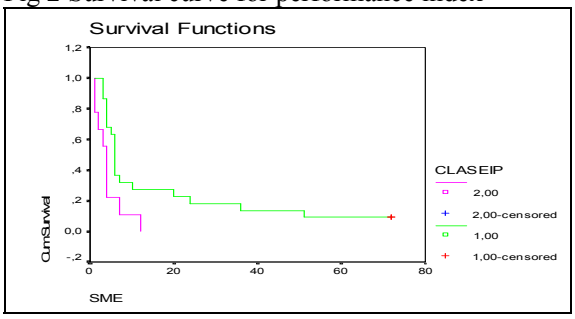
Table1.

Age osteosarcoma (soft tissue)		Gender		Environment	
<10	6.45%	Male	Female	Urban	Rural
(10;20]	38.71%(21.74 %)				
(20;30]	35.48%(1304 %)	45.16 % (48%)	54.84 % (52%)	77.42 % (52%)	22.58 % (48%)
(30;40]	6.45% (13.04%)				
(40;50]	9.68%(13.04%)				
(50;60]	13.04%(21.74 %)				
(60-70]	0%(13.74%)				
(70-80]	0% (13.04%)				
(80-90]	3.23%				

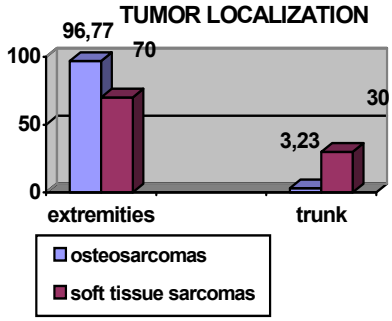
The average age of patients with osteosarcomas was 24.58 years, and that of patients with soft tissue sarcomas was 48.04 years. We noticed predominance among the 10 – 20 years age group, followed by 20 to 30 years for osteosarcomas (children and young adults) and 50 to 60 years for patients with soft tissue sarcomas. Age is not considered a prognosis factor in the survival of patients with soft tissue sarcomas. By dividing the batch of patients with soft tissue sarcomas into two age groups, less than 40 years and over 40 years and using the Kaplan – Mair method and the Long – Rank test, we obtained a statistical significant value of p = 0.450. Age is not an unfavorable factor of survival for patients with metastases, p = 0.9042, or for survival rate calculated starting with diagnose of the tumor, p = 0.3734 for osteosarcomas (not even if

we divide patients into two age groups: less than 15 years and greater than 15 years, p = 0.615).
The influence of the performance index is described as a host related prognosis factor which can influence survival. The performance index does not influence survival from the date of tumor diagnosis, p = 0.0730, but can have an impact on survival after the emergence of metastases, p = 0.0346 < 0.05.
The performance index becomes a prognosis factor for survival after the emergence of metastases if patients are divided into two performance groups. Patients with a good performance index (1 and 2), and the rest, meaning those with an unfavorable performance index (3 and 4). With the help of this classification, we determined the value of the LOG-Rank test parameter, obtaining a significant value, p = 0.013 which demonstrates that the performance index becomes a prognosis factor for survival after the emergence of pulmonary metastases According to the survival function diagram, the performance index can be a prognosis factor that influences survival for soft tissue sarcomas. Its evaluation with a framing based on tolerance to effort depicted 2 categories: good, 37.79% (performance index 1 and 2) and low, 52.18% (performance index 3 and 4). Performance index does not influence survival with metastasis, p = 0.552.

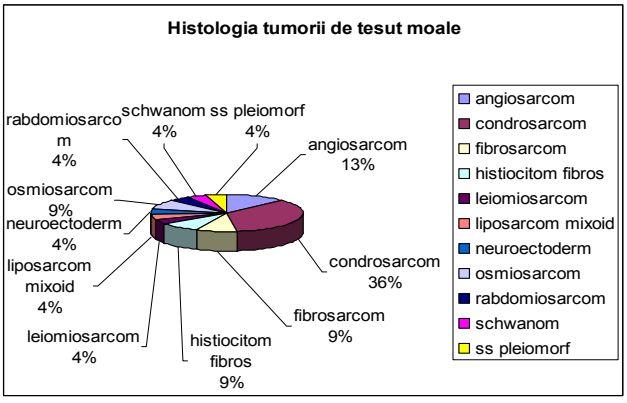
Fig 2 Survival curve for performance index



The free time interval from the emergence of symptoms until consultation by a physician and establishment of a diagnosis The average time interval between the apparition of symptoms and the doctor consultation was equivalent to 9.61 months for soft tissue sarcomas. A time interval shorter than 1 year (group 0 from diagram) and a second one with a time interval greater than 1 year made us consider it a risk factor in survival with metastases, p = 0.002; the average survival rate of patients with a time interval shorter than 1 year from symptoms to diagnosis was 34.75 months compared to that with a more than 1 year diagnosis where the average survival rate was just 9.64 months.
For osteosarcomas, the diagram indicates that patients with a free time interval greater than 12 months have a better chance of survival (30.19 months) than those with a free time interval shorter than 1 year (19.42 months) After the evaluation of host related prognosis factors (age, gender, environment, and performance index) we tried to evaluate primary tumor related factors (localization, size and histology of primary tumor).
Localization of the primary tumor was described in numerous studies as a prognosis factor. For our batch, the localization of the tumor in the extremities or trunk does not represent a prognosis factor in survival with metastasis, p = 0.1976, or for survival with a tumor, p = 0.1136. The means of the survival times from the emergence of the tumor are 23.43 months for the group whose tumor is localized in the extremities and 6 months for those whose tumor is localized within the trunk. Considering that we have just one case with central localization, data cannot be considered conclusive.
Survival after the emergence of pulmonary metastases was 13 months in the case of tumors localized at extremities and just 1 month for those with trunk localized metastases. Tumor localization on a certain segment did not represent a statistically significant prognosis factor.
Fig 3 Tumor localization



In the case of muscle-skeletal tumors (soft tissue sarcomas), literature studies depict tumor localization as an important prognosis factor. On our batch of patients (22 patients), tumor localization at different segments did not significantly influence survival.
Fig 4 Tumor histology



Tumor localization at extremities or within the trunk is also not a prognosis factor, p = 0.482. Due to the small number of patients enrolled in the study, it is possible not to obtain statistically significant p values.

The histology of the osteosarcoma tumor does not influence survival with metastasis, p = 0.123 or survival with tumor, p = 0.361, with a mention that we do not have a homogenous batch (we only have three cases of Ewing sarcoma). This can explain why we do not have statistically significant p values.

Soft tissue tumor histology is described as capable of influencing survival with metastasis, p = 0.662 > 0.05; or survival with a tumor, p = 0.267. These statistically insignificant p values may also be attributed to the reduced batch of patients.

Tumor's size does influence survival, p = 0.0303 < 0.05 for osteosarcomas.

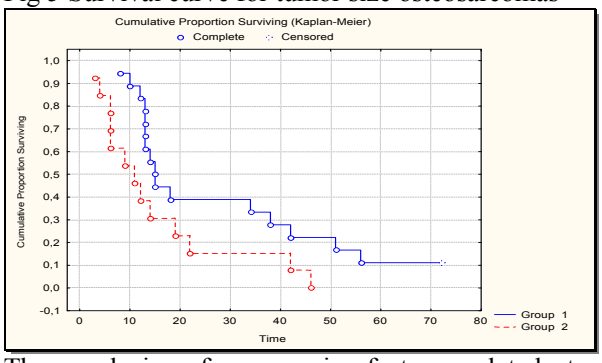
The diagram below demonstrates that a size of the osteosarcoma tumor larger than 10 cm (42%) leads to a lower rate of survival compared with one having a size between 5 and 10 cm (smaller than 10 cm) (58%).

Soft tissue sarcoma: we divided the batch into 2 categories based on the size of the tumor. *Between 5 and 10 cm (68.12 %)

*Over 10 cm (31.88%)

Tumor's size does influence survival with metastasis, p = 0.267 > 0.05 but does not influence survival with tumor, p = 0.040 < 0.05. The survival function diagram demonstrates that patients with a tumor size between 5 and 10 cm have a better survival rate than those whose tumor is larger than 10 cm.

Fig 5 Survival curve for tumor size osteosarcomas



The analysis of prognosis factors related to metastases presence (the type of pulmonary metastasis, the presence of other metastases with other localizations, the time of emergence of pulmonary metastases with an approximation of the free tumor – metastasis time interval) states that although not statistically significant, there are some differences of survival between various types of pulmonary metastases and therefore patients with mediastinal adenopathies have survived for 7 months, those with pleurisy survived for 4.33 months, multiple nodule patients survived for 15, 6 months and those with two types of disseminations for only 4.25 months (multiple nodules and pleurisy).

The type of pulmonary metastases does not influence survival with metastasis: p = 0.281.

Time of emergence for soft tissue: influences survival with metastases, p = 0.0008 < 0.05. If we group patients based on the time of emergence, meaning the first group will contain patients with emergence time 1, and group 2 will contain patients with emergence time 4, late emergence, after the end of treatment and using a multi-varied analysis, we established that patients with time 4 have a better survival rate than those from the first group, as the diagram below also demonstrates (p = 0.00038).

Response to treatment was framed as going into full remission for 1 case (favorable), partial remission for 2 cases and unfavorable (progressive) for 28 patients. Response to treatment does not influence survival with metastases. The mean of survival based on the response to treatment (mean of survival 1 is 22.25 for progressive and 7.00 for partial) (appendix 4). Response to treatment does not influence survival with a tumor, p = 0.087.

The classical prognosis factors used in the evaluation of muscle – skeletal tumors are connected mostly to the localization of primary tumors, their size, tumoral degree, presence of the recurrent disease as well as positive resection margins. Host related prognosis factors as gender, age, and environment are considered to be secondary from an importance and prognosis value point of view.

5 Discussions

Hence, our study emphasizes the predominance of women both in the osteosarcoma batch and in the soft tissue sarcoma subgroup even if gender is not a statistically significant prognosis factor, results conformant to other published data. Bacci and all [3] noted an increased frequency of men among patients with Ewing sarcoma but no gender related statistically significant survival rate was ascertained. Stefan Bielack and all also reported, in a survey conducted on 1720 patients with osteosarcoma, the predominance of men (1007 men and 695 women). [4]. Ewa Koscielniak reported a percentage of 1.19: 1 in the men / women ratio of patients with soft tissue sarcomas [5].

The average age was 24.58 (between 32 and 79 years) and based on the histological type we

observed a predominance during the first and second life decade for osteosarcoma. The average age for soft tissue sarcomas is 49.04; there was no record of a peak of any age group. Statistically speaking, age does not influence survival neither for the osteosarcoma subgroup nor for the soft tissue sarcoma subgroup (p = 0.3734 and p = 0.450) no matter in which age groups we framed the patie4nts (patients with osteosarcoma under and above 15 years, and patients with soft tissue sarcomas under or over 40 years). Michell Scur did not establish with certainty that the patient's increased age influences the survival of patients with Ewing sarcoma at an average age of 15 years [6]. Cotterill reported an increased proportion of men among patients with ages 15 and above (65%) compared to the group of patients with ages below 15 [7]. Rasquele Rosita also reported a better survival rate for younger patients in his study on children and young adults with Ewing sarcoma [8]. In his study of osteosarcomas, Bielack noted that patients older than 40 years have an increase probability to present axial tumors, metastases and are more exposed to therapeutic failure [4]. Bacci also emphasized the increased frequency of Ewing sarcomas in extremities (femur – shinbone, followed by pelvis and other localizations and statistically significant survival differences between extremities tumors and central tumors [3]. Carola A.S Arndt reported the localization of soft tissue tumors in any situ [9].

Size of primary tumor is also and important prognosis factor. Our batch contained cases of bone tumors with sizes between 5 and 10 cm and over 10 cm (p = 0.0303) and p = 0.040 within the soft tissue sarcoma batch. Jonathan Koea classified the entire risk group of tumors with significant survival differences (tumors smaller than 5 cm – reduced risk; between 5 and 10 cm – average risk; over 10 cm – high risk) (10) Paul Lussen reported in a Ewing tumor study the importance of survival based on the size of the tumor. He divided the batch into two risk groups: group 1 – small tumors, with less than 100 ml, situated at extremities ("standard risk"), and group 2, with tumors smaller or equal to 100 ml, positioned centrally, with increased risk [11]. Primary tumor histology may influence survival. Our study did not emphasize differences in survival rates with significant p values from a histology point of view. For osteosarcomas p = 0.361, and for soft tissue, p = 0.267. Ewa Koscielniac observed in the final German report of soft tissue sarcoma that patients with non resectable metastases and tumors at the moment of presentation were more frequent alveolar rhabdomyosarcomas compared with patients with non metastatic disease (p – 0.0001). The localization of primary tumors did not influence staging [5]. Cotterill did not report survival differences among the various histology subtypes among patients with Ewing sarcoma (Ewing sarcoma, atypical Ewing sarcoma or neuroectodermal tumors). [7, 10]. Glabbeke reported an increased survival rate in patients with liposarcoma and sinovial sarcoma, a high response rate for liposarcoma and a low survival rate for histiocytoma, as well as a low response to treatment rate for leiomyosarcoma [12]. The presence of metastases during the diagnosis of pulmonary tumors represents an important unfavorable prognosis factor. In our study, 29% of cases with osteosarcomas and 39% of cases with soft tissue sarcomas presented pulmonary metastases at the time of diagnosis. This is a higher percentage than that of other studies, maybe owed to a late presentation for consult (low level of education and medical assistance). Compared to patients with localized disease, patients with metastatic osteosarcoma upon presentation most likely had centrally positioned tumors (p – 0.008), larger tumors (p is smaller than 0.001) and a long array of symptoms before diagnose was established (p is smaller than 0.001) [4, 13, 14]. Karola AS Arndt published a study in 1999 [1, 9] where he reported relapses at a pulmonary level of patients with osteosarcoma (with one nodule or a limited number of pulmonary nodules, and a free interval greater than 1 year). After the initial therapy, they had 25% chances of healing if treatment was associated with the resection of all nodules [1, 9]. Koea reported the development of metastases in 25% of patients with a free interval of 14 months (10). Glabbeke also asserts an increase of the survival rate based on the statistically significant free interval (p = 0, 0004). A free interval greater than 36 months is considered a favorable prognosis factor [12]. In the study conducted at the Rizzoli center, Bacci reported the presence of distance metastases in 70.8% of cases, 42.6% of which had just pulmonary metastasis, 39.5% had bone metastases and 14.9% had both bone and lung metastases. He drew the conclusion that in contrast with the Rodriguez study, patients with local relapse do not have a significantly better prognosis than those with metastasis [3, 12]. Bielack reported a percentage of 54.8% patients with pulmonary metastasis who benefited from surgery of pulmonary metastases [4]. Cotterill also argued a 5 year survival of patients with Ewing sarcoma with exclusively pulmonary metastases of 29% compared to the 19% of patients with bone metastases and 8% with both types (p is smaller than 0.001) [7].

6 Conclusion

The evaluation of prognostic factors and the follow-up of metastases are major research areas that enable cancer patients to have maximum therapeutic benefits, increased quality of life and survival.

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