RESEARCH ARTICLE

Retrospective Analysis of 498 Primary Soft Tissue Sarcomas in a Single Turkish Centre

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Abstract

Background: Soft tissue sarcomas (STS) must be managed with a team involving pathologists, radiologists, surgeons, radiation therapists and medical oncologists. Treatment modalities and demographic charasteristics of Turkish STS were analysed in the current study. Material-Methods: Primary adult STS followed between 1999-2010 in Cukurova University Medical Faculty Department of Medical Oncology were analzied retrospectively Results: Of the total of 498 patients, 238 were male and 260 female. The most seen adult sarcomas were leomyosarcoma (23%). Localization of disease was upper extremity (8.8%), lower extremity (24.7%), head-neck 8.2%, thoracic 8%, retroperitoneal 5.6%, uterine 12.4%, abdominal 10%, pelvic region 3.6 and other regions 10%. Some 13.1% were early stage, 10.2% locally advanced, 8.2% metastatic and 12.2% recurrent disease. Patients were treated with neoadjuvant/adjuvant (12%) or palliative chemotherapy (7.2%) and 11.4% patients did not receive chemotherapy. Surgery was performed as radical or conservative. The most preferred regimen was MAID combination chemotherapy in the rate of 17.6%. The most common metastatic site was lung (18.1%). The overall survival was 45 months (95%CI 30-59), 36 months in men and 55 months in women, with no statistically significant difference (p=0.5). The survival rates were not different between the group of adjuvant and palliative chemotherapy (respectively 28 versus 18 months) (p=0.06), but radical surgery at 37 months was better than 22 months for conservative surgery (p=0.0001). No differences were evident for localization (p=0.152). Locally advanced group had higher overall survival rates (72 months) than other stages (p=0.0001). Conclusion: STS can be treated successfully with surgery, chemotherapy and radiotherapy. The survival rates of Turkish people were higher in locally advanced group; these results show the importance of multimodality treatment approach and radical surgery.

Keywords: Soft tissue sarcoma - surgery - chemotherapy - radiotherapy - Turkey

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Introduction

Sarcomas are a rare and heterogeneous group of malignant tumors of mesenchymal origin that comprise approximately 1 percent of all adult malignancies (Fletcher, 2002). Approximately 80 percent of sarcomas originate from soft tissue and the rest from bone. There are about 11,280 new cases of soft tissue sarcoma diagnosed each year in the United States, with 3900 deaths (Siegel, 2012).

More than 50 different histologic subtypes have been identified. The most common subtypes of STS are pleomorphic sarcoma (also known as malignant fibrous histiocytoma (MFH), liposarcoma, leiomyosarcoma, synovial sarcoma, malignant peripheral nevre sheat tumors (Coindre et al., 2001). Extremities (60%), the trunk (19%), retroperitoneum (15%) or head and neck (9%) are the most common primary sites. The most common site of metastasis is the lungs, and metastasis generally occurs within two to three years after the completion of therapy. (Cormier, 2004).

All patients should be managed by multidisciplinary team with expertise in STS (Clasby, 1997). We analysied 498 patients with STS retrospectively in this current study.

Materials and Methods

Enrollment was limited to patients with histologically confirmed, STS (excluding gastrointestinal stromal tumor, Kaposi Sarcom, malignant mixed mullerian tumor) that were followed up between 1999 and 2010 in Cukurova University Department of Medical Oncology. Patients associated parameters age, sex, tumor localization, histopathologic subtypes, grade, stage (divided as local, locally advanced, metastatic, recurrent disease) were analysied. Treatment modalities were analysied The patients were put into groups that treated with chemotherapy, radiation therapy, and combination therapy.

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Surgical treatment modalities were put into groups as pallative, radical and local surgery. Disease free survival and overall survival rates were analysied. A total of 498 patients were analysied 32 patients patients were excluded because of incomplete data. A total of 466 patients were icluded to the study.

Results

Retrospectively analyzed 498 patients with primary soft tissue sarcoma. Broad age distribution but mean age was 47.2±17.4 (14-87) for STS in Turkey. Age distrubition in patients with sarcomas originating from different sites of the body indicates that the peak age was between 50-55 years (Figure 1). Patients with malignant fibrous histiyocytom/Fibrosarcoma and liposarcoma are older, patients with Ewing, alveolar part and desmoid sarcomas are younger (Figure 2) Gender data shows a female predominence(1/1.1) with a small difference (47% vs 52%).The most seen adult sarcomas were leomyosarcoma in the rate of (23%). Leiomyosarcoma and liposarcoma contitutes 1/3 of all STS (23%+12%). Localization of disease was upper extremity (8.8%), lower extremity (24.7%), head-neck 8.2%, thoracal 8%, retroperitoneal 5.6%, uterin 12.4%, abdominal 10%, pelvic region 3.6 and the other regions 10%. STS predominantly were located in extremities (28% in lower, 10% in upper) and uterine (14%) regions. Lower extremity is the most common involved region for primary STS in TR (28%) and uterine sarcoma ist the 2. most common STS Histopathology, the most common subtypes (≥54%) Leiomyosarcoma (23%), Liposarcoma (12.2%), Chondrosarcoma (10.2%), Fibrosarcoma (9.4%). Patients were divided into four groups as early stage (localized), locally advanced, metastatic and recurrent disease. In the rate of 13.1% early stage, 10.2% locally advanced, 8.2% metastatic and 12.2% recurrent disease. Of 78% has no metastasis. In 25% metastatic site is lung (alone 18.1%) and liver follows lung with 11% frequency. Patients were treated with neoadjuvaant/adjuvant (12%), palliative chemotherapy (7.2%) and 11.4% patients did not receive chemotherapy. Radiation therapy was given to the patients in the rate of 5% as curative and in the rate of 3.6% as palliative. Surgery was performed as radical or conservative. The most preffered regimen was MAID combination chemotherapy in the rate of 17.6%. In the rate of 60% received any chemotherapy of which almost all were combination regimens. 46.4% of the patient took an antracyline combination and MAID was the most common regimen (17.6%). Almost 70% of the 72 patients could not receive any chemotherapy following first line. Gemcitabine, taxan, or platins were the most common agents selected for the second line treatments, 5.6%, 8.4% and 16.7% respectively.

The overall survival was 45 months (95%CI 30-59). The overall survival rate was 36 months in men and 55 months in women, statistically difference was not found (p=0.5). Patients with extermity and uterine sarcoma seem living longer but statistically significant different was not found (p=0.07) (Figure 3). The overall survival rates of patients treated with radical surgery 37 months and 22

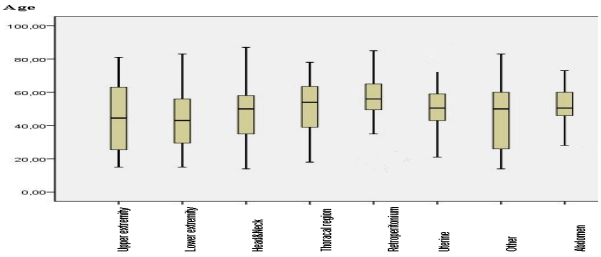

Figure 1. Age Distribution by Localization.

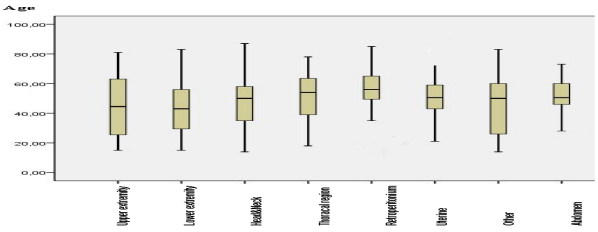

Figure 2. Age by Histologic Subtypes.

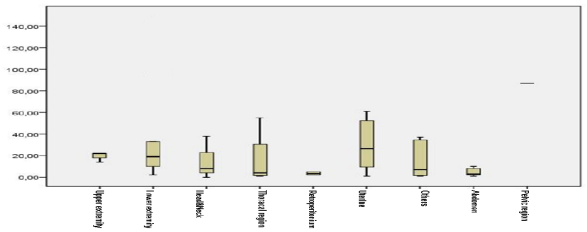

Figure 3. Survival Rates by Localization.

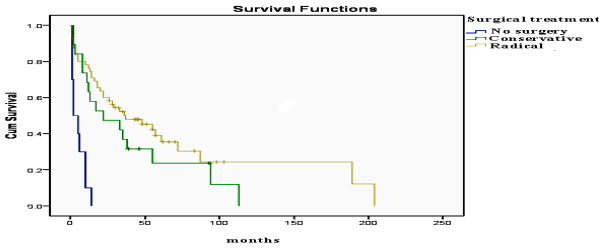

Figure 4. Survival by Surgical Treatment (Radical vs Conservative vs No Surgery)

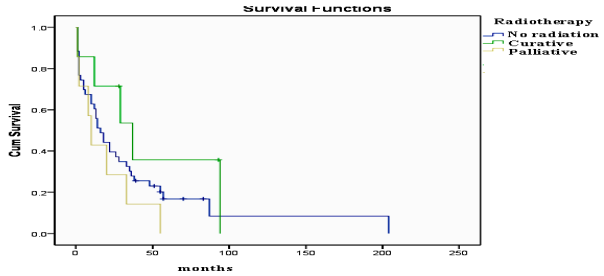

Figure 5. Radiotherapy: Overall Survival (Curative vs Palliative vs No Radiation).

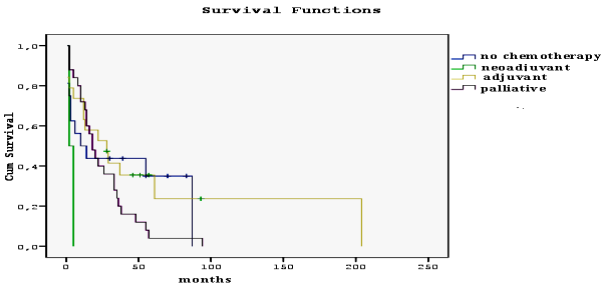

Figure 6. Chemotherapy (Neoadjuvant, Adjuvant vs Palliative)

months in conservative surgery (p=0.0001) (Figure 4). In the rate 89% of the patients received any kind of surgical treatment, mostly radical resection, radiation was limited within 31% of the patients as a locoregional treatment modality. Radiation therapy was not effect the OS in our study; OS rates, 16 months in group with no radiation, 37 months in curative RT and 10 months in palliative group. Curative radiation therapy group seems higher survival rates but statistically significant difference was not found (p=0.25) (Figure 5). The survival rates were not different between the group of adjuvant and palliative chemotherapy (respectively 28 versus 18 months). (p=0.06) (Figure 6). There was no statistically significant OS difference between chemotherapy regimens in first and second line.

The overall survival rates were not statistically different for localization (p=0.152). Locally advenced group had higher overall survival rates (72 months) than other stages, statistically significant was found (p=0.0001).

Discussion

Sarcomas are a rare and heterogeneous group of malignant tumors of mesenchymal origin. The histopathologic spectrum of sarcomas is broad, presumably because the embryonic mesenchymal cells from which they arise have the capacity to mature into striated skeletal and smooth muscle, adipose and fibrous tissue, bone, and cartilage. As classified by the World Health Organization (WHO), the group of soft tissue sarcomas includes more than 50 different histologic subtypes The most common subtypes that arise in adults are outlined in the Fletcher (2002). The most common STS subtypes and their incidence was leomyosarcoma 23%, malignant fibrous histiyocytoma 17.1%, liposarcomas 11.5%, dermatofibrosarcomas 10.5% rabdomyosarcomas 4.6%, angiosarcomas 4.1% in a Surveillance, Epidemiology and End Results program retrospective review of patients diagnosed between 1997 and 2001, using 2002 World Health Organization classification criteria (Ducimetière et al., 2011).

In our study the prevalance was same as first subtype leiomyosarcoma (23%), but the other common types were Liposarcom (12.2%), Chondrosarcoma(10.2%), Fibrosarcoma (9.4%) Alkıs et al. reported the common subtype was liposarcoma in the rate of 16.3% and respectively malignant mesenchimal tumor(not clasified) 13.9%, malignant fibrous histiyocytoma 11.2%, synovial sarcoma and rabdomyosarcoma 10.2% from Turkey.

The most common site for metastasis is lung. Visceral and retroperitoneal sarcomas show propensity to metastasize tol iver and peritoneum (Alkis et al., 2011). In our study the most common site for metatasis lung and than liver.

Soft tissue sarcomas occur at all anatomic body sites, but the majority are in the extremities. The anatomic distribution of soft tissue sarcomas in 4,550 adults reviewed by the American College of Surgery was as follows Thigh, buttock, and groin 46%, Upper extremity 13% percent, Torso 18%, Retroperitoneum 13%, Head and neck 9% (Lawrence et al., 1987). Some histologic types of soft tissue sarcoma have a predilection for certain anatomic sites. As an example, while only 14 percent of all soft tissue sarcomas present in the upper extremity, 40-50 percent of all epithelioid sarcomas arise on the forearm and finger (Baratti et al., 2007; Sakharpe et al., 2011). Common localizations were extremities and uterine in our study.

Surgical resection is the cornerstone of treatment for virtually all patients with soft tissue sarcoma. The combination of surgery and radiation therapy (RT) achieves better outcomes. RT can be administered as primary therapy preoperatively or postoperatively in STS. Advances in RT technology such as brachytherapy, intensity modulated radiation therapy (IMRT), and intraoperative radiation therapy (IORT) have led to improvement of treatment outcomes in patients with STS (DeLaney, 2005).

In our study;In a limited number of patients (207 of 490) 90% of the patients received any kind of surgical treatment, and mostly a radical resection (65%). Special surgeons difficultly operated the patients with locally advanced stage disease in a radical intend.Without enough RT and conservative approach, the patients probably had a low Quality of life at the end. As a locoregional treatment modality, limited number (31%) of the patients received radiation.The aim of this treatment was curative intend in 18% of the patients.Patients who received either curative or palliative RT seemed living longer than patient who did not receive any RT.

Chemotherapy and chemoradiation is used as an adjunct to surgery in many centers to downstage large high grade tumors The most recent analysis from the Sarcoma Meta-Analysis Collaboration (SMAC) suggests a significant 11 percent improvement in survival for doxorubicin and ifosfamide-based adjuvant chemotherapy compared to resection (Pervaiz et al., 2008).

In our study 60% received chemo of which almost all were combination regimens, 46.4% an antracyline combination and MAID (Doxorubicine 15 mg/m^2, Dacarbazine 250 mg/m^2, Iphosphamide 2000 mg/m^2, Mesna 2000 mg/m^2 was the most common regimen (17.6%). Patients who received either curative or palliative RT seemed living longer. Chemotherapy with single agents and antracycline-based combination regimens (doxorubicine or epirubicine with iphosphamide and/or dacarbazine) have been widely used for patients advanced, unresectable or metastatic disease (Bramwel, 2003). Other chemotherapeutic agents such as gemcitabine, docetaxel, vinorelbine, pegylated lipomosomal doxorubicin and teozolamid have also evaulated in clinical trials.

Gemcitabine alone or in combination with docetaxel or vinorelbine has been evaluated in phae II studies. The combination of gemcitabine, docetaxel was highly active against leomyosarcoma especially that progressed after antracycline terapy (Hensley et al., 2002; Maki et al., 2007). Gemcitabine, taxans and platins were commonly preferred drugs in 2nd line treatment in our study. Trabectidin is a novel DNA –binding agent that shown objective responses of patients with advanced STS (Cesne et al., 2012).

More recently, a number of targeted therapies have shown promising results in patients with histological

types of advanced or metastatic STS. Imatinib, Sunitinib, sorafenib shown efficacy in patients with advanced and/or metastatic STS (Maki et al., 2009; Stacchiotti et al., 2012a; 2012b). Pazopanib, a multitargeted tyrosine kinase inhibitor has demonstrated single-agent activity in patients with advanced STS subtypes except liposarcomas (Sleijfer et al., 2009). Crizotinib and Sirolimus has shown promising results in specific subgroups of STS (Bissler et al., 2008; Butrynski et al., 2010). Drugs like trabectedin, TK-inhibitors or m-TOR inhibitors are not commonly used in TR. But these will be preferable agents in the future.

In conclusion, this retrospective study, A rare cancer also in TR. Annual incidence was less than 1.9/100 thousand without a significant difference between regions of TR. Frequency peaked at age 40-55 years with a small female predominence. Common localizations were extremities and uterine. Leiomyosarcomas and liposarcomas were more common subtype. Majority of the patients had no metastatis but locally advanced or reccurrent disease.

Most of the patients were diagnosed at advanced stages due to probably non-specificed and unexperienced phycians. Most of the patients were treated in multimodality. Most of the patients (90%) were treated with surgery, many of them received chemo therapy (62%) but limited number of thepatients could receive RT. One-third adjuvant, one-fourth palliative and 3% received neoadjuvant chemotherapy. Of the 60% took a combination including mostly an antracyline, 70% could not receive a 2nd line treatment. Gemcitabine, taxans and platins were commonly preferred drugs in 2nd line treatment. Platins, taxan, or gemcitabine were the most common agents selected for the second line treatments, 16.7%, 8.4% and 5.6% respectively

Soft tissue sarcomas are ubiquitous in their site of origin, and are often treated with multimodality treatment. A multidisciplinary approach is therefore mandatory in all cases (involving pathologists, radiologists, surgeons, radiation therapists, medical oncologists and paediatric oncologists if applicable). This should be carried out in reference centres for sarcomas and/or within reference networks sharing multidisciplinary expertise and treating a high number of patients annually.

STS can be treated successfully with surgery, chemotherapy and radiotherapy. The survival rates of Turkish people were higher in locally advanced group; these results show the importance of multimodality treatment approach and radical surgery.

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