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Original Article

Treatment Of Pediatric Soft Tissue Sarcoma, The Experience of Simgle Institution

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ABSTRACT

Due to the small number of patients of pediatric soft tissue sarcoma, there are no clear recommendations for the treatment of those diseases. Most of the time they are treated according to the adult treatment recommendations, though the pediatric age group have different tolerance to chemotherapy and radiation and also seem to have different prognosis than adult and late adolescence. By doing this retrospective analysis we try to share the experience of our centre in the treatment of soft tissue sarcoma (non-rhabdomyosarcomatous) in such age group. Retrospective analysis of the files of 30 cases of pediatric soft tissue sarcoma attending the pediatric unit of Kasr-El-Einy Center of Oncology and Nuclear Medicine (NEMROCK), faculty of Medicine, Cairo University, from January 1994 till January 2000. Evaluation of the demographic data of the patients as well as their pathological subtypes, grade, stage and risk factors was done. All soft tissue sarcoma cases referred from the pediatric surgical department after pathological diagnosis and surgical interference during the stated period were the subject of the study. Low-grade and completely excised tumors received no adjuvant treatment. Incompletely excised low-grade tumors received radiation therapy delivering a dose of 60 Gys. High-grade tumors received adjuvant chemotherapy in the form of VACA for 35 weeks or neoadjuvant Ifosfamide + Doxorubicine for 6 cycles with radiation therapy. The median follow-up time was 44 months and the range was (4-107 months).

High-risk patients accounted for 56.7% and low-risk patients accounted for 43.4% of the cases. The 5 year survival for stages I and II and for stages III and IV was 77.78% and 11.11% respectively (Fig II), the difference was statistically significant ($P < 0.001$). The 5 year survival for low-risk patients and high-risk patients was 92% and 26.7% respectively (Fig III), the difference was statistically significant ($p = 0.001$). The 5-year survival in patients with bulky tumors (> 5 cms) was 20% versus 76% for non-bulky tumors (Fig IV). The difference was statistically significant ($p = 0.0075$). The 5-year survival for grade I and grade II pathologies was 91.67% versus 26.67% for grade III and grade IV pathologies (Fig V). The difference was statistically significant ($p < 0.001$).

Acute toxicity in patients receiving chemotherapy; grade I, grade II and III GIT toxicity was noticed in 14.3%, 14.2% and 7.1% of the cases respectively. Hepatic toxicity was observed in one case. Grade I myelo-suppression developed in 8% of the cases, grade II myelo-suppression in 20.5% and grade III myelo-suppression in 14.3% of the cases. Grade II and III dermatitis occurred in 14.3% and 21.4% of the cases respectively; and it was only seen in patients receiving radiation therapy.

By multivariate analysis, it has been concluded that the tumor grade is the most important independent prognostic factor affecting survival.

The 5-year overall survival in this study was 55.6% (Fig I) which was less than international standards seen in many of published studies. This difference in survival rates may be attributed to delayed presentation of the patients leading to a bigger number of advanced bulky tumors at presentation, and also, the unavailability of brachytherapy in our centre which helps provide, higher localized doses of radiation to residual tumors. Moreover, the poor performance status and economical status of the patients' leads to chemotherapy treatment delay and lag periods in radiation therapy, which in turn jeopardizes treatment outcome.

Keywords: soft tissue-pediatric-sarcoma

Introduction

Soft Tissue Sarcomas (STS) are very heterogeneous tumors, both pathologically and clinically, making standardization of therapy difficult. No single institution examines an adequate number of cases of the various histologic subtypes within a short period to allow treatment comparisons. Only large multi-center studies can accumulate enough information to improve prognosis and minimize late sequelae in children

with STS.[1]

The non-rhabdomyosarcomatous soft tissue sarcomas (NRSTS) are a rare group of neoplasms of mesenchymal origin, which account for approximately 5% of all cancers in patients younger than 20 years. The incidence of specific subtypes of soft tissue sarcomas is age dependent. For example, rhabdomyosarcoma accounts for 60% of the cases of soft tissue sarcomas in children younger than 5 years, in contrast, more than three fourths of all soft tissue sarcomas in patients aged 15 to 19 years are NRSTSs. The distribution of histologic subtypes of NRSTS is also age dependent [1]. Fibrosarcomas predominate in children younger than 1 year. Synovial sarcomas and malignant peripheral nerve sheath tumors (MPNSTs) are more frequently encountered in patients older than 10 yeas [1-2].

Because NRSTSs are more common in adults, with approximately 6000 new cases per year, much of the experience regarding their natural history and treatment is extrapolated from adult trials either single institution or multi-centric ones. In some specific circumstances, the prognosis for children with individual soft tissue sarcomas is much better than that for adults, resulting in remarkably different treatment recommendations [3]. The difference in prognosis is most pronounced for infants and young children, whose tumors often have a benign behavior and excellent prognosis with surgery alone. In contrast, NRSTS that occur in adolescents often behave more like sarcomas that occur in adult patients, and their management resembles that of adults [4].

Patients and methods

This is a retrospective analysis of the treatment results of pediatric soft tissue sarcoma cases who attended to the pediatric unit of Kasr-El-Aini Center of Radiation Oncology and Nuclear Medicine (NEMROCK), faculty of Medicine, Cairo University; from January 1994 until January 2000.

All soft tissue sarcoma cases referred from the pediatric surgical department after surgical interference and pathological diagnosis during the stated period were included in the study. The files of all cases were reviewed. Clinical history, laboratory, and radiological examinations as chest x-ray, abdominal ultrasonography, preoperative and postoperative MRI or CT scan to the operative bed were reviewed and analyzed. Patients were classified into low and high-risk cases according to the American Joint Cancer Committee (AJCC) criteria. Low-risk patients included patients with stage I and II disease, tumor bulk < 5 cm and grade I or II pathology [5]. High-risk patients included patients with stage III or IV disease, bulky tumors > 5 cm, and / or grade III or IV pathology [5].

Postoperative therapy was given to a total dose of 60 Gy on cobalt 60 at a focal skin distance of 80 cm by 2 parallel opposing fields, 5 sessions per week for 6 weeks. The initial tumor volume included the tumor bed and 5 cm safety margin to a dose of 50 Gy, then localized to the original tumor bed for a boost of 10 Gy in incompletely resected tumors. Low-grade non-bulky tumors with complete surgical excision did not receive radiation therapy.

All high-grade resected tumors received adjuvant chemotherapy in the form of VACA for 35 weeks or Ifosfamide + Doxorubicine for 6 cycles along with radiation therapy. The same regimens where given to advanced unresectable or metastatic tumors.

VACA regimen includes: (Vincristine 1.5 mg/m^2 i.v. day 1, Endoxan 650 mg/m^2 i.v.day 1, Adriamycin 60 mg/m^2 i.v. day 1 alternating with Cosmogen 15 micrograms/Kg i.v. day 1 to day 5).

Holoxan was given at a dose of 1.8 gm /m^2 i.v. infusion over 3 hours with mesna, day 1 to day 5, and Doxorubicine was given at a dose of 60 mg/ m2 i.v. day 1.

All patients were followed up every 3 months during the first two years by chest x-ray, abdominal ultrasonography and CT or MRI to the operative bed then every 6 months thereafter for a period of 5 years. Recurrent cases received palliative radiation therapy or salvage chemotherapy (cisplatinum 80 mg/m2 infusion Day 1 and Etoposide 100 mg/m2 day 1 to day 3 IV infusion) [10].

The overall survival, disease free survival, and complications of treatment were assessed and statistically analyzed.

The responses to treatment were assessed; whether complete response (CR), partial response (PR), stable disease (SD) or disease progression (PD) Correlation between various prognostic factors with survival and disease free survival was done.

Statistical methods

The Kaplan Meier method was used to estimate overall survival and disease free survival and log rank test was used to compare the different groups. P value is significant at 0.05 levels [11].

Results

Thirty cases of pediatric soft tissue sarcoma were

encountered in this study. Males constituted 53.5% of the cases (16 cases), while females constituted 46.7% of the cases (14 cases). History of consanguinity was present in 2 cases (6.7%).

The median age was 8 years (range 4-14 years). The most common site of involvement was the extremities (53.3%) followed by the trunk (20%). The retro-peritoneum, gastrointestinal tract and head and neck each had the same prevalence of (6.7%). The genitourinary tract and liver each had the same prevalence (3.3%).

The most common pathological subtype was fibrosarcoma (30%), followed by synovial sarcoma (20%) then malignant fibrous histiocytoma (10%), malignant peripheral nerve sheath tumors (10 %), liposarcoma (10%), leiomyosarcoma (10%), then haemangioendothelioma, angiosarcoma and undifferentiated sarcomas, all had the same prevalence (3.3%).

As regards stage; stage I constituted 6.7% of the cases (2 cases), stage II 46.7% (14 cases), stage III 36.6% (11cases) and stage IV 10% (3 cases). Three cases were metastatic at presentation. One case had isolated lung metastases, one had liver metastases and one had lung and brain metastases.

Seventeen cases were high-risk patients (56.7%) and 13 were low-risk patients (43.3%). Bulky tumors (>5 cm) were present in 11 cases (36.7%). Grade I tumors were found in 8 cases (26.7%), grade II in 8 (26.7%), grade III in 6 (20%) and grade IV in 8 (26.7%).

Surgical biopsy was performed in 10 cases (33.3%). Three of them were metastatic at presentation and 7 were locally advanced, 4 cases had incomplete surgery with microscopic or macroscopic residual tumor (13.3%) and complete surgery with clear safety margins in 16 cases (53.3%).

Fourteen of the patients whose tumours were completely resected with safety margins were low-grade and two were high-grade. From the low-grade patients only three were classified as high-risk and received postoperative radiotherapy, while eleven where classified as low-risk and received no adjuvant therapy. As for the high-risk patients; one received adjuvant radiation and chemotherapy (VACA) and the other received radiation therapy alone due to his poor performance status from co-morbid disease.

Three patients who had an incomplete resection with either microscopic or macroscopic unresectable disease were high-grade and received postoperative radiation and chemotherapy (VACA). The fourth patient had a low-grade tumor and received postoperative radiation only.

All seven patients who had an unresectable tumor were high-grade and all received neo-adjuvant chemotherapy in the form of Ifosfamide + doxurubicine; five of them were then amenable to surgery and were completely resected and received postoperative radiation therapy, two had an incomplete surgery and received also postoperative radiation therapy and one of them had progressive disease and received palliative radiation therapy (haemostatic).

Three patients were metastatic at presentation, they all received palliative chemotherapy (Ifosfamide + Doxorubicine) with variable primary responses and eventually disease progression. Only one case received palliative irradiation for brain metastases.

Seventeen patients received radiation therapy (56.6%). Five patients with totally resected tumors and four with incomplete surgery received radiation in an adjuvant setting. One patient with metastatic disease received palliative whole brain irradiation. The remaining seven patients received radiation therapy either as adjuvant after neo-adjuvant chemotherapy and surgery or as a palliative approach after chemotherapy.

Fourteen patients received chemotherapy (46.6%). Four received it as adjuvant treatment (VACA regimen), seven received it as neo-adjuvant (Ifosfamide + Doxorubicine) and three as palliative.

Response was assessed in fourteen cases: in whom the tumor was not excised with safety margins. CR was achieved in eight cases (57%), four of them were patients who had an incomplete resection with either microscopic or macroscopic disease, and the rest were primary unresectable tumors who had neo-adjuvant chemotherapy then surgery followed by radiation therapy. Partial remission on neo-adjuvant chemotherapy was seen in two unresectable tumors (14%), they were then operated upon and the two of them had volumetric macroscopic residual at end of surgery for which they were given radiation therapy with failure to achieve CR. Two cases (14%) had stationary disease, the first had an unresectable tumor and received chemotherapy and radiation therapy, and the second had lung metastasis. They both received second line chemotherapy and eventually had disease progression. Progressive disease occurred in 2 cases (14%), they were both metastatic, the first died just after beginning

second line chemotherapy and the second was lost to follow-up before receiving second line chemotherapy.

Relapse occurred in six cases (20%). One case relapsed locally and 5 cases relapsed distantly. As regards relapsed, stationary and progressed cases (12 cases), 1 case was lost to follow-up, 10 cases received second line chemotherapy; cisplatinum and etoposide, and 1 case received palliative radiation therapy.

The 5-year overall survival was 55.6% (Fig I). The 5 year survival for stages I and II and for stages III and IV was 77.78% and 11.11% respectively, the difference was statistically significant ($P < 0.001$). (Fig II). The 5-year survival for low-risk patients and high-risk patients was 92% and 26.7% respectively, the difference was statistically significant ($p = 0.001$) (Fig III). The 5-year survival in patients with bulky tumors (> 5 cm) was 20% versus 76% for non-bulky tumors. The difference was statistically significant ($p=0.0075$) (Fig IV).

The 5-year survival for grade I and grade II pathologies was 91.67% versus 26.67% for grade III and grade IV pathologies. The difference was statistically significant ($p = 0.001$) (Fig V). To emphasize matters; by multivariate analysis it has been concluded that tumor grade is the most important independent prognostic factor affecting survival with a 95% Confidence Interval. OR=14.14 (1.812-110.34).

After a 5-year period of follow-up 15 cases were alive free of disease (50%), 12 cases had died (40%) and 3 cases were lost to follow-up (10%).

As regards acute toxicity in patients receiving chemotherapy; grade I, grade II and III GIT toxicity was 14.2%, 14.2% and 7.1% respectively. Hepatic toxicity was observed in one case. Grade I myelosuppression developed in 8% of the cases, grade II myelosuppression in 20.5% and grade III myelosuppression in 14.3% of the cases. Grade II and III dermatitis occurred in 14.3% and 21.4% of the cases respectively; and was seen only in patients receiving radiation therapy.

Discussion

Males constituted about 53.5% of the cases and females 46.7%. This coincides with international literature [12].

In the present study the most common sites of involvement were the extremities (53.3%) followed by the trunk (20%). The retro-peritoneum, GIT, and head and neck each constituted 6.7% of the cases, then, the genitourinary track. This is in agreement with other studies as Portera [13] where the extremities constituted 44% of cases, followed by the trunk (20%), the head and neck in 12% and the retro-peritoneum in 8% of cases. It also agrees with what was reported by Vraa [12] where extremities were the most common site of involvement (30%) followed by the trunk (19%).

The most common pathological subtype in our study was fibrosarcoma (30%). This finding was also observed in most of the international literature [9,12].

As for the percentages of the different stages at presentation it conforms with international norms as in the study published by Skytting; stage I constituted 20%, stage II 52%, stage III 28%, and stage IV 10% of the cases [15].

In addition, in this work, surgical biopsy was performed in 10 cases, incomplete surgery in 4 cases and 16 cases underwent complete surgical excision, which resembles what is also seen in international standards [16].

In the present study, the 5-year survival for stages I and II was 91.67% and for stages III and IV it was 26.67%. This survival resembles the work of Ben Arush [9] where the 5-year survival for stage I was 87%, stage II 60%, stage III 32% and finally stage IV 17%. Moreover, Skytting [15] also obtained a 5-year survival for grade III disease of 41% and for grade IV disease of 27%.

The 5-year survival for bulky tumors was 20% versus 76% for non-bulky tumors, which also resembles international standards [19].

In our present study the toxicity of chemotherapy and radiation therapy was within acceptable ranges in comparison to those seen in other international publications [22].

The 5-year overall survival in this study is 55.6% which is less than the international standard that was seen in many of the published studies. For example; Skytting [15] obtained a 5-year survival rate of 69% and Callister, [17] obtained a 5-year survival of 72%. Portera [13] obtained a 5-year survival of 77% and Pratt [18] a 5-year survival of 73.3%. This difference in survival rates may be attributed to the delayed presentation of the patients to medical care leading to a bigger number of advanced bulky tumors at presentation. The unavailability of brachytherapy in our centre which helps providing higher localized doses of radiation to residual tumors and the poor performance and economical status of the patients which leads to chemotherapy treatment delay and

lag periods in radiation therapy also jeopardize treatment outcome.

Conclusion

The management of pediatric soft tissue sarcomas has improved markedly in comparison to the past. This has been achieved using multimodal combined therapy. Combining salvage surgery with adjuvant chemotherapy and radiotherapy (when indicated) with high precision to the tumor bed has resulted in much better tumor control and a consequent impact on the survival figures and the disease free survival values. Multimodality therapy not only has led to improved survival indices but has also resulted in better functional and cosmetic results as well. The ultimate goal is diagnosing the patient before the tumor becomes bulky, being an important prognostic factor. Non-bulky tumors have a better treatment outcome in comparison to bulky tumors.

With further clinical trials and improved radiation techniques such as brachytherapy, we expect to continue to optimize therapy for pediatric patients with soft tissue sarcomas [24].

Our ultimate goal is improving survival, minimizing acute toxic events and avoiding late effects as handicapping and deformity. We have to promote the importance of early diagnosis among local population through the media and the idea of prompt referral to specialized centers among family doctors, general practitioners, and physicians of other specialties. Early referral will help in decreasing the number of bulky and unresectable tumors and so improving survival regarding this disease in our Egyptian population.

In addition, improving cooperation between specialties in the same centers by forming specialized multidisciplinary combined clinics where oncologists, surgeons, radiologists, and pathologists see and discuss the cases together will help a lot in improving the multidisciplinary approach to the cases and decrease the time lost in inter-departmental referral.

Fig (1): Overall survival of 30 cases of pediatric soft tissue sarcoma.

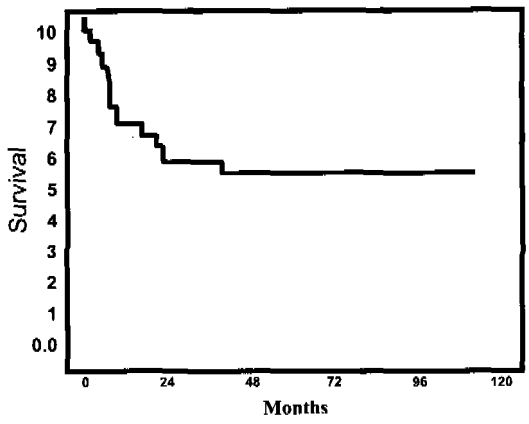


Fig (2): Overall Survival curves of both early and late stages

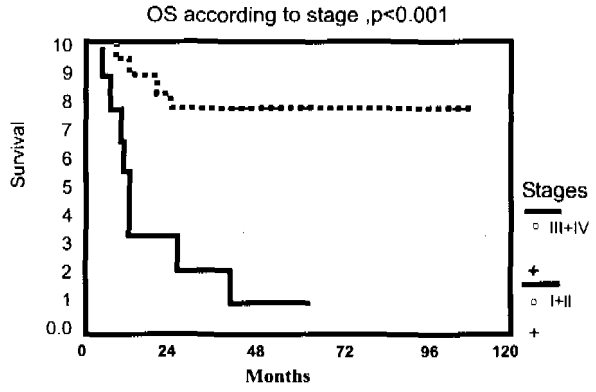
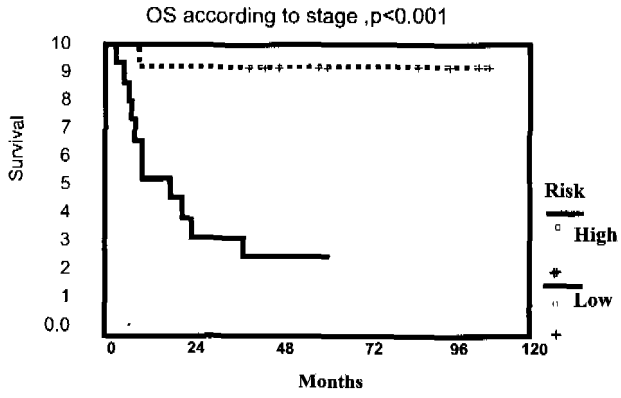
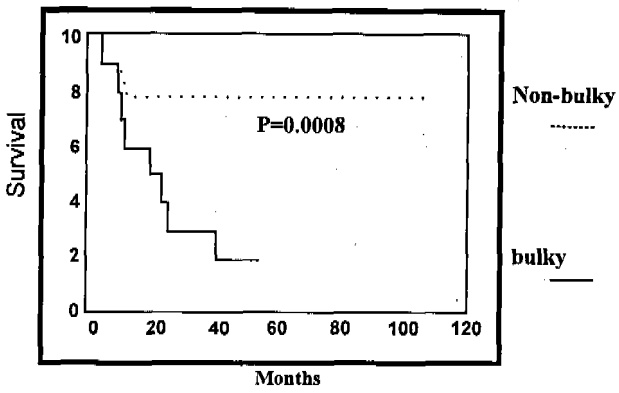


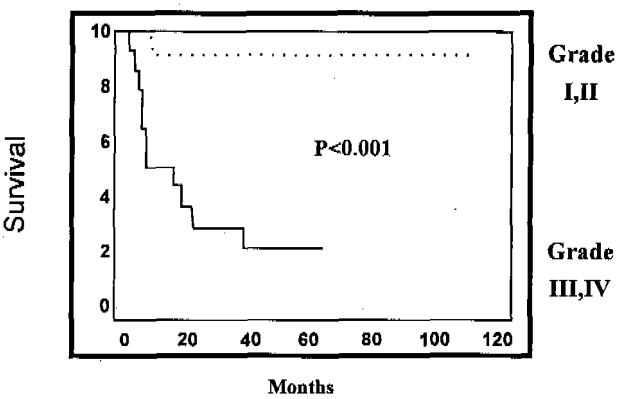
Fig (3): Overall Survival curves of both high and low risk stages



Fig(4): Overall survival curves according to tum or size



Fig(5):Overall Survival according to tumor grade



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