ABSTRACT

Purpose: Evaluation of demographic, pathological, and clinical patterns in addition to treatment outcome of pediatric NRSTS patients treated at the NCI, Egypt.

Procedure: 21 pediatric patients of NRSTS between 2001 and 2006 were included. Clinical and pathological diagnosis and subtyping verification were done. Patients’ cohort formed of 3 treatment groups. (1) Patients who underwent complete surgical resection with no adjuvant therapies. (2) Patients who received chemotherapy and complete surgical resection, and group (3) Patients with localized unresectable tumors for whom systemic chemotherapy only was given. Demographic, clinicopathological variables, and treatment modalities were statistically evaluated and compared with the outcome.

Results: Tumors of unknown histiogenesis followed by MPNST and myxofibrosarcoma were the most frequent tumor subtypes. Low tumor grade was in favor of better outcome. With a median follow up of 2-years; respectively 100% and 81.1% of patients who had complete surgical resection of a localized disease with or without chemotherapy entered in CR (p=0.01). Local failure rate was 27.2% among CR patients (n=17). Two patients suffered local recurrence and one had distant disease metastasis.

Conclusion: Complete surgical resection with or without chemotherapy is the mainstay of therapy for localized NRSTS. Tumor grade and surgical resection of NRSTS are 2 important predictors of prognosis.

Key Words: Nonrhabdomyosarcoma – Soft tissue sarcoma – Pediatric.

INTRODUCTION

Nonrhabdomyosarcoma soft tissue sarcoma (NRSTS) is a heterogeneous group of mesenchymal origin tumors accounting for 3-5% of all cancers under age of 20 years [1,2]. Incidence is higher in adolescents, but infants characterized by distinctive types like infantile fibrosarcoma and malignant hemangiopericytoma have a relatively benign course and much better prognosis [2,3]. Diagnosis of each subtype was an area of disagreement and controversy before the advent of immunohistochemistry and sarcoma-specific chromosomal translocation [4]. Rhabdomyosarcoma (RMS), primitive neuroectodermal tumor (PNET), and extraosseous Ewings sarcoma are segregated from NRSTSs [5]. While age at diagnosis was considered to be one of the prognostic factors by some investigators, yet the established ones have included tumor grade, invasiveness, size, and intergroup rhabdomyosarcoma (IRS) group [1,6,7]. Wide surgical resection for localized disease remains-being relatively chemoresistant- the goal in all NRSTS tumors. Upfront resectability found to be an independent prognostic factor in many trials [6,8,9]. However, more conservative, and function-preserving surgery with or without radiation should be attempted [10]. The aim of our study is to trace the demographic, pathologic, and clinical patterns in addition to treatment outcome of that set of unusual pediatric tumors (NRSTS) at a specified time interval.

PATIENTS AND METHODS

In this study, data of 21 pediatric patients diagnosed as nonrhabdomyosarcoma soft tissue sarcomas were reviewed. Patient’s has been treated between 2001 and 2006 at the Pediatric Oncology Department, NCI-Cairo University.
Sample included patients of either sex between 0 and 18 years old with a confirmed diagnosis of NRSTS (RMS, PNET, and extraosseous ES were not eligible). Every eligible patient should have had a complete medical record as well as paraffin tissue block available before enrollment. Patients were considered not evaluable and consequently not candidates for the study if they received whole or part of their treatment elsewhere but the NCI.

Clinical assessment:

Patient characteristics, data of disease presentation, treatment modalities as well as post treatment status till last follow-up date were abstracted from patients' medical records. Primary tumor site, size, invasiveness, and both regional and distant metastasis as well as work up studies (local CT/MRI, chest radiographs and CT, Tc$^{99m}$ bone scan, abdominal US, bone marrow (BM) aspiration/biopsy ± others, accordingly) were interpreted. Tumor topographic distribution was classified into 2 main groups arising from: Either extremity; or non extremity; including the trunk, head and neck structures. Tumor size was also divided according to its maximal diameter into ≤5cm Vs. >5cm. Loco-regional invasiveness included intra–compartmental and extra-compartmental tumors with the former restricted to the anatomical compartment of origin and the latter spreading beyond their anatomical compartment of origin. Disease staging was done according to the Clinical International Union Against Cancer Staging System For Pediatric Soft Tissue Tumors [3].

Pathological parameters:

Pathological diagnosis and subtyping verification were reviewed and looked into by 2 pathologists:

I- Histopathology:

Hematoxylin and eosin (H&E) 5 micron stained sections were prepared from tissue specimens to evaluate the following 5 objectives for each of the studied samples: 1-Confirming malignancy, 2-Histologic subtyping, 3-Tumor histopathologic grading according to the Pediatric Oncology Group Histologic Grading System [4], 4-Histopathologic evaluation of surgical margins for 19 excised specimens. Histopathologic tumor typing was performed according to the WHO soft tissue sarcomas classification standards [11], that included eight major groups namely; fibro/myofibroblastic sarcomas, lipomatous sarcomas, fibrohistiocytic sarcoma, myogenic sarcomas, vascular and perivascular sarcomas, neurogenic sarcomas, extraskeletal soft tissue osteo-chondroid sarcomas, and sarcomas of unknown histiogenesis.

II- Immunohistochemistry:

Immunohistochemical studies were performed with the following perspectives; tumor inclusion in the study was according to +ve vimentin immunohistochemical reactivity in all 21 cases, actin (clone HHF-35, DAKO) was utilized to exclude RMS in myogenic tumors and confirmatory of leiomyosarcoma, whereas cytokeratin (pan) (clone 12E7, 34βE12) positive and CD99 (clone 12E7) negative reactions were considered exclusive for PNET in cases of diffuse round cell tumor [13]. Only positive vimentin cytoplasmic immunohistochemical reactivity was considered confirmatory for the mesenchymal origin of the tumor. In leiomyosarcoma, actin positive cytoplasmic immunoreactivity was exclusive for RMS. Both cytokeratin (pan) positive cytoplasmic and CD99 negative reactions were considered exclusive for PNET [12]. Standard immunohistochemical methods were adopted [13], and tissue sections were routinely microwave-treated to unmask the epitopes of the antigen. The primary monoclonal antibodies used were all “DAKO” products and the following universals were used; Ultravision detection system (Labvision) and LSAB-2 system (DAKO). Diaminobenzidine (DAB) was used as a chromogen since it allows a permanent reaction. The autostainer TTS030f (DAKO) was employed for all immunohistochemical studies in order to minimize human technical errors. Positive controls for the biomarkers included: Normal smooth muscle tissue for both actin (HHF-35) and vimentin reactivity, while normal skin was considered a reliable positive control for cytokeratin (pan) immunoreactivity. A case of PNET was used as a positive control for CD99 reactivity.

Treatment strategies:

Patients in this study were allocated into 3 groups based on the given treatment modalities; group (1) – Patients with localized resectable tumor that underwent complete surgical resection with no adjuvant therapies (n=8), group (2) – Patients with resectable tumors that received systemic chemotherapy after upfront
complete excision for high grade and large sized tumors (n=11), and group (3) – Patients with localized unresectable (n=2) disease; for which chemotherapy only was given. Second look operation was not attempted in any of those patients. Operable cases in our series were stage 1-2, for which wide local excision with adequate margins was done. Incomplete resection (debulkig or biopsy only) was indicated when complete excision short of major morbidities and/or disabilities was unavoidable. Systemic chemotherapy was in form of anthracycline based regimens combined of: Vincristine, doxorubicin, cyclophosphamide, actinomycin D, etoposide, ifosfamide, and platinum compounds. High dose methotrexate was additionally given to extraosseous osteosarcoma (EOO) patients. Radiotherapy was given to 2 patients with postexcisional positive surgical margins and high histologic grade as part of their local control.

Follow-up of disease and response to treatment:

Studied patients were followed-up since presentation and throughout their first line of therapy at the NCI. Patients who received no systemic therapy after complete surgical resection entitled as disease free until an event of either local or distant failure was documented. Chemotherapy response was assessable every 2-3 cycles during their active treatment then with post-therapy follow-up visits. Response evaluation was according to the Response Evaluation Criteria in Solid Tumors (RECIST); defined as complete response (CR), partial response (PR), stable disease (SD) or, progressive disease (PD) \[14\].

Data management and statistical analysis:

Patients data were tabulated and processed using SPSS version 15 for analysis. Simple frequencies were used for data checking. Percentages were used for summary of categorical variables, while descriptive statistics were used for summary of quantitative continuous variables. Associations between categorical variables were examined using Chi Square/Fisher’s exact test. A “p” value <0.05 was used for detection of statistical significance in all tests.

RESULTS

Total of 12 males and 9 females (M/F=1.3:1) were eligible, their median age was 10.5 years (0.3-16 years). Fourtien patients had stage 1 disease Vs. 5 with stage 2, and 2 with stage 3. According to the “upgraded WHO classification standards”; the seven histopathological groups were represented in the study (Table 1). Main 3 tumor subtypes tumors of unknown histiogenesis including synovial sarcoma, (23.8%), followed by both neurogenic sarcomas (MPNST), and fibro/myofibroblastic sarcomas (myxofibrosarcoma) (19.0% each). All 21 cases showed positive cytoplasmic immune reactivity for vimentin. Three tumor cases showed positive actin cytoplasmic immunoreactivity, confirmatory of leiomyosarcoma (Fig. 1). Two cases were diagnosed as desmoplastic round cell tumor (DRCT) confirmed by cytokeratin positive cytoplasmic reaction (Fig. 2) and CD99 negative immunoreactivity which excluded PNET. Patients have been followed-up for a mean duration of 24±17.2 (4.1-57.8) months, during which all patients were alive with 15 of them (71.4%) free of disease (AF) Vs. 6 (28.5%) with disease (AD).

Fig. (1): Actin (HHF-35) positive cytoplasmic immunoreactivity in leiomyosarcoma section (x40).

Fig. (2): Cytokeratin (pan) positive cytoplasmic immunoreactivity in a case of DRCT (x40).
Correlations of the outcome among different treatment groups (Table 2) showed that; the 8 patients (100%) in group (1) Vs. 9 out of 11 (81.8%) in group (2) and none of group (3), entered into "CR" in response to their first line of therapy \( (p=0.01) \). After 2-years of follow-up; 6 out of 8 (75%) patients in group (1) and 9 of 11 (81.8%) in group (2) remained "AF". On the other hand the 2 patients in group (3) stayed "AD", (100%) \( (p=0.14) \).

Three of the 17 patients attained post therapy "CR" had disease recurrence. Two of them belonged to group (1) and developed local recurrence of synovial sarcoma, both characterized by high grade and tumor size >5cm at initial presentation, creating a local failure rate of 17.6%. The third case was an EOO patient under group (2) who had distant failure in form of lung metastasis. No statistical difference found between the 2 mentioned groups as regards disease recurrence \( (p=0.56) \).

A battery of correlations was done to test significance of epidemiological and tumor related factors (Table 3). Of the total study subjects; 19 patients (90.4%) underwent complete gross resection of their primary tumors; positive Vs. negative surgical margins had no effect on the outcome. Tumor grade; though did not show statistical significance in correlation with treatment response \( (p=0.13) \), low grade disease was in favor of better outcome in terms of final disease status \( (p=0.04) \) but not with recurrence rate \( (p=0.22) \). None of age, sex, or tumor size was significantly correlated with any of; post therapy status or final outcome. Another 2 variables (invasiveness and site of the primary tumor) statistically were also insignificantly correlated with the tested parameters despite noticed numerical difference.

<table>
<thead>
<tr>
<th>Table (1): Histopathological subtypes, distribution, and corresponding patients' status.</th>
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<td>WHO Group</td>
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<tr>
<td>1- Tumors of Unknown Histiogenesis:</td>
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<tr>
<td>2- Fibro/Myofibroblastic Tumors:</td>
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<tr>
<td>3- Neurogenic Sarcomas:</td>
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<tr>
<td>4- Myogenic Sarcomas:</td>
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<td>5- Lipomatous sarcomas:</td>
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<td>6- Extraskeletal Osteo/Chondroid soft tissue sarcomas:</td>
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<td>7- Fibrohistiocytic sarcomas:</td>
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<table>
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<th>Table (2): Correlations of different treatment groups to disease status and outcome.</th>
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<td>Treatment Modality</td>
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<tr>
<td>1- Complete surgery alone</td>
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<tr>
<td>2- Complete surgery plus chemotherapy</td>
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<td>3- Inoperable/incomplete surgery plus chemotherapy</td>
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\( p \)-value: 0.01 0.14 0.56
DISCUSSION

While in adults liposarcoma, malignant fibrous histiocytoma (MFH), and leiomyosarcoma are routinely among the top five [15,16], synovial sarcoma followed by MFH are the commonest histological subtypes in children [17,18]. In other reports MPNST has followed synovial sarcoma in frequency [7,18,19]. Extremities are known to be the most common primary sites of primary tumors followed by trunk areas [20,21]. In our series the most frequent histologic types were sarcomas of unknown histiogenesis (including synovial sarcoma), MPNST, and myxofibrosarcoma. Extremity location of the primary tumors constituted 57.1% of the cases, and the non-extremity sites affected 42.8% of the patients under study.

Owing to rarity of the disease subtypes and lack of prospective randomized trials, no comparison was systematically done for different treatment approaches. However as many of tumors were scarcely chemosensitive, surgery with adequate clear margins remained the mainstay of therapy. Role of primary reexcision has also been made clearer. Thus gross total resection is to be attempted with aggressive effort at time of diagnosis and NRSTS is considered unresectable when wide, non-mutilating resection is not feasible based on clinical and radiological evaluation [22]. Children with completely resected tumors ± radiotherapy approached 90% 5-year survival in some series [6]. With 70% are expected to be cured [6,22].

Over the past 25 years, extensive effort has also been directed toward determining whether anthracycline-based adjuvant chemotherapy offers a clinically meaningful benefit in patients with localized soft-tissue sarcoma [10]. In an earlier study, POG trial addressed this question by giving V AD alternating with V AC every 3 weeks till week 31 followed by V AC only till week 50 to a group of children with resected NRSTS, it didn’t improve the outcome [22]. A summary of the second-generation randomized adjuvant chemotherapy trials is provided. These studies generally included more modernized chemotherapy (formed of: Epirubicin single agent, epirubicin + ifosfamide, doxorubicin + ifosfamide + dacarbazine) than those agents used in earlier-generation adjuvant chemotherapy trials performed in the 1970s and 1980s.
None of the trials demonstrated any statistically significant impact of adjuvant chemotherapy on overall survival. None of the mentioned regimens had superiority over observation only [10]. A positive margin was also a prognosis predictor that indicates increased local recurrence [6]. Chemotherapy has been shown not to benefit local control in patients with involved margins [1].

Consistently, our data also confirmed the role of complete surgical resection with or without chemotherapy which strongly correlated with patients’ response to treatment. Patients who had complete surgical resection of their locoregional disease ± chemotherapy have shown a distinctive improvement in response to therapy compared to others who had not. Collectively, 80.9% of the 2 groups (1+2) went into “CR” by end of their therapy Vs. none of group 3 (p=0.01). No statistical significant difference was found between different treatment modalities and outcome (p=0.14).

Though 75% of group (1) Vs. 81.8% of group (2) patients remained ”AF” at 2 years with 2 cases of recurrent disease in group (1) and only 1 case in group (2), this did not reflect a statistical significance (p=0.56). Again, in accordance with most of literature there is no superior outcome if patients receive chemotherapy following complete surgical resection for a localized disease.

Surgical margins on the other hand, did not statistically show influence on the outcome in this study even with all 3 cases of disease recurrences were on the negative margins side (Table 3). However, small sized patients sample should always be taken in consideration.

Radiotherapy was also found to improve local control. Its indications vary according to tumor grade, histiotype, size, location, extent of resection, and other clinical factors including the overall plan). In adults radiation may not be required if resection margins is >1cm. Data are limited in children on the indication for radiation based on the extent of the surgical margin. Data coming from St. Jude hospital revealed that in high grade tumors with resection margins <1cm adequate local control was achieved in 5 of 7 not treated with radiation and in 7 of 7 received postoperative radiotherapy. On the other hand, 15 of 20 (75%) high grade completely resected tumors with margins >1cm had maintained local control for extended periods of time without postoperative radiation [3]. Except for small superficial tumors in very young patients with >0.5cm margin of resection radiotherapy is currently recommended to high grade tumors that are resected completely unless convincing margins have been demonstrated. Also local radiation is given to high or intermediate grade tumors with positive, inadequate, or indeterminate margins regardless of its size or anatomic location. Low grade tumors are irradiated only when risk of recurrence and resection morbidity is high or on recurrence [3,23]. From our data no impression can be taken since radiotherapy was beyond analysis being given to only 2 patients till closure of this study. Some patients with high grade tumors or positive margins have not had radiotherapy due to one or more reasons such as; young age, delayed radiation timing by protocol of therapy, lack of consensus about the indication in some instances.

Higher tumor grade was found to have poorer outcome correlation in NRSTS [4,22,24]. While tumor size >5cm alone was associated with increased local recurrence rate [25,26], considered together, tumors with large size and high grade were considered to have the greatest risk of poor outcome [18]. This can virtually explain why patients with grade 3 tumors and >5cm are candidates for adjuvant chemotherapy [5]. Moreover tumor invasiveness (invading bone or neurovascular structures) has also carried a prognostic significance as infiltrating tended to do worse than non infiltrating tumors [6,26]. Similarly, we also found clear significance for histological grade in correlation with final disease status. Eight of 9 patients with grade 1 tumors Vs. 7 of 13 with grade 3 were ”AF” (p=0.04). Despite insignificant ”p” value (0.22), 3 out of 9 patients (33.3%) with grade 3 tumors who attained ”CR” developed recurrence later on, while all of the 8 patients of grade 1 disease were still in ”CR” with failure rate of 0.0%. This evidence also agrees with the POG trial published in 1999; which considered tumor grade as the most important predictor of clinical outcome in patients with resected NRSTS and its incorporation into patients’ risk stratification was recommended [22]. On the other hand, though our data didn’t show such significant role neither for tumor size nor invasiveness
from the statistical point, yet we found an increased proportion of patients with disease recurrence (3 of 16) among patients with big tumor size (>5cm) compared to others (0 of 5) whose tumors were <5cm. As well for tumor invasiveness; 13 of 15 (81.6%) with intra- compartmental Vs. only 4 out of 6 (66.6%) with extra compartmental tumors attained "CR" ($p=0.54$), besides 2 of the former and one of the latter had recurrence ($p=1.0$).

Tumor primary site also showed an observed numerical difference. Among extremity located tumors (n=12) 83.3% went into "CR" Vs. only 77.7% of the non extremity ones (n=9; 8 trunk & 1 scalp tumors). However this difference was even lost later when 66.6% and 77.7% were respectively "AF" with 3 cases of recurrent disease among the former group; "p" value was always insignificant.

In conclusion; complete surgical resection with or without chemotherapy is the mainstay of therapy for localized NRSTS. Tumor grade and complete surgical resection of NRSTS are 2 important predictors of prognosis. Futural well designed and prospective trials are required, however their design is likely to be complex because the need for large sample sizes for such a rare disease especially if it is going to be histology specified. Some new medications are in their way to be introduced into practice. As an example, epidermal growth factor receptor which is over expressed in high grade MPNST constitutes a potential target for new therapies [27].

REFERENCES


