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SOFT TISSUE SARCOMA IN CHILDREN CLINICAL BEHAVIOUR , OUTCOME AND MANAGEMENT

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ABSTRACT

Background:

Soft tissue sarcoma are the fifth common solid tumours in children, account for 7 % of all childhood malignancies. They have great differences in histology , distribution and response to therapy .

Aim of work:

Is to evaluate the clinical behaviour and outcome of pediatric soft tissue sarcoma (PSTS) and to give a suggestion about the prior line of treatment for such type of cancer .

Patients and methods:

From January 1995 to December 2000, 21 children with definitive diagnosis of primary soft tissue sarcoma, at different tumour stages and sites, were admitted and treated in Surgery Department, Sohag University Hospital, South Valley University. They were stratified as groups I, II, III & IV according to the post-surgical grouping system of the Inter-group Rhabdomyosarcoma Study (IRS) and classified as rhabdomyosarcoma (RMS) and nonrhabdomyosarcoma soft tissue sarcoma (NRSTS) with respect to the histology. Treatment plan included surgery, chemotherapy and radiotherapy. Surgical descions varied between wide local excision, local excision. debulking, amputation and biopsy. Reconstructive surgery included primary closure, rotational flap, primary Theirsh grafting and lay-opened with delayed grafting .

Results:

RMS was diagnosed in 10 patients (47.6 %) whereas diagnosis of NRSTS was present in 11 patients (52 : 4 %) without statistically significant differences. A highly statistically significant differences were recorded between patients with RMS and NRSTS counterparts with respect to median age at presentation (10.3 years versus 7.3 years respectively; p = 0.011), median tumour size (7.8 × 5.2 cm versus 9.1 × 6.4 cm respectively; p = 0.013), tumour grade (high in 100 % versus 45.5 % respectively; P = 0.021), regional lymph node involvement (70% versus 18.1 % respectively; P = 0.009) and distant metastasis (60 % versus zero % respectively, P = 0.0003). In advanced groups(III & IV) of RMS and NRSTS, the use of palliative resection, debulking and amputation combined with radiotherapy and / or chemotherapy ; had failed to show significant improvement in survivals whereas wide local

excision alone or combined with chemotherapy and / or radiotherapy had a success rate of 100 % & 60% in groups I & II respectively. Infantile fibrosarcoma, malignant heamangiopericytoma in young children had the best prognosis. The trunk and retroperitoneum had the poorest prognosis among all sites of presentation.

Conclusion:

RMS is a highly aggressive neoplasm that tends to metastasize early in the course compared with NRSTS . NRSTS have different clinical behaviour depending on the age of presentation. Infantile fibrosarcoma and malignant heamangiopericytoma in young children are typically less agressive , rarely metastasize neoplasms. Treatment as defined by the IRS protocols is acceptable. Wide local excision with pathologically proven safety margins is the treatment of choice. Preoperative chemotherapy is of benefit in cases with extended tumours to achieve tumour regression. Postoperative chemotherapy and radiotherapy are the primary mode of treatment in incompletely resceted, irresectable and metastasizing tumours. The prognosis in infants and children with NRSTS is much favorable than in older children with similar diagnoses.

INTRODUCTION

Pediatric soft tissue sarcomas (PSTS) are a group of malignant tumours that originate from primitive mesechymal tissue and account to 7 % of all children tumours (Pappo & Pratt, 1997). Rhabdo-myosarcomas (RMS), tumours of striated muscle account for about half of these tumours whereas nonrhabdomyosarcoma soft tissue sarcoma (NRSTS) account for the remainder (Miser *et al.*, 1997) .

NRSTS includes neoplasms of smooth muscle (fibrous and adipose), vascular tissue (blood and lymphatic vessels), and the peripheral nervous system (Enzinger & Weiss, 1995). Synovial sarcomas, fibrosarcomas, and neurofibrosarcomas predominate in pediatric patients (Rao, 1993). PSTS arise most commonly in the trunk and extremities and many are quite large by the time of diagnosis (Marcus *et al*, 1997). The clinical behaviour of RMS is much different than NRSTS (Grouch *et al.*, 2003) . RMS is a highly malignant and locally invasive neoplasm that tends to disseminate rapidly early in the course and occurs in older children and adolescents (Walterhouse *et al.*; 2001). The embryonal variant of RMS commonly metastasize to the regional lymph nodes and has a relatively better outcome than the alveolar and pleomorphic variants (Hussein *et al.*, 1994). On the other hand the prognosis in patients with NRSTS depend on the age of the patient, tumour site, tumour size, tumour invasiveness, histologic grade, depth of invasion and extent of the disease (Dillon *et al*, 1995 & Marcus *et al*, 1997) .

The two commonest pitfalls in management of PSTS are failure of early diagnosis and inadequate surgical treatment. This type of cancer is often mistaken for benign lesion leading to diagnostic confusion (Miser *et al*, 2002). For preoperative diagnosis , magnetic resonance imaging (MRI) is considered the modality of choice for evaluation of the disease in the extremities, head & neck and pelvis (Lee, *et al*.. 1996 & Marcantonio, *et al*., 1998 and Kaste *et al*., 2002). Definitive diagnosis require a properly planned biopsy for histologic and immuno-histochemical studies (Ceccetto *et al*., 2001). Improper biopsy may violate anatomic compartemental boundaries or may contaminate vital structures, such as the neurovascular bundle (Grouch *et al*., 2003). Therapeutic strategies for PSTS are different to those for adult in that the biology of the primary tumour is quite different , limb-sparing procedures are more difficult to perform in pediatric age and the morbidity of radiation therapy in young children may be much greater than in adults (Miser *et al*., 1997). Treatment options depend on whether the cancer has spread or the amount of tumours left after surgery (Neville *et al*., 2000). So, the aim of this study , is to evaluate the clinical behaviour and outcome of PSTS and to give a suggestion about the prior lines of treatment for such type of cancer .

PATIENTS AND METHODS

This study was undertaken for all children with definitive diagnosis of primary soft tissue sarcomas, presented to Sohag University Hospital , South Valley University, in the period between January 1995 and December 2000. A total of 29 patients were admitted during this period. Of these, 5 patients were referred simply for ongoing management, having had primary treatment at other institution and we didn't have sufficient data in a further 3 patients after leaving the hospital. These patients (n = 8) were excluded, reducing the study population to 21 patients. The presenting symptoms and its duration before the diagnosis was made, were recorded for each patient on admission. Other tumours that cause masses in children such as benign lesions (e.g lipoma) , lymphosarcoma , osteosarcoma and Ewing's sarcoma were also excluded from our study .

Dianostic work – up:-

Diagnostic work – up started with an adequate physical examination , especially with regard to the tumour region.

Complete blood picture, liver and , renal function tests were assessed to provide basline parameters prior to chemotherapy and to evaluate for bone marrow and hepatic involvement. Radiographic examination included a conventional x-ray of the tumour to differentiate between a primary osseus lesion and a primary soft tissue lesion followed by C.T scanning and / or ultrasonography to determine the size of the mass and the extent of local involvement. In 1998 , MRI became available in our location and it was the imaging technique of choice for evaluation of the tumour region. The presence of metastatic disease was examined by pulmonary x-ray and , if necessary , followed by pulmonary C.T scan. Bone surveys were performed to rule out bone metastasis .

Tissue diagnosis was established either by excisional biopsy , a properly planned incisional biopsy (taking into consideration obviating the risk of local implantation thus facilitating the need for wide surgical excision) or by radiology guided core biopsy. For pathological identification and differentiation of NRSTS different immunohistochemical stains have been used including vimentin, desmin, cytokeratin in addition to vascular endothelial factor (CD 34). Sarcomas were classified as low grade and high grade according to the degree of anaplasia and mitotic activities .

Staging classification :-

Tumour extent was assessed according to both the clinical pretreating staging system (TNM) of the International Union Against Cancer (Harmer., 1982) and the post-surgical grouping system of the Intergroup Rhabdomyosarcoma Study (IRS) (Maurer *et al.*, 1988). The TNM definition , T_1 lesion referred to the organ or tissue of origin, while T_2 lesions invaded contiguous structures, T_1 and T_2 were further classified as A or B according to tumour diameter < or > 5 cm, respectively. Regional involvement was designated as N_1 (no node involvement , No), distant metastasis at onset as M_1 (no metastasis, Mo). After initial surgery, patients were classified according to the IRS system into 4 groups : group I included completely – excised tumour , group II indicated grossly resected tumours with microscopic residual disease , group III included patients with gross residual disease after incomplete resection or biopsy, group IV comprised patients with metastasis at the onset .

Treatment :-

Our treatment plan included surgery, rathiotherapy and

chemotherapy. Treatment options depended on tumour extent (localized & metastatic) , tumour location , histologic type (RMS & NRSTS) , and tumour grade. Treatment strategies didn't change substantially over the years .

Surgery :-

Complete resection was defined by the intent of the surgeon and the ability to excise all macroscopic disease and has histologic margins free of tumours (Karakousis *et al* , 1995). Wide local excision, three dimentional in scope to obtain clear tissue margins in all directions was the mainstay of our treatment. Re-excision of the affected area , was performed when the margins were positive or an excisional biopsy was obtained for unsuspicious superfacial lesion .

In extremity tumours , the decision to treat the patient by amputation was taken when wide local excision of the affected area leaves little functional potential. The amputation site was above the joint of the involved muscle groups. In head and neck , some relatively small tumours were upstaged because of its invasion to the vital neurovascular structures proved by C.T scan or MRI. Surgery alone was considered curative in group I patients with low grade NRSTS. Adjuvant chematherpy and / or radiotherapy were indicated in microscopically positive tumour margins (group II), high grade sarcoma and rhabdomyosarcoma.

When resection became impossible without leaving gross residual (group III), surgical descision varied between biopsy, palliative resection and amputation depending on the site of the primary tumour. Patients were deemed as having unresectable disease if they had distant metastasis, peritoneal implants or extensive neurovascular invasion (group IV) .

Lymphadenectomy was performed only when clinically positive lymph nodes were present. Reconstructive surgery varied between primary closure, primary Theirsh grafting, rotational flaps and lay-opened with delayed grafting.

Radiation:-

Radiotherapy was given to patients considered at high risk of local relapse due to microscopically (group II) or macroscopically (group III) positive resection margins and in high grade sarcomas. In advanced disease (group IV), postoperative radiotherapy was the primary mode of treatment to achieve local tumour control. External beam radiation was administrated with conventional fractionation (180 cGY / day)

for a total dose ranging from 3500-5500 cGY. The radiation target volume included the initial mass bed plus 2-3 cm margins and the surgical scar as well .

Chemotherapy:-

Preoperative chemotherapy was given to patients with large-sized and retroperitoneal tumours to induce tumor regression prior to surgical resection. Postoperative chemotherapy was given to all patients with RMS , debulking procedures and metastatic disease. A multiagent chemotherapy was administrated in the form of VAC regimen (vincristine 1-5 mg /m_2/I.V ; adriamycin 30 mg / m_2 / I.V and cyclophosphamide 2.0 gm / m^2 / I.V) .

Follow – up:-

Patients were called for follow – up by sending letters to their pairents or their relatives. They were evaluated for local and distant relapses. Local recurrence was defined as a diagnosis of tumour within or contiguous with the previously excised field > 3 months after primary resection (Pappo & Pratt, 1997). Follow–up started from the day of therapy and December 2003 or death of the child was considered the closing date of follow – up .

End results and data analysis :-

The acturial overall and disease – free survival rates were calculated by Kaplan – Meir methed , 1958 at 3 – years survival probability and comparisons were made by the Wilcoxon long rank test .

RESULTS

Between January 1995 and December 2000, 21 children with primary soft tissue sarcoma at different tumour stages and sites were admitted and treated in Sohag University Hospital , South Valley University. Ten patients (46.6 %) had confirmed diagnosis of RMS, whereas 11 patients (53.4%) had NRSTS without statistically significant difference (P = NS) .

Rhabdomyosarcomas:-

The clinicopathologic characteristis, treatment and outcome of the 10 patients who were diagnosed as RMS are present in table (1).

Table (1): Shows the clinicopathological characteristics, treatment and outcomes of patients with RMS (n=10).

No	Age in years	Sex	Tumour site	Tumour size (cm)	TNM	IRS	Histologic type	Grade	Operative procedure	Chemotherapy		Adjuvant radio therapy	Outcome
										Pre.	post		
1	13		Trunk	8 x 5cm	$T_2B/N_1/MI$	IV	Embryonal	High	Biopsy	-	+	+	D.O.D, 7 months
2	1/12		Left foot	7x5cm	$T_2B/NI/MI$	IV	Congenital alveolar	High	Biopsy	-	+	-	D.O.D, 2 months
3	14		Right dorsal aspect of the hand extended to the forearm	8x6cm	$T_2B/NI/MI$	IV	Alveolar	High	Above elbow amputation, L.N dissection	-	+	+	D.O.D, 10 months
4	11		Trunk	9x6cm	T_2 B/No/Mo	III	Embryonal	High	Local excision lay opened delayed grafting	+	+	+	D.O.D, 18 months
5	4		Head & neck	6x5cm	$T_2B/NI/MI$	IV	Embryonal	High	Biopsy	-	+	+	D.O.D, 12 months
6	12		Left palmar hypo thenar	9x5cm	T1B/NI/MI	IV	Pleomorphic	High	Biopsy	-	+	+	D.O.D, 10 months
7	13		Left medial thigh	7x4cm	$T1B/N_1/MO$	III	Embryonal	High	Local excision, L.N dissection, delved grafting	+	+	+	D.O.D, 21 months
8	10		trunk	8x4cm	$T_2B/NI/MI$	IV	Embryonal	High	Biopsy	-	+	+	D.O.D, 9 months
9	12		Retroperitoneal	12x9cm	$T_2B/NO/Mo$	III	Embryonal	High	Debulking	+	+	-	D.O.D, 14 months
10	14		Left anterior thigh	4x3cm	$T_1A/NO/Mo$	II	Embryonal	High	Wide local excision, primary closure	-	+	+	NEOD, 37 months

L.N dissection= Lymph node dissection . D.O.D= Died of disease . NEOD= No evidence of disease .

There were 6 boys (60%) and 4 girls (40%) with male to female ratio 1.5 : 1 without statistically significant difference (P = NS). Mean age at the time of presentation was 10.3 years (range one month – 14 years). Median period of follow-up was 15.9 months (range 2-37 months). The commonest sites involved by the disease were the extremities (50%, n = 5) followed by the trunk (30%, n = 3). Head & neck and retroperitoneal RMS were equally recorded in this series (one patient for each ; 10 %). All patients presented with mass or swelling of the affected area. One patient (case, 2) presented with metastatic raised skin lesions at birth and 2 patients presented with metastatic symptoms (Jaundice in one and heamoptosis in another) .

The mean duration of symptoms was 4.5 months. Tumour size varied between 4-12 cm in length × 3-9 cm in width (median size 7.8 × 5.2 cm) radiologically. The preoperative staging criteria (TNM) showed that 6 (60%) out of the 10 patients , had distant metastasis at the onset reflecting the aggressive nature of the disease.

Regional lymph node involvement were recorded in 7 patients (70%). Moreover, the IRS grouping system showed that of those patients who had localized RMS, 3 (30%) were staged as group III, and one case only (10%) was staged as group II . Embryonal carcinoma was the predominant histologic variant recorded in this series (n = 7 ; 70%) followed by alveolar (fig. 3) (n = 2; 20%) and pleomorphic variants (n = 1 ; 10%). Histologic grading of RMS showed that all cases (100%) had high grade sarcomas.

Nonrhabdomyosarcoma soft tissue sarcomas (NRSTS):-

Table (2) shows the clinicopathologic characteristics, treatment and outcome of the 11 patients who were diagnosed as NRSTS. There were 6 boys (54.5%) and 5 girls (45.5%) with male to female ratio 1.2 : 1 without statistically significant difference. Median age at the time of presentation was 7.3 years (range 3 months-12 years). Median period of follow–up was 41.8 months (range 16-90 months). The lower limb was affected in 4 patients (36.3 %), the upper limb in 3 (27.2 %) , the trunk in 2 (18.1 %), the head & neck in one (9%). and the retroperitoneum in one (9%). All patients presented with a mass or swelling of the affected region and one patient (patient , 6) also had an associated congenital anomoly in the form of complete cleft palate. The mean duration of symptoms was 5.3 months. Tumour size varied between 3-20 cm in length x 3-11 cm in width (median size 9.1 x 6.4 cm) radiologircally. The

Table (2): Shows the clinicopathological characteristics, treatment and outcomes of patients with NRSTS (n=11).

No	Age in years	Sex	Tumour site	Tumour size (cm)	TNM	IRS	Histologic typr	Grade	Operative procedure	Chemotherapy		Adjuvan radio therap	Outcome
										Pre.	post		
1	10		Left popliteal fossa	8x6	$T_1B/NI/MO$	III	Synovial sarcoma	High	Local excision , L.N dissection, delayed graling	-	+	+	D.O.D, 22 m.
2	11		Right posterior leg	12x10	$T_2B/NO/MO$	III	Synovial sarcoma	High	Biopsy	-	+	+	D.O.D, 16 m.
3	8		Left posterior thigh	4x3	$T_1B/NO/MO$	I	malgnant fibrous histiocytoma	low	Wide local excision , primary closure	-	-	-	D.O.D, 40 m.
4	9		Left buttock	20x12	$T_2B/NI/MO$	III	Fibro-sarcoma (adult form)	High	Local excision , nodal dissection, delayed graft	-	+	+	D.O.D, 18 m.
5	12		trunk	6x4	$T_1B/NO/MO$	II	Synovial sarcoma	High	Wide local excision , rotational flap	-	-	+	D.O.D, 25 m.
6	3/12		Left anterior forearm	10x6	$T_1B/NO/MO$	I	Infantile fibrosarcoma	low	Wide local excision, primary Theirsh grafting	-	-	-	NEOD, 68 m.
7	12		Retroperitoneum	15x10	$T_2B/NO/MO$	III	Liposarcoma	High	Debulking	+	+	-	D.O.D, 20 m.
8	12		Trunk	8x5	$T_2B/NO/MO$	II	Dermato fibrosarcoma (classic form)	low	Wide local excision, primary grafting	-	-	+	D.O.D, 30 m.
9	5/12		Face	7x5	$T_1B/NO/MO$	I	infantile fibrosarcoma	low	Wide local excision, primary closure	-	-	-	NEOD, 52 m.
10	7		Left shoulder region	8x6	$T_1B/NO/MO$	II	malignant fibrous histiocytoma	low	Wide local excision primary grafting	-	-	+	NEOD, 47 m.
11	1		Left index	3x3	$T_2B/NO/MO$	II	Malignant heamangio pericytoma	low	Ray ampulation	-	-	+	NEOD, 44 m.

pretreating TNM system showed that , two patients had nodal metastasis (patients 1,4) (18.1%) , however no patient had distant metastasis. The IRS grouping system showed that 3 patients were staged as group I (27.6 %) , 4 as group II (36.3 %) and the remainder as group III (n = 4; 36.3 %). Tissue diagnosis and immunohistochemical analysis confirmed that fibrosarcoma was the commonest histologic subtype (n = 4 , 36.3 %) , followed by synovial sarcoma (n = 3; 27.2 %). Malignant fibrous histiocytomas was recorded in two patients (18.1 %) , whereas malignant heamangiopericytoma and liposarcoma were equally represented in this series (one patient for each , 9%). For fibrosarcomas, 2 patients had infantile type (18.1 %) , one had adult form (9 %) and another had dermatofibrosarcoma protuberance (fig. 4) (classic form, 9 %). Histologic grading of NRSTS showed that 5 cases (45.5 %) had high grade sarcoma whereas 6 cases (54.5 %) had low grade sarcoma .

By comparing the clinical behaviour of RMS and NRSTS , it appeared that , there were no statistically significant differences as regard to sex , tumour location or the mean duration of symptoms (P = NS). There were statistically significant differences with respect to the median age at presentation (10.3 years versus 7.3 years respectively ; P =0.011) , median tumour size (7.8 × 5.2 cm versus 9.1 × 6.4 cm respectively ; P = 0.013) , tumour grade (high in 100 % versus 45.5 % respectively; P = 0.021), regional lymph node involvement (70 % versus 18.1 % respectively; P = 0.009) and metastatic spread (60 % versus zero % respectively; P = 0.0003) .

Results of treatment:-

Surgery for RMS comprised biopsy only (n = 5 ; 50 %), local excision (n = 2 ; 20 %) and one case each of above elbow amputation, debulking, and wide local excision (10%). Two patients (patients 3, 7) underwent regional lymph node dissection for bulky metastatic disease. Reconstructive surgery included delayed grafting in 2 patients and primary closure in one. All patients received multiagent chemo-therapy. Three patients, (4, 7, 9), received primary chemo-therapy to achieve tumour regression prior to surgical resection. Eight patients (80%) were given radiotherapy. Only in one (patient, 10) microscopic residual disease was followed by adjuvant radiation whereas in the other 7 cases radiation was the primary mode of control for metastatic sites.

Surgical procedures for patients with NRSTS included, wide local excision (n = 6 ; 54.5 %) , local excision (n = 2 ; 18.1 %)

and one case each of biopsy only , debulking ; and ray amputation (9%). Two patients (patients 1,4) also had injuinal lymph node dissection for bulky metastatic deposits. Reconstructive surgery varied between primary closure in 2 patients, primary Theirsh grafting in 3, delayed grafting in 2 , and rotational flap in one. Only one child (patient 7 ; 9%) was given primary chemo-therapy prior to palliative resection, whereas post-operative mutiagent chemotherapy was administrated in 4 children (36.3%) with large sized tumours (patients 1,2,4,7). Seven cases (63.7%) were eligible for radiotherapy, to control microscopic residual in 4 and macroscopic residual in 3 .

There were no significant therapy-related complications among patients in our study .

Survival analysis results :-

The end results of the all patients (n = 21) according to the IRS grouping system were recorded in table (3) and Fig. (1 & 2) .

Table (3)

Groups	Patients		Over all survival period	3-years over all survival		3-years disease free survival		P value
	No	%		No	%	No	%	
Group I	3	14.2%	70 months	3	100%	3	100%	
Group II	5	3.8%	42.2 months	4	80%	3	60%	Significant
Group III	7	3.3%	21.1 months	1	14.2%	Zero	Zero %	
Group IV	6	8.5%	8.3 months	Zero	Zero%	Zero	Zero%	
Total	21	00%	29.5 months	8	38.1 %	6	28.5%	0.0005