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RESEARCH ARTICLE

SPECTRUM OF SOFT TISSUE TUMOURS AT TERTIARY CARE CENTER

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ABSTRACT

Introduction: In the recent years, there is an upward trend in the incidence of soft tissue tumors due to advances in diagnostic modalities. Histopathology is the reliable guide for diagnosis, but immunohistochemistry and cytogenetics provide greater accuracy.

Aims and Objective: The present study was aimed at evaluation of spectrum of soft tissue tumours and to categorize them into revised WHO classification of soft tissue tumours 2013. Study highlights common type of tumours, age and sex distribution.

Materials and Methods: The present study is a retroprospective study of 276 specimens. Tissue was processed as per the standard protocol. Pertinent clinical data were retrieved from case records. Thorough microscopic examination was done. A panel of immunostains was applied as per the merit of the case for final diagnosis. Data were analyzed and tumours were categorized as per WHO classification 2013.

Results: Major contributors were benign consisting 91.3% of cases, followed by intermediate 5.44% and malignant tumours 3.26%. Adipocytic tumours were the commonest subtype (70.23%), followed by nerve sheath tumours (17.46%). Amongst malignant category, wide ranges of tumours were found.

Conclusion: Light microscopy is indispensible but greater accuracy can be achieved by performing ancillary techniques like immunohistochemistry, cytogenetics and electron microscopy for definitive diagnosis. IHC has therapeutic implications in sarcomas like rhabdomyosarcomas, epithelioid sarcoma, clear cell sarcoma, desmoplastic round cell tumour and gastrointestinal stromal tumours

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INTRODUCTION

Soft tissue tumors are 'mesenchymal proliferations arising in the extra skeletal nonepithelial tissue of the body excluding viscera, brain coverings and lympho-reticular system (Horvai 2015, Jo and Fletcher, 2013). There is an upward trend in the incidence and a significant increase in the understanding of these tumours, from histopathological and genetic points of view (Badwe, 2014, Yusuf *et al*., 2013). Histology is the most reliable diagnostic guide and predictor of its clinical behavior. (Coindre, 2006) Their close histopathologic similarities with only subtle differences detectable only on careful microscopic examination, pose a diagnostic challenge. (Vahini, 2015) Hence the ancillary diagnostic modalities like IHC, genetic studies are must for the final diagnosis.

MATERIAL AND METHODS

This was a retro prospective observational study of 5 years, comprising of 276 specimens excluding recurrent and tumours of female genital tract.

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The specimens were received as incisional, excisional biopsy and radical. Thorough gross examination was done with special emphasis to capsule, size, shape, consistency, color, cut surface, areas of necrosis, hemorrhage, calcification and adhesions to the adjacent structures. Bits were given as per the Rosai J Appendix E guidelines. (Rosai, 2011) Processing and H&E staining were done as per the protocol and special staining as per the merit of the case. Immunohistochemical studies were done with Biogenex antigen Retrieval System wherever necessary. Cytokeratin and CD20 were done to exclude epithelial and lymphoreticular malignancies respectively. Antibodies like Desmin, Vimentin, Cytokeratin, S-100, Smooth Muscle Actin, CD31, CD34, CD99, CD117, Myogenin and Ki-67 were performed to confirm the diagnosis. The final diagnoses based on clinicohistopathological and immunohistochemical findings were formulated, analyzed and classified according to 'WHO 2013' classification.

RESULTS

During this period, 276 were soft tissue tumors with a frequency of 2.75% (Figure 1).

Major contributors being benign consisting 91.3% of cases. Malignant and intermediate tumors were 5.44% and 3.26% respectively. Soft tissue tumors showed a male preponderance with M:F ratio being 1.5:1. which remained same for benign too, while intermediate and malignant tumors were twice common in males than in females (Figure 2). The highest frequency of soft tissue tumours was noted in the age group of 31-40 years (30.07%), followed by 41-50 years (22.83%). The maximum occurrences of soft tissue tumours were seen in the age group of 31 to 50 years. They comprised 52.9% of cases. In the present study, the youngest and the oldest age of presentation were 1 and 89 years respectively, with a mean of 38.97 years. Adipocytic tumours were the commonest accounting for 70.23% cases. Neurofibroma and Schwannoma comprised 9.92% and 7.54% respectively of all the benign soft tissue tumours. Intramuscular hemangioma, lymphangioma, benign fibrous histiocytoma, tenosynovial giant cell tumours were observed in 1.98%, 2.78%, 1.98% and 1.59% of cases respectively. Two cases of nuchal fibroma and fibroma of the tendon sheath were observed accounting for 0.79% each. Case one each of arteriovenous hemangioma, synovial hemangioma, nodular fasciitis, elastofibroma, leiomyoma and calcifying fibrous tumor was observed accounting for 0.40% of the total tumours (Table 1). Gastrointestinal stromal tumors and undifferentiated pleomorphic sarcoma were the commonest malignant tumors constituting 20% each of all. Leiomyosarcoma, malignant peripheral nerve sheath tumors and extraskeletal Ewing's sarcoma comprised of 13.33% each of all malignant tumors.

One each of a synovial sarcoma, alveolar soft part sarcoma and undifferentiated round cell sarcoma were seen contributing to 6.67% of all malignant soft tissue tumors (Figure 3). Dermatofibrosarcoma protuberans comprised majority (55.56%) of all intermediate tumors. Desmoid tumour and well differentiated liposarcoma comprised 22.22% each. Fifteen cases were subjected for panel of immunostains after thorough histological examination. Initially on histomorphology, all possible differential diagnoses were entertained. Battery of immunostains was run and slides were interpreted. Results of markers and clinical features were taken into consideration after careful and thorough examination of slides to arrive at a definitive diagnosis. Two cases of well differentiated liposarcomas were encountered in the study. Microscopically, plenty of classical multivacuolated lipoblasts were identified in both the cases. Both the tumours were confirmed by positive Vimentin and S-100 immunostains (Table 2).

Two cases of leiomyosarcoma were found in the present study. Both were 44 years and 60 years male with huge mass on thigh and shoulder respectively, either showing hyperchromatic pleomorphic cells with predominance of spindle cells. Wide range of differential diagnoses were entertained and immunostains were performed. Both the cases showed positivity for SMA and Vimentin. CD 31, CD 34, S-100, Myogenin and Desmin were negative. Based on histology and markers, diagnosis of pleomorphic leiomyosarcoma was formulated (Table 2). Two cases of MPNST were seen in the present study. A male in mid-fifties, with histopathologically proved neurofibromatosis, & 8X4X3 cm size nodule was biopsied. (A strong family history) He had café-au-lait spots on the trunk. Biopsy showed soft tissue sarcoma with many bizzare cells and brisk mitoses and rhabdomyoblast like cells. Immunostains showed S-100 positivity and rhabdomyoblasts were Desmin positive confirming the diagnosis of MPNST with rhabdomyoblastic differentiation (Table 2) (Figure 4). Another case was 45 years old male with single hard swelling over right thigh measuring 16X14X6 cm. Clinically and radiologically, diagnosis of sarcoma was suspected. Histopathological examination revealed features of MPNST, which was confirmed by S-100. Three cases of GIST were encountered in the present study. All had abdominal lump, a classical picture of GIST on microscopy. Two cases had mitotic figures more than 5 per 50 HPF. All the cases showed diffuse positivity for CD34 and CD117. Ki-67 activity was brisk in two cases that had high mitotic figures (Table 2) (Figure 5).

In the present study two malignant cases had (high risk) behavior and a case had (low risk) behavior. Single case of synovial sarcoma was found in 69 years male who had left knee swelling of size 11X8X7 cm. Microscopy revealed classical biphasic pattern. Vimentin and CD99 showed diffuse whereas S-100 showed focal positivity. Two cases of extra skeletal Ewing's sarcoma were encountered in 72 and 55 years female who had right shoulder and right upper limb mass respectively. All the differential diagnoses of malignant small round cell tumor were considered. Immunoprofile showed CK, CD20, Desmin, SMA, S-100, CD34, CD31, Myogenin negativity. Vimentin showed diffuse cytoplasmic and CD 99 diffuse membranous positivity.

Table 1. Histopathological type of benign tumors- Distribution of cases,

n=252

Sr. no	Histopathological type	No. of cases	%
I.	Adipocytic tumors:	177	70.23
	Lipoma	173	68.65
	Spindle cell lipoma	2	0.79
	Myolipoma	2	0.79
II.	Fibroblastic/myofibroblastic tumors:	7	2.78
	Nodular fasciitis	1	0.40
	Elastofibroma	1	0.40
	Fibroma of tendon sheath	2	0.79
	Nuchal type fibroma	2	0.79
	Calcifying fibrous tumor	1	0.40
III.	Fibrohistiocytic tumors	9	3.57
	Tenosynovial giant cell tumor	4	1.59
	Benign fibrous histiocytoma	5	1.98
IV.	Smooth muscle tumors	1	0.4
	Leiomyoma	1	0.40
V.	Pericytic/perivascular tumors	0	-
VI.	Skeletal muscle tumors	0	-
VII.	Vascular tumors	14	5.56
	Intramuscular hemangioma	5	1.98
	Arteriovenous hemangioma	1	0.40
	Synovial hemangioma	1	0.40
	Lymphangioma	7	2.78
VIII.	Nerve sheath tumors	44	17.46
	Schwannoma	19	7.54
	Neurofibroma	25	9.92
	Total	252	100

Three cases of undifferentiated pleomorphic sarcoma were observed. They were 45, 49 years males and 72 years female who had left thigh, left arm and left leg mass respectively All cases microscopy showed findings of high grade sarcoma. Panels of markers were performed. All the cases were negative for CK, CD20, Desmin, SMA, S-100, CD32, CD34 and Myogenin. No line of differentiation was observed. The diagnosis of undifferentiated pleomorphic sarcoma was formulated (Table 2).

Table 2. Histological types and its immunoreactivity

Type of tumour	Cytokeratin	Vimentin	Desmin	SMA	CD 31	CD 34	S100	CD 20	CD117	CD 99	Myogenin
Well dif. Liposarcoma	N	+	N	N	N	N	+	N	N	N	-
Leiomyosarcoma	N	+	+	+	N	N	N	N	N	N	N
GIST	N	N	N	N	N	+	N	N	+	N	-
MPNST with rhabdo. diff.	N	N	+	N	N	N	+	N	N	N	-
MPNST	N	N	N	N	N	N	+	N	N	N	-
Synovial sarcoma	+	+	N	N	N	N	N	N	N	+	-
Ewings sarcoma	N	+	N	N	NN	N	N	N	N	+	-
UPS	N	+	N	N	N	N	N	N	N	N	N
Und.ro.cell sar	N	+	N	N	N	N	N	N	N	N	N

N (Negative);+ (positive);GIST- Gastrointestinal stromal tumor; MPNST- Malignant peripheral nerve sheath tumor; MPNSTwith rhabdo. diff.- Malignant peripheral nerve sheath tumor with rhabdomyoblastic differentiation; UPS- Undifferentiated pleomorphic sarcoma; Und. ro. cell sar.- Undifferentiated round cell sarcoma.

Table 3. Comparison of distribution of benign, intermediate & malignant tumors

Study	Benign	Intermediate	Malignant
Makino Y[12] (1979)	96%	-	4%
Myhre-Jensen O[13] (1981) n=1403	94.6%	-	5.4%
Kransdorf MJ *et al*[14,15] (1995) n=31047	60.2%	-	39.8%
Agravat AH *et al*[16] (2010) n=100	86 %	2%	6% / 6% tumor like
Hassawi BA *et al*[17] (2010) n=93	75.2	-	24.8
Inamdar SS *et al*[9] (2012) n=232	85.8%	-	14.2%
Batra P *et al*[18] (2013) n=157	89.2%	-	10.8%
Jain P *et al*[8] (2014) n=370	90.6%	-	9.4%
Umarani MK *et al*[19] (2015) n=220	92.73%	2.27%	5%
Janaki M *et al*[10] (2015) n=210	92%	3.8%	4.2%
Vahini G[5] (2015) n=105	87.62%	-	12.38%
Dowerah S *et al*[20] (2016) n=50	88%	2%	10%
Navya Narayan O *et al*[11] (2016) n=291	93.8%	3.4%	2.8%
Present study (2016) n=276	91.30%	3.26%	5.44%

Table 4. Comparison of distribution of soft tissue tumours according to the type

Studies Type	Jain P *et al*[8] n=370	Badwe A *et al*[27] n=301	Baig MA[7] n=137	Janaki M *et al*[10] n=210	Umarani M K *et al*[19] n=220	Navya Narayan O *et al*[11] n=291	Present study n=276
Adipocytic	50.27	54.81	40.15	37.7	57.73	61.52	64.86
Fibroblastic	2.97	4.31	14.60	11.5	4.09	4.12	5.07
Fibroistiocytic	3.24	1.99	6.57	4.7	0.90	6.87	3.27
Smooth muscle	1.62	1.66	2.19	0	1.36	1.03	1.08
Pericytic	0	0	2.19	0.4	0.45	0.69	0
Skeletal muscle	1.35	0	0	0	1.36	0	0
Vascular	20	25.24	16.78	26.3	12.27	16.84	5.07
Chondroosseous	0	0.33	3.65	0	0	0.34	0
Nerve sheath	19.72	9.63	6.57	15.7	19.09	6.53	16.67
GIST	0	0.33	0	0.9	0.9	0	1.08
Uncertain diff.	0.81	1.32	2.92	1.4	1.82	2.06	1.45
Undifferentiated	0	0.33	4.38	1.4	0	0	1.45

Figures indicate percentage

Table 5. Comparison of spectrum of malignant soft tissue tumours

Sr no.	Study	Hassawi BA *et al*[17]n =23	Jain P *et al*[8] n=35	Janaki M *et al*[10] n=9	Baig MA[7] n=24	Sharma M *et al*[25] n=17	Present study n=15
I.	Adipocytic:	13.04	31.43	0	12.5	11.76	0
II.	Fibroblastic:	0	0	0	8.33	11.76	0
III.	Fibrohistiocytic:	8.7	14.29	0	20.83	29.41	0
IV.	LMS:	13.04	11.43	0	0	11.76	13.33
V.	RMS:		14.29	0	0	11.76	0
VI.	Vascular:	4.35	11.43	11.11	8.33	17.66	0
VII.	Pericytic:	0	0	0	12.5	0	0
VIII.	GIST:	34.78	0	22.23	0	0	20
IX.	Nerve sheath:	0	11.43	0	4.17	5.89	13.33
X.	Uncertain diff.	26.08	5.71	33.33	16.67	0	26.68
XI.	Undifferentiated:	0	0	33.33	4.17	0	26.68
XI.	Others:	-	-	-	12.5	-	-

Figures indicate percentage LMS- Leiomyosarcoma; RMS- Rhabdomyosarcoma; GIST- Gastrointestinal stromal tumour; Uncertain diff.- Uncertain differentiation

Single case of undifferentiated round cell sarcoma was seen. This was 11 years boy with 5X5cm mass below left knee. Histopathology showed dual population of cells with brisk mitotic activity. Cytokeratin, LCA and CD20 were unequivocally negative ruling out epithelial and haematolymphoid origin. SMA, S-100, CD31, CD34, CD99, Desmin and Myogenin were all negative which ruled out alveolar rhabdomyosarcoma, vascular tumours and PNET. Available markers and histomorphology helped to finalize the diagnosis of undifferentiated round cell sarcoma (Table 2).

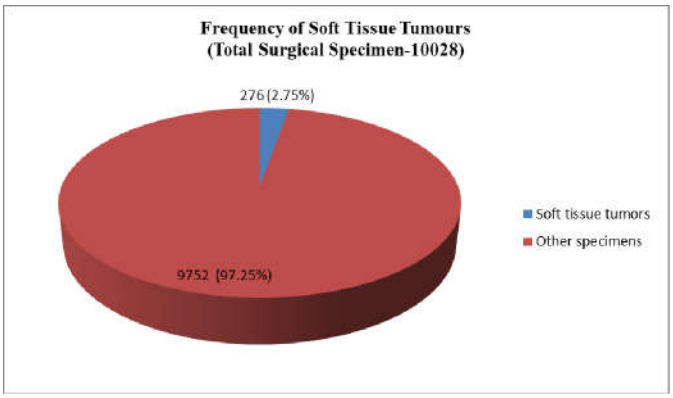


Figure 1.

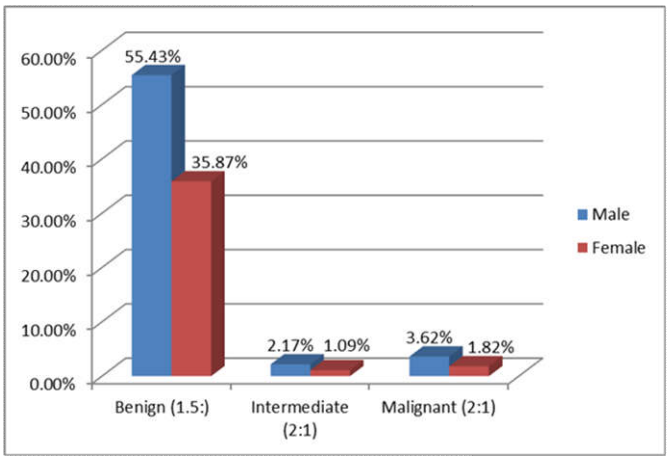
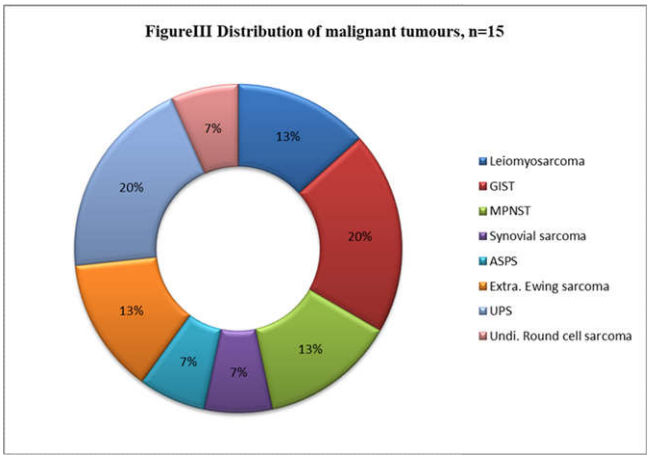


Figure 2. Sex wise distribution of soft tissue tumours, n=276



GIST- Gastrointedtinal stromal tumour
ASPS- Alveolar soft part sarcoma
MPNST- Malignant peripheral nerve sheath tumor;
UPS- Undifferentiated pleomorphic sarcoma
Und. round cell sarcoma- Undifferentiated round cell sarcoma

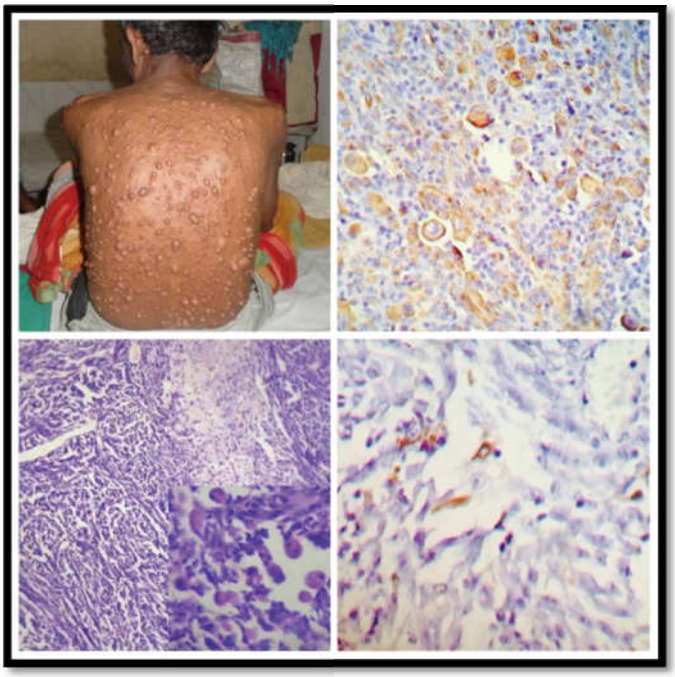


Figure 4a. Photograph showing multiple neurofibromas. Figure 4b: Photomicrograph showing hypercellular areas (Antoni A) and hypocellular areas (Antoni B) (H&E, 100 X). Inset shows rhabdomyoblastic differentiation (H&E, 400 X). Figure 4c: desmin positivity in rhabdomyoblasts (400X). Figure 4d: focal S100 positivity in spindle cells (400X)

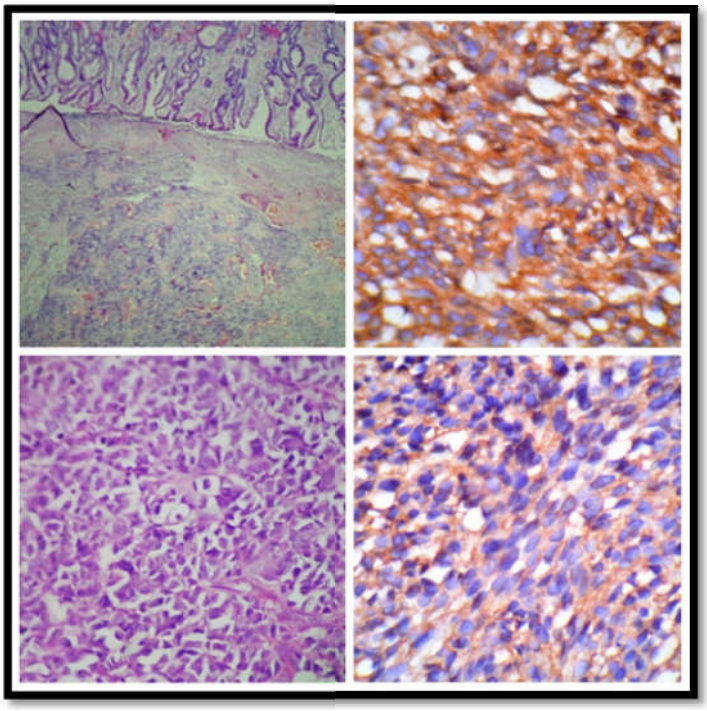


Figure 5a. GIST showing submucosal tumour cells (H&E,100X).Figure 5b:GIST showing spindle shaped tumour cells arranged in fascicles (H&E,400X).Figure 5c: GIST showing membranous positivity of CD117 (400X).Figure 5d GIST showing CD 34 positivity (400X).

DISCUSSION

Soft tissue tumors are not a common biopsy material of surgical pathology. Sarcomas account for less than 1% of all new malignancies detected every year.

Benign soft tissue tumours outnumber malignant by a margin of about 100:1. Enzinger FM and WW Weiss 1983, Robbins *et al* 1994, Myhre Jensen *et al* 1981 reported an incidence of soft tissue tumours as 0.8-1%, 0.8% and < 2% respectively (Vahini, 2015). Present study had similar frequency as Jain P *et al* and Inamdar SS *et al*. (Jain *et al.,* 2014, Inamdar *et al.,* 2014) (Table 2). In the various studies conducted by different authors as mentioned in the Table III, the benign tumours predominated constituting almost 85 to 96% of cases. However, the higher incidence of malignancy was observed by Kransdorf *et al*. because the data was collected from referral center where malignant and difficult cases were referred and services of immunohistochemistry were uninterrupted. (Kransdorf *et al*., 1995) Hassawi *et al*. conducted study in Mosul (Iraq) and found little higher incidence of malignancy (Hassawi *et al*., 2010).

That could be attributed to the geographical, environmental, genetic, dietary and life style variations. Male to female ratio in the present study was in accordance with most of the studies. On considering the spectrum of soft tissue tumours, adipocytic tumours were the commonest tumours in the majority of the studies. Jain P *et al* reported that the adipocytic tumors (50.27%) were the commonest soft tissue tumours followed by vascular tumours (20%). (Jain *et al*., 2014) Myhre Jensen *et al* reported that commonest benign tumours were of adipocytic (48.1%), followed by fibrohistiocytic tumours (15.8%). (Myhre Jensen *et al* 1981) (Table 4) Badwe *et al* also reported adipocytic tumors as the commonest soft tissue tumours (54.81%) followed by vascular tumours (25.24%). (Badwe *et al*., 2014) Janaki M *et al* found adipocytic tumours as the commonest soft tissue tumour 37.7% followed by vascular tumours 26.3% (Janaki *et al*., 2015), Whereas Umarani *et al*. noticed adipocytic as the commonest tumour 57.73% followed by nerve sheath tumours 19.09% (Umarani *et al*., 2015).

In the present study, commonest tumours were adipocytic 64.86% followed by nerve sheath tumours 16.67%. Our findings were in accordance with the study of Umarani MK *et al* and in discordance with the other above-mentioned studies due to the fact that, in the present study, tumours were classified according to the newer WHO classification (2013), whereas previous studies adopted the older classification. Current classification did not include superficial and cavernous hemangiomas under the category of 'Hemangioma' (Table 4)

In the present study, tumors of uncertain differentiation and undifferentiated tumors formed the major bulk amongst malignant soft tissue tumors constituting 26.68% each. (Figure 3). Findings in the present study were discordant with the most of the studies (Table 5). This is due to the fact that, according to the WHO classification of soft tissue tumours 2013, GIST is newly added entity to the soft tissue tumor category and malignant fibrous histiocytoma, previously categorized in fibrohistiocytic tumours is now included under the heading of undifferentiated/unclassified tumours and renamed as undifferentiated pleomorphic sarcoma. Studies conducted by different authors at different institutions showed different frequencies of the malignant soft tissue tumours. This may be due to the fact that soft tissue sarcomas on H&E staining have gross subjective differences as final categorization needs immune markers. Many authors didn't adopt the immune markers for final categorization of the tumours (Table 5).

Tumours classified as undifferentiated/ unclassified pleomorphic sarcoma should only be labeled after exclusion of specific line of differentiation.

Conclusion

Present study would like to emphasize that, even though the role of light microscopy is indispensible, the diagnostic accuracy can be greatly increased by performing ancillary techniques like immunogistochemistry, cytogenetics and electron microscopy. This has been widely applied in few research centers to solve the difficult cases and arrive at the definitive diagnosis. For some sarcomas, immunohistoch emistry is considered necessary for the therapeutic implications. This is the case for rhabdomyosarcomas, epithelioid sarcoma, clear cell sarcoma, desmoplastic round cell tumour and gastrointestinal stromal tumours. Correct identification of GIST with C-Kit positivity is very important because of the availability of specific molecular targeted therapy with inhibitors such as ematinib mesylate.

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