Original Article

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A Retrospective Study of Soft Tissue Tumors - Role of Histomorphology in Diagnosis

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ABSTRACT

Background: The field of soft tissue tumors is vast and yet to be explored. The diagnosis of these tumors is always challenging for the pathologists. The overlap in the clinical and radiological features makes histopathology very crucial in their identification.

Methods: This is a retrospective study of soft tissue tumors over a period of 18 months from January 2014 to June 2015 conducted in the Department of Pathology. The gross specimens were fixed in 10% formalin and the slides were stained by Hematoxylin and Eosin. Immunohistochemistry was performed wherever necessary.

Result: A total of 235 soft tissue tumors were studied of which benign cases were 225 (95.75%), intermediate 04 (1.70%) and malignant 06 (2.55%). The tumors had a male preponderance, with majority in the third decade, predominantly occurring in the head neck region. Of a total of eleven categories of soft tissue tumors in our study, the adipocytic category was the most common followed by the nerve sheath and vascular tumors.

Conclusion: Molecular diagnosis have started to gain momentum in the field of soft tissue tumors, however histomorphology still remains the gold standard.

Keywords: *Benign, Malignant, Soft Tissue Tumors, Histopathology*

Introduction

In anatomy, the term 'soft tissue' includes the tissues that connect, support and surround other structures and organs of the body, not being hard tissues such as bone. Soft tissue includes tendons, ligaments, fascia, skin, fibrous tissue, fat and synovial membranes (which are connective tissues), and muscles, nerves and blood vessels (which are not connective tissue). [1]

'Soft tissue tumours' (STTs) are defined as "Mesenchymal proliferations that occur in the extraskeletal, non-epithelial tissues of the body, excluding the viscera, coverings of the brain and the lympho-reticular system". [2]

These tumors arise everywhere in the body, most commonly on the extremities, trunk, abdominal cavity and head neck region. The pathogenesis of most of the STTs is still unknown. Various physical, chemical, environmental, genetic factors, radiation, viral infections and immune deficiencies have been considered in the etiopathogenesis of these tumors. [2] [3]

STTs can occur at any age. It has been noted that the histologic distribution of these tumors is rather specific for a particular age group at a particular anatomical site. Both benign and malignant STTs commonly present as a painless mass. A biopsy is necessary when a patient with no history of trauma presents with a swelling or when the swelling persists after 6 weeks after local trauma. [3]

There is a rise in the incidence of STTs, but it is unclear whether this represents a true increase in the tumors or reflects better diagnostic capabilities and newer advances in the field. [4]

Though histopathology remains the gold standard for the diagnosis of these tumors, the diagnostic accuracy of conventional light microscopy can be increased by using special stains, electron microscopy, immunohistochemical techniques and molecular/ cytogenetic methods. [5]

Thus, STTs pose a challenge to not only pathologists but treating surgeons too, especially their diverse biological behaviour. The overlapping histopathological features of many STTs can stretch the pathologist's diagnostic ability to a limit. [6]

Aims and Objectives

1. To study the distribution of STTs as per age, sex and anatomical site.
2. To study the gross and microscopy of various STTs and to correlate them clinically.
3. To study the histopathological pattern for understanding the classification and type of STT.

4. To study the relative frequencies of benign and malignant cases.

Materials and Methods

This was a retrospective study of STTs received in the Department of Pathology in our institute done over a period of 18 months from January 2014 to June 2015. The study was approved by the institutional ethics committee. **Inclusion criteria**: Only the extra-skeletal STTs over the extremities, trunk and head neck. **Exclusion criteria**: Age group less than 12 years was not included in the study. A total of 235 cases of STTs fulfilled the above criteria. The patient data was retrieved from pathological requisition forms and medical records and included demographic data such as age, sex and relevant clinical history. The tissue specimens were fixed in 10% formalin and cut into 3 micron thick sections and stained by Hematoxylin and Eosin. Gross and microscopic examination was done. Immunohistochemistry (IHC) was performed wherever necessary. The tumors were classified using the WHO 2013 classification of tumors of soft tissue and bone as benign, intermediate and malignant.

The category of nasopharyngeal angiofibroma was not included in the WHO (2013) classification of tumors of soft tissue and bone but they are STT as per literature and hence included in the study. [7]

Results

A total of 235 soft tissue tumors were studied of which benign cases were 225 (95.75%), intermediate 04 (1.70%) and malignant 06 (2.55%) **[Table.1]**. The ratio of benign to malignant STTs was 37.5:1.These tumors were more common in males, with male to female ratios in benign, intermediate and malignant tumors being 1.61:1, 3:1 and 2:1 respectively and overall 1.64:1 **[Table 2]**. The age range of occurrence of these tumors was 13-85 years with a mean of 37.05 years. Overall the STTs occurred predominantly in the third decade which included the benign tumors; the malignant tumors were common in the second decade **[Table 3]**. The classification was done using the WHO classification of tumors of soft tissue (2013) **[Table 4]**. The overall most common sites of STT was head neck region 92(39.15%) **[Table 5]**.

All the patients (100%) had presented with a swelling or lump of which maximum patients i.e.197 (83.8%) had a painless lump, whereas the rest had pain. The symptoms of the swelling had varied duration ranging from childhood/ birth or for some patients even greater than 20 years. Most patients had presented within 3 months of onset of symptoms (36.59%), of which lipomas were the most common. Of the patients having symptoms since birth, five cases were neurofibromas, three hemangiomas and one case had lymphangioma.

The adipocytic tumors were the most common category of STTs in our study with 121 cases (51.49%) occurring predominantly in males, in the fourth decade and most commonly on the trunk. Of the 120 benign adipocytic tumors, 116 cases were of conventional lipoma, 2 cases of angiolipoma, one case each of synovial lipomatosis and spindle cell lipoma. There was one malignant case of myxoid liposarcoma. All lipomas had a classical gross and histomorphology. Myxoid liposarcoma was seen in a 60 year old male on the thigh. The mass was 25×20×18 cms. **[Fig. 1]** Histologically, the tumor was capsulated with tumor cells in pattern less sheets, the adipocytes with atypical cells (lipoblast like) were scattered in background with a myxoid stroma, thin delicate vasculature. Mitosis of 3-4 per 10 hpf with focal necrosis seen.

The nerve sheath tumors were the second most common category with 48 cases (20.42%) mostly in the head neck of males in the third decade. Of the 48 cases of benign nerve sheath tumors, 28 were of neurofibromas and 20 of schwannomas. The neurofibromas in our study were, localized [most common, (67.86%)], plexiform **[Fig. 2]** and diffuse types. Microscopically, the tumor cells in neurofibromas were spindled with wavy nuclei, arranged in bundles and fasicles in a collagenous stroma. Schwannomas were encapsulated, gray-white, glistening with areas of haemorrhage and cystic degeneration **[Fig. 3].** Histologically 90% were conventional schwannomas and one case each of ancient and cellular schwannoma. Conventional schwannomas had a typical morphology with Antoni A and Antoni B areas, Verocay bodies and hyalinised blood vessels.

The vascular tumors were the third most common category with 29 cases (12.34%) mostly in the head neck, with a male preponderance and common in the second decade. Of the 29 vascular tumors, 26 were hemangiomas, two lymphangioma and one case of hemangioendothelioma (intermediate grade). The hemangiomas were grossly hemorrhagic with a spongy/sieve like cut section, while lymphangioma was cystic and filled with gelatinous material. Histologically, capillary hemangiomas 22(84.62%) and cavernous hemangioma 4(15.38%) were noted. Hemangioendothelioma (intermediate) consisted of many spindle shaped endothelial cells many of which show presence of intra-cellular lumina with very few containing RBCs in a myxoid stroma. Few proliferative vascular channels noted, with no mitosis or necrosis.

In the so called fibrohistiocytic tumour category, there were three cases of Tenosynovial Giant Cell Tumor and

two cases of Benign Fibrous Histiocytoma which depicted classical histology findings. The pericytic/perivascular category included five cases of glomus tumors which histologically were composed of vascular channels and glomus cells. **[Fig. 5]** The tumor cells were positive for CD34 and SMA.

The Fibroblastic/ Myofibroblastic tumours category included four tumors-Desmoid, plantar fibromatosis and extrapleural Solitary Fibrous Tumor (SFT) of intermediate category, while fibrosarcoma of the malignant category. Desmoid fibromatosis and plantar fibromatosis both had a similar gross appearance. **[Fig. 4]** Microscopically this tumor had infiltrative margins, the tumor cells were arranged in fasicles, spindle cells with bland nuclear features and collagenous stroma, with no mitosis. On IHC, the tumor was positive for vimentin and negative for desmin, SMA and S100. An upper eyelid swelling in a 65 year old man showed a tumor with hypocellular and hypercellular areas with thin walled vascular channels few with classical staghorn like morphology. Tumor cells were ovoid; the nuclei were vesicular to hyperchromatic. The tumor cells were positive for CD34 and negative for Desmin, SMA, and S100. This was a case of extrapleural SFT, CD34 positivity is characteristic of it. Fibrosarcoma occurred as 11.5x9x3.5cms, firm, irregular, greyish white, fleshy mass in the lower leg of a 45 year old male. Microscopically, it was a hypercellular tumor with spindle cells arranged in long fascicles at places in Herring bone pattern.**[Fig. 7]** The cells had hyperchromatic nucleus, with inconspicous nucleoli, mitosis was high 18 per 10hpf. The tumor was positive for Vimentin. Desmin and SMA were negative.

Tumours of uncertain differentiation: This category included one case each of myxoma, angiomyxoma and synovial sarcoma. Myxoma was gray white glistening, nodular, firm mass composed of spindled to stellate shaped tumor cells with elongated cytoplasm with few cells showing nuclear inclusions against abundant myxoid stroma. **[Fig.6]** Synovial sarcoma histologically showed malignant tumour cells arranged in sheets and fasicles. The cells are spindled with high nucleo-cytoplasmic ratio, hyperchromatic nuclei and mitosis of 2-3 per 10hpf. The tumor was positive for CD99, BCL2 and EMA and was negative for SMA, CD34, S100 and Pan-CK.

In smooth muscle tumor category there was a single case of leiomyoma on the trunk with classical gross and histology. The tumor was positive for SMA, confirming the diagnosis. In skeletal muscle tumor category was a single case of embryonal rhabdomyosarcoma with malignant cells arranged in sheets and nest having high nucleo-cytoplasmic ratio, round to angulated hyperchromatic nuclei, few cells had eosinophilic cytoplasm, few tadpole like cells were seen. Mitosis was 5-6 per 10hpf. The tumor cells were Desmin, Vimentin positive and LCA, CK, CD99 negative.

The undifferentiated/unclassified sarcomas included two cases which grossly were gray white, firm, fleshy. Microscopically the tumor was infiltrating the surrounding tissue, cells were large, pleomorphic, high N:C ratio cells with prominent nucleoli, arranged in pattern less sheets and fasicles. Bizzare and multinucleate cells were seen. Mitosis was 18-20 per 10hpf, with foci of haemorrhage and necrosis. **[Fig. 8]** The tumor cells were positive for vimentin and negative for CK, SMA, S100, desmin.

Nasopharyngeal Angiofibromas - There were 16 cases (6.81%), majority in second decade with male

Table 1: Grades of soft tissue tumours: (WHO, 2013).

Grades of soft tissue tumours	Number of cases(n=235)	Percentage (%)
Benign	225	95.75%
Intermediate	04	1.70%
Malignant	06	2.55%
Total	**235**	**100%**

Table 2: Sex distribution of benign, intermediate and malignant tumours:

Grades of soft tissue tumours	Male(n=146)	Female(n=89)	Total(n=235)
Benign	139 (59.15%)	86 (36.60%)	225 (95.75%)
Intermediate	03 (1.28%)	01 (0.43%)	04 (1.70%)
Malignant	04 (1.70%)	02 (0.85%)	06 (2.55%)
Total	**146 (62.13%)**	**89 (37.87%)**	**235 (100%)**

Table 3: Age and sex distribution of soft tissue tumours.

Age group(years)	Male(n=146)	Female(n=89)	Total(n=235)
12-20	21	14	35
21-30	39	26	65
31-40	32	20	52
41-50	25	12	37
51-60	21	10	31
61-70	04	05	09
71-80	03	02	05
81-90	01	00	01
Total	**146**	**89**	**235**

Table 4: Classification of Soft tissue tumours in our study: (as per WHO - 2013).

S. no.	Types of soft tissue tumours	Total cases(n=235)
1.	Adipocytic tumours	121(51.49%)
2.	Nerve sheath tumours	48(20.42%)
3.	Vascular tumours	29(12.34%)
4.	So called fibrohistiocytic tumours	5(2.13%)
5.	Pericytic/perivascular	5(2.13%)
6.	Fibroblastic/ myofibroblastic tumours	4(1.70%)
7.	Tumours of uncertain differentiation	3(1.28%)
8.	Smooth muscle tumours	1(0.42%)
9.	Skeletal muscle tumours	1(0.42%)
10.	Undifferentiated/ unclassified sarcomas	2(0.85%)
11.	Nasopharyngeal angiofibroma*	16(6.81%)
	Total	**235(100%)**

**The category of nasopharyngeal angiofibroma was not included in the WHO (2013) classification of tumours of bone and soft tissue but it is a STT as per literature.* [7]

Table 5: Site wise distribution of soft tissue tumours:

S. no.	Sites	Benign	Intermediate	Malignant	Total
1.	Head neck	89	02	01	92
2.	Upper extremities	52	00	02	54
3.	Lower extremities	34	02	03	39
4.	Trunk	50	00	00	50
	Total	**225**	**04**	**06**	**235**

Fig. 1: Myxoid liposarcoma: Cut surface is greasy predominantly myxoid, gelatinous and is lobulated separated by fibrous septae.

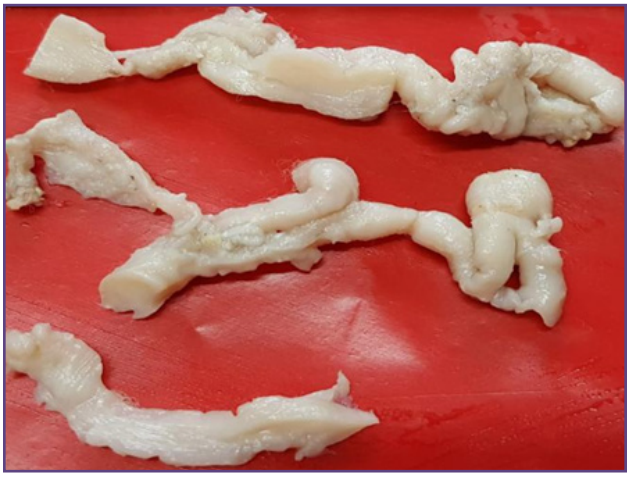

Fig. 2: Plexiform neurofibroma: Gray white linear thickened nerves, commonly referred to as 'bag of worms'

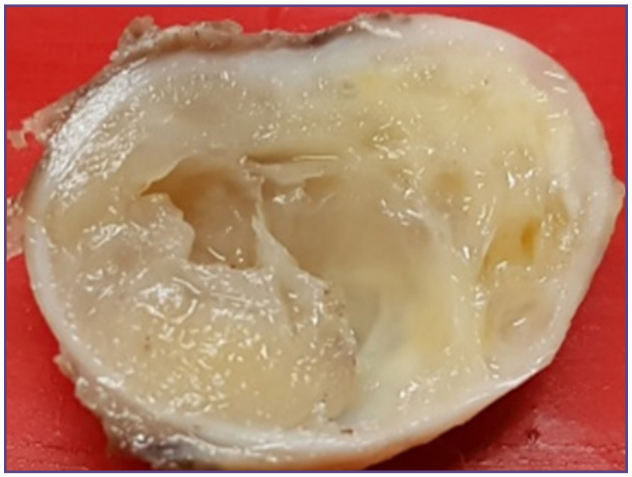

Fig. 3: Schwannoma: Encapsulated tumor with gelatinous cut surface with areas of cystic degeneration.

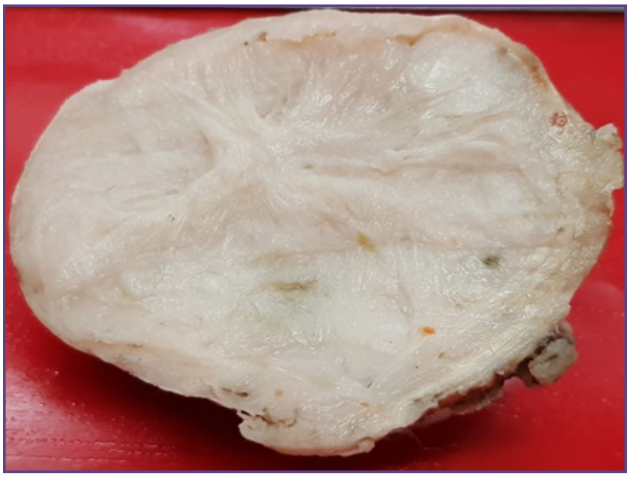

Fig. 4: Plantar Fibromatosis: Cut section is whitish, gritty with trabeculated appearance.

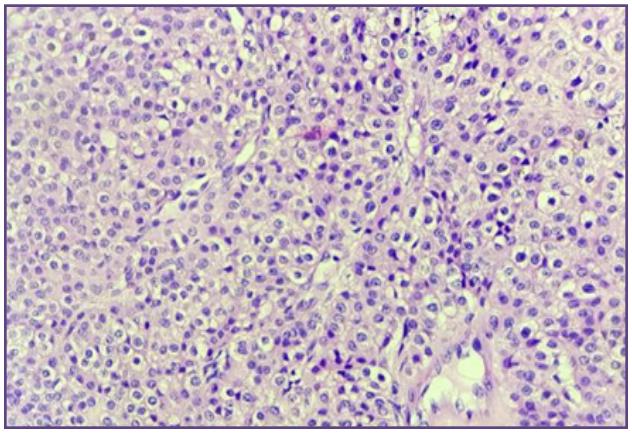

Fig. 5:Glomus tumour: composed of glomus cells which were round cells with clear to eosinophilic cytoplasm and well defined cell margins and vascular channels in between the cells (arrow) (H&E, 400x).

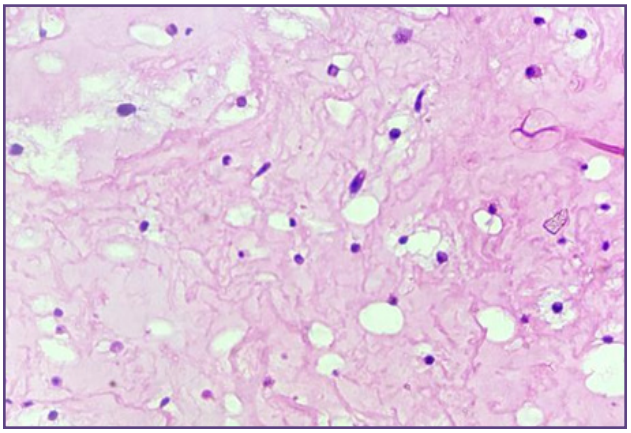

Fig. 6: Myxoma: Tumour is composed of spindle to stellate shaped cells against an abundant myxoid background (H&E, 100X).

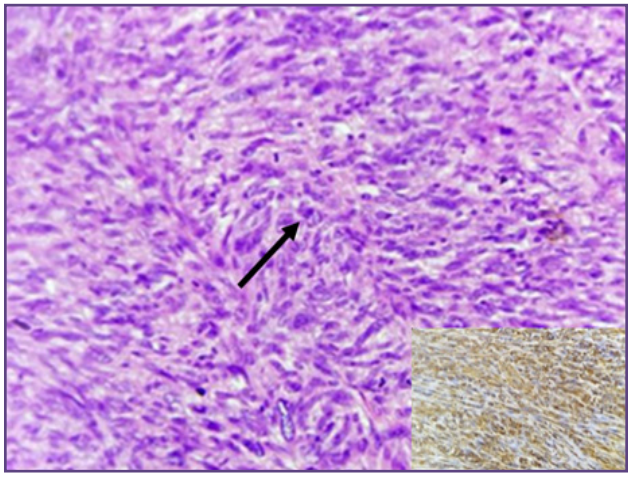

Fig. 7: Fibrosarcoma: Spindle shaped tumour cells arranged in a herring bone pattern and show nuclear pleomorphism, atypia and mitosis (arrow) (H&E, 400X). INSET: Fibrosarcoma: showing diffuse Vimentin positivity in the tumour cells (Immunohistochemistry, 400X).

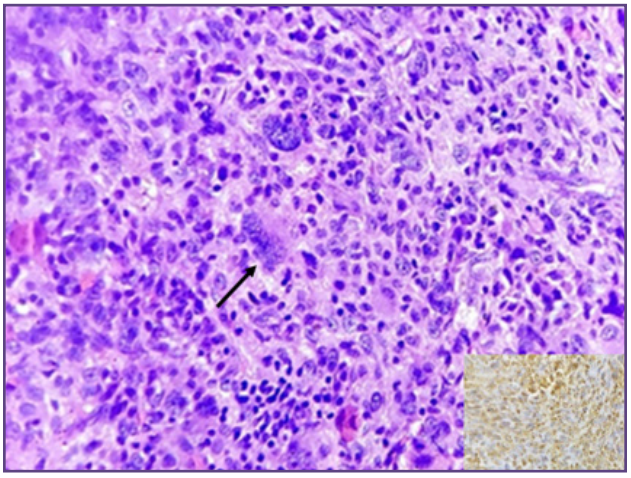

Fig. 8: Pleomorphic sarcoma: A highly cellular tumour with markedly pleomorphic cells. Some of the cells are bizzare (arrow) with nuclear indentation and high mitosis (H&E, 400x). INSET: Pleomorphic sarcoma: Vimentin strong positive. (Immunohistochemistry, 400X).

preponderance. Grossly, polypoidal with stalk, grey white to red brown tissue with slit like spaces on cut section. Histologically, all the tumors were composed of vascular channels separated by fibrocollagenous stroma, few vessels show incomplete muscle coat. Stroma showed fibroblast, foci of inflammatory cells and bony fragments in few cases.

Discussion

STTs are frequently encountered in everyday practice, but still our experience in them is limited. Enzinger F.M. & W.W. Weiss (1983), Robbins et al (1994) and Myhre Jenson et al (1981) reported an incidence of soft tissue tumors as 0.8-1%, 0.8% and < 2% respectively. [6]

A total of 13,065 specimens were received in the department of pathology during the study period of which 235 specimens (1.79%) were diagnosed as STTs as per the inclusion criteria. Of these 225 were benign, 04 intermediate grade and 06 malignant tumors. Benign soft tissue tumors exceeded malignant counterparts by a substantial margin.

Various studies have shown, the incidence of benign, intermediate and malignant STTs ranging from 92.3% to 95.72%, 0.67% to 3.4 and 2.8% to 7.7% and it was comparable with ours. **[Table 6]**

Studies found these tumors to be more common in males (range 57.3% to 67.8%) than females (32.2% to 42.7%) with the male: female ratio ranging from 1.3:1 to 2.1:1 **[Table 7]**

The most common age group of STTs, in our as well as most other studies mentioned was 21-30 years [**Table 8].**

Even the benign STTs occurred predominantly in third decade of life as depicted in studies by Rao B.S. et al [10], Khattak M.S.et al[9], and Harpal S. et al [8] , similar to our study. While malignant tumors occurred commonly in the sixth decade as per Harpal S. et al [8], Rao B.S. et al [10], Vahini G. [6] and Tellapuram V. et al [11]. In our study, malignant tumors occurred most commonly in second decade, this may be because of less number of malignant cases in our study.

In study by Goyal S et al [12] all the patients had presented with swelling followed by pain in (100%) while Gogi A.M. [13] described swelling in all patients (100%), of which 32.43 % also had pain, 5.40% had neurovascular symptoms whereas 4.05% had deformity. These findings were comparable with ours.

Overall the most common site of STT by Rao B.S. et al [10] and Vahini G. [6] was the head neck and face region, which was concordant with our study, whereas Jain P et al [2] found the most common site to be the extremities. The predominant site of benign STT in our study and Rao B.S. et al [10] was the head neck face. Like our study Rao B.S. et al [10], Jain P et al [2] and Goyal S et al [12] found the most common sites for malignant STTs to be the lower extremities.

The most common STT in studies by Jain P et al [2], Harpal S. et al [8] and Agravat A.H. et al [14] and Baste B.D. et al [3] were adipocytic tumors. It was followed by nerve sheath and vascular tumors in study by Baste B.D. et al [3], our study had concordant results.

Studies by Ramnani B.G. et al [15] and Rao B.S. et al [10] for adipocytic tumors, Rao B.S. et al [10] and Vahini G.et

al [6] for neurofibromas and schwannomas, showed a male preponderance and were common in the fourth and third decades respectively, similar to our study. Vascular tumors were more common in males in the second decade as described by Harpal S. et al [8], Chakrabarti P.R.et al [16] which was similar to our study. Nasopharyngeal angiofibromas most commonly occurred in males in the second decade as shown by Deepak M B et al [17] and Chakrabarti P.R. et al [16] which was similar to our study.

As far as site-wise distribution of individual tumors are concerned, the most common site of occurrence of lipomas in studies by Bharti Devi et al [18], Rhydholm A & Nils 0 Berg [19], Chakrabarti P.R. et al [16] and Rao B.S. et al [10] for lipomas and Tellapuram V. et al [11] for liposarcomas were the trunk and the lower extremities respectively which was concordant with our study. For neurofibromas and schwannomas, Chakrabarti P.R. et al [16], Lin BT et al [20], Vahini G. [6] and Deepak M B et al [17] found the head neck region to be the predominant site of occurrence like our study. The head neck region was also the most common site for vascular tumors as described by Rao B.S. et al [10], Narhire VV et al [21] and Deepak M B et al [17], similar to our study.

Umarani M.K.et al [23] and Anand G. et al [24] found conventional lipoma to be the most common histological variant in their study with 89.7% and 95.08% cases respectively which was similar to our study with 96% conventional lipomas. The gross and microscopic findings of adipocytic tumors were found to be concordant to studies by Rao B.S. et al [10], Chakrabarti P.R. et al [16], Deepak M B et al [17] and Agravat A.H. et al [14]. Amongst the neurofibromas, Gabhane S.K. et al [25] found the usual (localized pattern) in 68.5% cases, diffuse in 20.37% whereas plexiform in 11.11% cases, which was like in our study where localized constituted 67.86%, diffuse 17.86% and plexiform 14.28% of all cases of neurofibromas. Gabhane S.K. et al [25] and Rao B.S. et al [10] in their studies described the gross morphologies of neurofibromas while microscopic findings in studies by Narhire VV et al [21], Chakrabarti P.R. et al [16] and Gabhane S.K. et al [25] were found to be having similar results.

For schwannomas the most common histological type was conventional type which was also described by Vahini G. [6] and Gabhane S.K. et al[25] in which they composed 90% and 79.7% of all the schwannomas, in our study it was 90%. The external and histological findings described by Gabhane S.K. et al [25] and Narhire VV et al [21] of ancient, cellular and conventional schwannomas and S100 positivity used by Vahini G. [6] was compatible with ours. Vahini G[6], Rao B.S. et al[10] and Tellapuram V. et al[11] found the most common type of vascular tumor to be hemangioma composing 90.9%, 100% and 88.8% of all the vascular tumors respectively, in our study it was 89%. Tellapuram V. et al [11] found the incidence of hemangioendothelioma to be 5.6%, while in our study it was 3.44%. Chakrabarti P.R. et al [16] and Narhire VV et al [21] described hemangiomas as irregular polypoidal tissues with a brownish cut surface. The microscopic morphologies of capillary, cavernous hemangiomas, hemangioendothelioma and lymphangioma

Table 6: Grades of soft tissue tumours and ratio:

Study	Total cases(n)	Benign	Malignant	Intermediate	Ratio (B:M)
Present study	235	225(95.75%)	06(2.55%)	04(1.70%)	37.5:1
Navya Narayanan [5]	291	273(93.8%)	08(2.8%)	10(3.4%)	34.1:1
Baste B.D. et al [3]	70	67(95.72%)	03(4.28%)	-	22.3:1
Umarani M.K. et al [23]	220	204(92.73%)	11(5%)	05(2.27%)	18.5:1
Chakrabarti P.R. et al [16]	150	140(93.33%)	09(6%)	01(0.67%)	15.6:1

Table 7: Sex distribution of soft tissue tumours:

Study	Male	Females	Male : Female Ratio
Present study (n=235)	146(62.13%)	89(37.87%)	1.64:1
Vahini G.et al [6] (n=105)	66(62.8%)	39(37.2%)	1.69:1
Rao B.S. et al [10] (n=90)	61(67.8%)	29(32.2%)	2.1:1
Baste B.D. et al [3] (n=70)	45(64.3%)	25(35.7%)	1.8:1

Table 8: Age group distribution of soft tissue tumours

Age group (years)	Present Study (n=235)	Khattak M.S.et al [9] (n=267)	Rao B.S. et al [10] (n=90)	Harpal S. et al [8] (n=200)	Vahini G.[6] (n=105)
0-10	-	43(16.1%)	0(0%)	15(7.5%)	17(16.2%)
11-20	35(14.8%)	47(17.5%)	13(14.4%)	22(11%)	12(11.4%)
21-30	**65(27.6%)**	**56(20.9%)**	**38(42.2%)**	**44(22%)**	**29(27.6%)**
31-40	52(22.1%)	39(14.5%)	25(27.8%)	27(13.5%)	11(10.6%)
41-50	37(15.7%)	44(16.5%)	04(4.4%)	39(19.5%)	12(11.4%)
51-60	31(13.2%)	24(9%)	07(7.8%)	29(14.5%)	12(11.4%)
61-70	09(3.8%)	15(5.5%) (>60 years)	03(3.4%) (>61yrs)	18(9%)	1 (11.4%) (>60yrs)
71-80	05(2.1%)	--	--	05(2.5%)	--
81-90	01(0.4%)	--	--	00(0%)	--
90-100	--	--	--	01(0.5%)	--

by Narhire VV et al [21], Rao B.S. et al [10], Kanth et al [26] and Agravat A.H. et al [14] matched our findings. Gaillard A.L., et al [27] and Deepak M B et al [17] also described the classical features of nasopharyngeal angiofibroma as found in our study.

Conclusion

This study therefore makes us realize that our understanding in the field of STTs is still limited. We are at the shore of the ocean of these spectacular tumors. Though STTs are being studied in extreme details throughout the globe, with immunohistochemistry, genetic and molecular advances revealing the new mysteries in this field, what has to be kept in mind is "Histomorphology" still remains the "gold standard" for the diagnosis of these tumors.

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Competing Interests

Nil

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